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(71) Applicant (for all designated States except US): NOVARTIS AG [CWCH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors:

Inventors/Applicants (for US only): BAESCHLIN, Daniel, Kaspar [CWCH]; Austr. 1A, CH-4144 Arlesheim (CH); SEDRANI, Richard [LU/CH]; Herrengabenweg 15, CH-4054 Basel (CH); FLOHR, Stefanie [DEJCH]; Passwangstrasse 3, CH-4153 Reinch (CH); NAMOTO, Kenji [JP/CH]; Kandererstrasse 29, CH-4057 Basel (CH); SIROCKIN, Finton [FR/FR]; 17, rue des Asperges, F-68730 Blotzheim (FR); GEISSIER, Francois [FR/FR]; 19, rue des Vallons, F-68130 Altkirch (FR); FENTON, Garry [GB/GB]; Argenta Discovery Ltd., Units 7/9, Spire Green Centre, Flexmeadow, Harlow, Essex CM19 5TR (GB); BESWIK, Mandy, Christine [GB/GB]; Argenta Discovery Ltd., Units 7/9, Spire Green Centre, Essex CM19 5TR (GB).

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(54) Title: 1-AMINOMETHYL- L-PHENYL- CYCLOHEXANE DERIVATIVES AS DDP-IV INHIBITORS

(57) Abstract: Compounds of the formula (I) are provided: wherein V, W, X, Y, Z, R², R⁴, R², R³, R⁵ and m are as defined in the specification; and pharmaceutically acceptable salts and prodrugs thereof. The compounds may be useful in the treatment or prevention of various diseases and conditions in which dipetidylpeptidase-IV (DPP-IV) is implicated.

(74) Agent: VOEGELI-LANGE, Regina; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).


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Field of the Invention

The present invention relates to compounds and their use in therapy.

Background to the Invention

Dipeptidylpeptidase-IV (DPP-IV) is a serine protease which cleaves N-terminal dipeptides from a peptide chain containing, in general, a proline residue in the penultimate position. DPP-IV is widely expressed in mammalian tissue as a type II integral membrane protein. The protease is expressed on the surface of differentiated epithelial cells of the intestine, liver, kidney proximal tubules, prostate, corpus luteum, and on leukocyte subsets such as lymphocytes and macrophages. A soluble form of the enzyme is found in serum that has structure and function identical to the membrane-bound form of the enzyme but lacks the hydrophobic transmembrane domain.

DPP-IV has many physiologically relevant substrates including chemokines (e.g. eotaxin and macrophage-derived chemokine), neuropeptides (e.g. neuropeptide Y and substance P), vasoactive peptides, and incretins (e.g. GLP-1 and GIP). GLP-1 (glucagon-like peptide-1) is a hormone produced in the L cells of the distal small intestine in response to ingested nutrients. GLP-1 receptor binding on various tissues stimulates insulin gene expression, biosynthesis and glucose-dependent insulin secretion, inhibits glucagon secretion, promotes satiety, slows gastric emptying and promotes growth of pancreatic beta cells.

Although the biological role of DPP-IV in mammalian systems has not been completely established, it is believed to play an important role in neuropeptide metabolism, T-cell activation, attachment of cancer cells to the endothelium and the entry of HIV into lymphoid cells. It has also been discovered that DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1). Since GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, DPP-IV inhibition appears to represent an attractive approach for treating, for example, non-insulin-dependent diabetes mellitus (NIDDM).
DPP-IV has also been shown to play a part in the immune response. Expressed by T-CD4+ lymphocytes, where it is synonymous with the antigen CD26, DPP-IV plays an important part in the mechanism of transplant rejection (Transplantation 1997, 63 (10), 1495-500). By allowing more selective suppression of the immune response, inhibition of DPP-IV accordingly represents an extremely promising approach in the prevention of transplant rejection in transplant patients.


WO 03/063797 discloses the following compounds as intermediates for the synthesis of inhibitors of potassium ion channel function:

In addition, WO 2005/105096 discloses the following compounds as intermediates for the synthesis of inhibitors of potassium ion channel function:
WO 03/00676 describes the following compound as being useful in the treatment of malaria:

\[
\begin{align*}
\text{Compound 1} & : \hspace{2cm} \text{Compound 2}
\end{align*}
\]
Summary of the Invention

According to the invention there is provided a compound of the Formula (I):

\[
\begin{align*}
Y & \quad Z \quad R^6 \\
\quad V & \quad (R^7)_m \\
\quad W & \quad \quad X \quad R^5 \\
\quad H_2 N & \quad R^3 \quad R^4
\end{align*}
\]

(1)

wherein

one of V and W is selected from a bond, -(CH₂)ₙ-, O-, NH- and -N(R⁸)⁻; and the other is selected from a bond, -(CH₂)ₙ- and -O⁻;

X is a bond or a linker having 1 to 5 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)ᵣ, -N(R⁸)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R¹⁰; with the proviso that, when at least one of V and W is O-, NH- or N(R⁸)⁻, X is a bond;

Y is a bond; or Y and an R⁷ moiety taken together with the atom(s) to which they are attached form a carbocycle or a heterocycle, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰, and may be saturated or unsaturated;

Z is a bond or a linker having 1 to 12 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)ᵣ, -N(R⁸)-, hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R¹⁰, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R¹⁰;

R³ and R⁴ are each independently hydrogen or R¹⁰; or R³ and R⁴ taken together with the carbon atom to which they are attached form carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰;
R$^5$ is selected from hydrogen, except when X is a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$; and -(CH$_2$)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$;

R$^6$ is selected from hydrogen, except when Y and 2 are each a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$; and -(CH$_2$)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$;

R$^7$ is independently selected from R$^{10}$;

or two R$^7$ moieties taken together may form a bridge between the atoms to which they are attached, wherein the bridge is a hydrocarbylene or -(CH$_2$)$_i$-O-(CH$_2$)$_j$ bridge, wherein i and j are each independently 0, 1 or 2;

R$^8$ is selected from R$^9$, -OR$^9$, -C(O)R$^9$, -C(O)OR$^9$ and -S(O)$^1$R$^9$;

R$^9$ is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$; and -(CH$_2$)$_k$-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$;

each R$^{10}$ is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR$^{11}$, -OR$^{11}$, -C(O)R$^{11}$, -C(O)OR$^{11}$, -OC(O)R$^{11}$, -S(O)$^1$R$^{11}$, -N(R$^{11}$)R$^{12}$, -C(O)N(R$^{11}$)R$^{12}$, -S(O)|N(R$^{11}$)R$^{12}$ and R$^{13}$;

R$^{11}$ and R$^{12}$ are each independently hydrogen or R$^{13}$;

R$^{13}$ is selected from hydrocarbyl and -(CH$_2$)$_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C$_{1-6}$ alkyl and C$_{1-6}$ alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6;

Ms 0, 1 or 2;

rn is 0, 1, 2, 3, 4, 5 or 6; and
n is 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

Also provided are pharmaceutical formulations comprising a compound of the invention and, optionally, a pharmaceutically acceptable diluent or carrier.

The invention also provides a product comprising a compound of the invention and a therapeutic agent; as a combined preparation for simultaneous, separate or sequential use in therapy.

Compounds of the invention may be useful in the treatment or prevention of a disease or condition selected from non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, calcitonin-osteoporosis, heart failure, impaired glucose metabolism or impaired glucose tolerance, neurodegenerative diseases, cardiovascular or renal diseases, and neurodegenerative or cognitive disorders. Compounds of the invention may also be useful for producing a sedative or anxiolytic effect, attenuating post-surgical catabolic changes or hormonal responses to stress, reducing mortality and morbidity after myocardial infarction, modulating hyperlipidemia or associated conditions, or lowering VLDL, LDL or Lp(a) levels. Accordingly, other aspects of the invention concern the use of the present compounds in such therapies and the use of the compounds for the manufacture of a medicament for use in such therapies. Therapeutic methods comprising administering a therapeutically effective amount of a compound of the invention to a patient are also provided.

The compounds of the invention can exist in different forms, such as free acids, free bases, esters and other prodrugs, salts and tautomers, for example, and the disclosure includes all variant forms of the compounds.

The extent of protection includes counterfeit or fraudulent products which contain or purport to contain a compound of the invention irrespective of whether they do in fact contain such a compound and irrespective of whether any such compound is contained in a therapeutically effective amount.
Included in the scope of protection are packages which include a description or instructions which indicate that the package contains a species or pharmaceutical formulation of the invention and a product which is or comprises, or purports to be or comprise, such a formulation or species. Such packages may be, but are not necessarily, counterfeit or fraudulent.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

**Description of Various Embodiments**

*Hydrocarbyl and hydrocarbylene*

The terms "hydrocarbyl" and "hydrocarbylene" as used herein include reference to moieties consisting exclusively of hydrogen and carbon atoms; such a moiety may comprise an aliphatic and/or an aromatic moiety. The moiety may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Examples of hydrocarbyl groups include C_{1-6} alkyl (e.g. C_{1}, C_{2}, C_{3} or C_{4} alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl); C_{1-6} alkyl substituted by aryl (e.g. benzyl) or by cycloalkyl (e.g. cyclopropylmethyl); cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl); alkenyl (e.g. 2-butenyl); alkynyl (e.g. 2-butenyl); aryl (e.g. phenyl, naphthyl or fluorenyl) and the like.

*Alkyl*

The terms "alkyl" and "C_{1-6} alkyl" as used herein include reference to a straight or branched chain alkyl moiety having 1, 2, 3, 4, 5 or 6 carbon atoms. This term includes reference to groups such as methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, sec-butyl or tert-butyl), pentyl, hexyl and the like. In particular, alkyl may have 1, 2, 3 or 4 carbon atoms.

*Alkenyl*
The terms "alkenyl" and "C₂ alkenyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one double bond, of either E or Z stereochemistry where applicable. This term includes reference to groups such as ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl and 3-hexenyl and the like.

**Alkynyl**

The terms "alkynyl" and "C₂₆ alkynyl" as used herein include reference to a straight or branched chain alkyl moiety having 2, 3, 4, 5 or 6 carbon atoms and having, in addition, at least one triple bond. This term includes reference to groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl and 3-hexynyl and the like.

**Alkoxy**

The terms "alkoxy" and "C₁₆ alkoxy" as used herein include reference to -O-alkyl, wherein alkyl is straight or branched chain and comprises 1, 2, 3, 4, 5 or 6 carbon atoms. In one class of embodiments, alkoxy has 1, 2, 3 or 4 carbon atoms. This term includes reference to groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like.

**Cycloalkyl**

The term "cycloalkyl" as used herein includes reference to an alicyclic moiety having 3, 4, 5, 6, 7 or 8 carbon atoms. The group may be a bridged or polycyclic ring system. More often cycloalkyl groups are monocyclic. This term includes reference to groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl and the like.

**Aryl**

The term "aryl" as used herein includes reference to an aromatic ring system comprising 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring carbon atoms. Aryl is often phenyl but may be a polycyclic ring system, having two or more rings, at least one of which is aromatic. This term
includes reference to groups such as phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

**Carbocyclyl**

The term "carbocyclyl" as used herein includes reference to a saturated (e.g. cycloalkyl) or unsaturated (e.g. aryl) ring moiety having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 carbon ring atoms. In particular, carbocyclyl includes a 3- to 10-membered ring or ring system and, in particular, a 5- or 6-membered ring, which may be saturated or unsaturated. A carbocyclic moiety is, for example, selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl, phenyl, naphthyl, fluorenyl, azulenyl, indenyl, anthryl and the like.

**Heterocyclyl**

The term "heterocyclyl" as used herein includes reference to a saturated (e.g. heterocycloalkyl) or unsaturated (e.g. heteroaryl) heterocyclic ring moiety having from 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen, phosphorus, silicon and sulphur. In particular, heterocyclyl includes a 3- to 10-membered ring or ring system and more particularly a 5- or 6-membered ring, which may be saturated or unsaturated.

A heterocyclic moiety is, for example, selected from oxiranyl, azirinyl, 1,2-oxathiolan-1-yl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyrany1, thiopyranyl, thiophenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, especially thiomorpholino, indoliziny1, isoindolyl, 3H-indolyl, indolyl, benzimidazolyl, cumary1, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthoquinolyl, quinoxalyl, quinazoliny1, quinazoliny1, cinnoliny1, pteridinyl, carbazolyl, β-carboliny1, phenanthridiny1, acridiny1, perimidiny1, phenanthroliny1, furazany1, phenaziny1, phenothiaziny1, phenoxyazinyl, chromeny1, isochromany1, chromany1 and the like.
**Heterocycloalkyl**

The term "heterocycloalkyl" as used herein includes reference to a saturated heterocyclic moiety having 3, 4, 5, 6 or 7 ring carbon atoms and 1, 2, 3, 4 or 5 ring heteroatoms selected from nitrogen, oxygen, phosphorus and sulphur. The group may be a polycyclic ring system but more often is monocyclic. This term includes reference to groups such as azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxiranyl, pyrazolidinyl, imidazolyl, indolizidinyl, piperazinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, quinolizidinyl and the like.

**Heteroaryl**

The term "heteroaryl" as used herein includes reference to an aromatic heterocyclic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen and sulphur. The group may be a polycyclic ring system, having two or more rings, at least one of which is aromatic, but is more often monocyclic. This term includes reference to groups such as pyrimidinyl, furanyl, benzo[b]thiophenyl, thiophenyl, pyrrolyl, imidazolyl, pyrrolidinyl, pyridinyl, benzo[b]furanyl, pyrazinyl, purinyl, indolyl, benzimidazolyl, quinolinyl, phenothiazinyl, triazinyl, phthalazinyl, 2H-chromenyl, oxazolyl, isoxazolyl, thiazolyl, isoindolyl, indazdyl, purinyl, isoquinolyl, quinazolinyl, pteridinyl and the like.

**Halogen**

The term "halogen" as used herein includes reference to F, Cl, Br or I. In a particular, halogen may be F or Cl, of which F is more common.

**Substituted**

The term "substituted" as used herein in reference to a moiety means that one or more, especially up to 5, more especially 1, 2 or 3, of the hydrogen atoms in said moiety are replaced independently of each other by the corresponding number of the described substituents. The term "optionally substituted" as used herein means substituted or unsubstituted.
It will, of course, be understood that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort whether a particular substitution is possible. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds. Additionally, it will of course be understood that the substituents described herein may themselves be substituted by any substituent, subject to the aforementioned restriction to appropriate substitutions as recognised by the skilled man.

*Pharmaceutically acceptable*

The term "pharmaceutically acceptable" as used herein includes reference to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. This term includes acceptability for both human and veterinary purposes.

*Independently*

Where two or more moieties are described as being "each independently" selected from a list of atoms or groups, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties.
**Compounds**

The invention provides compounds of the Formula (I):

$$\begin{align*}
\text{V} & \text{W} \\
\text{X} & \text{Y} \\
\text{Z} & \text{R}_1 \\
\text{R}_2 & \text{R}_3 \\
\text{R}_4 & \text{R}_5 \\
\text{R}_6 & \text{R}_7 \\
\text{(R}_7^n & \text{m}) \\
\text{H}_2\text{N} & \text{W} \\
\text{R}^3 & \text{R}^4 \\
\text{X} & \text{R}^5 \\
\end{align*}$$

wherein V, W, X, Y, Z, R$_1$, R$_2$, R$_3$, R$_4$, R$_5$, R$_6$, R$_7$ and m are as defined herein;

or a pharmaceutically acceptable salt or prodrug thereof.

In embodiments, the compound is not one of the following compounds:
Further embodiments of the invention are described below. It will be appreciated that the features specified in each embodiment may be combined with other specified features, to provide further embodiments.

\( V \& W \)

In Formula (I), one of \( V \) and \( W \) is selected from a bond, \(-(\text{CH}_2)_n\), \(-\text{O}-\), \(-\text{NH}-\) and \(-\text{N}(\text{R}^8)\); and the other is selected from a bond, \(-(\text{CH}_2)_n\) and \(-\text{O}-\); wherein \( n \) is 1 or 2. Usually, \( n \) is 1. It will be appreciated that any \(-\text{NH}-\) or \(-\text{CH}_2-\) group present may be unsubstituted or substituted with one or more \( \text{R}^7 \). Also, as mentioned above, when at least one of \( V \) and \( W \) is \(-\text{O}-\), \(-\text{NH}-\) or \(-\text{N}(\text{R}^8)\), \( X \) is a bond.

The invention includes compounds in which the ring shown in Formula (I) is a 5-membered ring, e.g. compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Of particular mention are compounds of the formula (II) and pharmaceutically acceptable salts or prodrugs thereof.

The invention also includes compounds in which the ring shown in Formula (I) is a 6-membered ring, e.g. compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

The invention also includes compounds in which the ring shown in Formula (I) is a 7- or 8-membered ring, e.g. compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Of particular mention are compounds of the Formula (VII) and pharmaceutically acceptable salts or prodrugs thereof.

In other embodiments, -NH- ring moieties shown in the above Formulae are replaced by -N(R^8)-, wherein R^8 is other than hydrogen.

**R^3 & R^4**

R^3 and R^4 are each independently hydrogen or R^{10}; or R^3 and R^4 taken together with the carbon atom to which they are attached form carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^{10}.

In one embodiment, R^3 and R^4 are each independently hydrogen; C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1, C_2, C_3 or C_4 alkoxy, for example methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In another embodiment, R^3 is hydrogen; C_1, C_2, C_3 or C_4 alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C_1.
C₂, C₃ or C₄ alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms; and R⁴ is typically hydrogen.

In a further embodiment, R₃ is hydrogen or C₁₋₆ alkyl; and R⁴ is hydrogen.

In a further embodiment, R₃ is hydrogen or methyl; and R⁴ is hydrogen.

In a further embodiment, R₃ and R⁴ taken together with the carbon atom to which they are attached form cycloalkyl or heterocycloalkyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. Examples of heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. The or each R¹⁰ may be, for example, hydroxy, halogen (for example, chlorine or fluorine); C₁, C₂, C₃ or C₄ alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C₁, C₂, C₃ or C₄ alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In a further embodiment, R₃ and R⁴ are each hydrogen. The invention therefore includes compounds of the following Formula:

\[ \text{Formula XVI} \]

or a pharmaceutically acceptable salt or prodrug thereof.

\[ -X-R^5 \]
X is a bond or a linker having 1 to 5 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)\textsubscript{r}- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}; wherein R\textsuperscript{8} is selected from R\textsuperscript{9}, -OR\textsuperscript{9}, -C(O)R\textsuperscript{9}, -C(O)OR\textsuperscript{9} and -S(O)\textsubscript{r}R\textsuperscript{8}; and wherein R\textsuperscript{9} is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}; and -(CH\textsubscript{2})\textsuperscript{k}-heterocycl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. R\textsuperscript{8} is often hydrogen or C\textsubscript{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. Also, when at least one of V and W is -O-, -NH- or -N(R\textsuperscript{8})\textsubscript{s}, X is a bond.

In one embodiment, X is selected from the following linkers:

- X\textsuperscript{1};
- X\textsuperscript{1}X\textsuperscript{2};
- X\textsuperscript{1}X\textsuperscript{2}X\textsuperscript{3};
- X\textsuperscript{1}X\textsuperscript{2}X\textsuperscript{3}X\textsuperscript{4}; and
- X\textsuperscript{1}X\textsuperscript{2}X\textsuperscript{3}X\textsuperscript{4}X\textsuperscript{5};

wherein X\textsuperscript{1}, X\textsuperscript{2}, X\textsuperscript{3}, X\textsuperscript{4} and X\textsuperscript{5} are each independently selected from -O-, -C(O)-, -S(O)\textsubscript{r}, -N(R\textsuperscript{8})- and hydrocarbylene (e.g. C\textsubscript{1-5} alkylene) optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. More usually, X is -X\textsuperscript{1} or -X\textsuperscript{1}X\textsuperscript{2}.

In another embodiment, X is a bond or a linker comprising 1, 2 or 3 linkages selected from selected from -O-, -C(O)-, -S(O)\textsubscript{r}-N(R\textsuperscript{8})- and -CH\textsubscript{2}-. The linker typically comprises 1, 2 or 3 in-chain atoms. Thus, X may be selected from a bond, -O-, -C(O)-, -S(O)\textsubscript{r}-N(R\textsuperscript{8})-, -CH\textsubscript{2}-, -CH\textsubscript{2}CH\textsubscript{2}-, -OCH\textsubscript{2}-, -OCH\textsubscript{2}CH\textsubscript{2}-, -CH\textsubscript{2}O-, -CH\textsubscript{2}CH\textsubscript{2}O- and -CH\textsubscript{2}OCH\textsubscript{2}-. In certain compounds, X is selected from a bond, -CH\textsubscript{2} and -O-.

R\textsuperscript{5} is selected from hydrogen, except when X is a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}; and -(CH\textsubscript{2})\textsuperscript{k}-heterocycl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}.

In one embodiment, R\textsuperscript{5} is hydrogen and X is other than a bond.

In another embodiment, R\textsuperscript{5} is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. In this case, R\textsuperscript{5} is often selected from C\textsubscript{1-6} alkyl (e.g. C\textsubscript{1}, C\textsubscript{2}, C\textsubscript{3} or C\textsubscript{4} alkyl) or -(CH\textsubscript{2})\textsuperscript{k}-carbocycl (e.g. -(CH\textsubscript{2})\textsuperscript{k}-cycloalkyl or -(CH\textsubscript{2})\textsuperscript{k}-aryl), either of which is optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. In particular, R\textsuperscript{5} may be C\textsubscript{1-6} alkyl (e.g. C\textsubscript{1}, C\textsubscript{2}, C\textsubscript{3} or C\textsubscript{4} alkyl),
-(CH$_2$)$_k$-cycloalkyl (e.g. cyclopropyl or cyclopropylmethyl) or -(CH$_2$)$_k$-aryl (e.g. phenyl or benzyl), any of which is optionally substituted with 1, 2, 3, 4 or 5 R$^5$.

In a further embodiment, R$^5$ is -(CH$_2$)$_k$-heterocycl optionally substituted with 1, 2, 3, 4 or 5 R$^5$. Typically, k is 0 or 1, more usually 0. The heterocycl group may be heterocycloalkyl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$^5$. The heterocycl group may be monocyclic or bicyclic, usually monocyclic. Exemplary heterocycl groups include oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuranyl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxadiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, especially thiomorpholinolo, indolizinyl, isoindolyl, 3H-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinolinizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranl, benzo-thiophenyl, dibenzo-thiophenyl, phthalazinyl, naphthridinyl, quinoxalyl, quinazolinyl, quinoxalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoazinyl, chromenyl, isochromanly and chromanly, any of which is optionally substituted with 1, 2, 3, 4 or 5 R$^5$.

In a further embodiment, R$^5$ is carbocycl or heterocycl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$^5$.

In a further embodiment, R$^5$ is aryl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$^5$.

In a further embodiment, R$^5$ is aryl, in particular phenyl or naphthyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$^5$. In embodiments, R$^5$ is phenyl optionally substituted with 1, 2, 3, 4 or 5 R$^5$, wherein the or each R$^{10}$ is, for example, hydroxy, halogen (for example, chlorine or fluorine); C$_1$, C$_2$, C$_3$ or C$_4$ alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C$_1$, C$_2$, C$_3$ or C$_4$ alkoxy, for example methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. For
example, R⁵ may be phenyl optionally substituted with 1, 2, 3, 4 or 5 halogen (e.g. fluorine or chlorine) atoms.

In a further embodiment, R⁵ is heteroaryl (often monocyclic), for example, thienyl or benzothiophenyl, and is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰, wherein the or each R¹⁰ is, for example, hydroxy, halogen (for example, chlorine or fluorine); C₁, C₂, C₃ or C₄ alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C₁, C₂, C₃ or C₄ alkoxy, for example methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In further embodiment, X is a bond or a linker comprising 1, 2 or 3 linkages selected from selected from -O-, -C(O)-, -S(O),- and -N(R⁸)- and -CH₂-; and R⁵ is selected from C₁₆ alkyl, cycloalkyl, aryl (e.g. phenyl) and heterocyclyl (e.g. pyridinyl or pyrrolidinone, in particular pyrrolidin-2-one), any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. In particular, X may be selected from a bond, -CH₂- and -O-.

The invention includes a compound of the following Formula:

![Chemical Structure](image)

wherein p is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.
With regard to Formula (XVIII), X is often a bond or a linker comprising 1, 2 or 3 linkages selected from -O-, -C(O)-, -S(O)R, -N(R$_8$) and -CH$_2$-.

For example, X may be selected from a bond, -CH$_2$- and -O-.

In particular, the invention includes compounds of the following Formula:

![Chemical structure](image)

or a pharmaceutically acceptable salt or prodrug thereof.

Also of mention are compounds of the following Formula:

![Chemical structure](image)

or a pharmaceutically acceptable salt or prodrug thereof.

In embodiments of the above formulae, when p is 1, 2, 3, 4 or 5, at least one R$_{10}$ is halogen or C$_{1-6}$ alkyl. In particular embodiments, the or each R$_{10}$ is independently halogen or C$_{1-6}$ alkyl.

In other embodiments, when p is 1, 2, 3, 4 or 5, at least one R$_{10}$ is halogen. In particular embodiments, the or each R$_{10}$ is halogen.
In further embodiments, when \( p \) is 1, 2, 3, 4 or 5, at least one \( R_{10} \) is fluorine or chlorine. In particular embodiments, the or each \( R_{10} \) is independently fluorine or chlorine. Of particular mention are compounds in which \(-X-R^{5}\) is 2-chlorophenyl.

In further embodiments, \( p \) is 0, 1, 2 or 3. In particular embodiments, \( p \) is 0, 1 or 2.

\( Y \)

\( Y \) is a bond; or \( Y \) and an \( R^{7} \) moiety taken together with the atom(s) to which they are attached form a carbocycle or a heterocycle, either of which is optionally substituted with 1, 2, 3, 4 or 5 \( R_{10} \), and may be saturated or unsaturated.

In one embodiment, \( Y \) is a bond. The invention therefore includes compounds of the following Formula:

![Formula](image)

or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment, \( Y \) and an \( R^{7} \) moiety are attached to adjacent ring carbon atoms and taken together with those atoms form a carbocycle or a heterocycle, either of which is optionally substituted with 1, 2, 3, 4 or 5 \( R_{10} \).

The invention therefore includes compounds of the following Formula:
wherein

A, D and G are each independently selected from -C(O)-, -(CH₂)ₙ-, =CH-, -NH-, =N-, -O-, and -S(O),-;

E is selected from a bond, -C(O)-, -(CH₂)ₙ-, =CH-, -NH-, =N-, -O-, and -S(O),-;

m’ is 0, 1, 2, 3, 4 or 5;

q is 0, 1, 2, 3, 4 or 5; and

— represents an optional second bond;

or a pharmaceutically acceptable salt or prodrug thereof.

It will be appreciated that any -CH₂-, =CH- or -NH- group present may be unsubstituted or substituted with one or more substituents selected from -Z-R⁶ (when other than hydrogen) and R¹⁰ moieties.

In certain compounds, A is selected from -C(O)-, -O-, -S- and -CH₂--; D and G are each independently selected from -CH₂-, =CH-, -NH- and =N--; and E is selected from a bond, -CH₂- and CH.

The invention includes compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment, Y and an R⁷ moiety are attached to the same carbon atom and taken together with that atom form a carbocycle or a heterocycle, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰, and may be saturated or unsaturated.

The invention therefore includes compounds of the following Formula:

![Formula XXX]

wherein

J, M, T and U are each independently selected from -C(O)-, -(CH₂)ₙ-, -NH-, -O- and -S(O)₁⁻;

Q is selected from a bond, -C(O)-, -(CH₂)ₙ-, -O-, -NH- and -S(O)₁⁻;

m' is Q, 1, 2, 3, 4 or 5; and

t is o, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.
It will be appreciated that any -CH\textsubscript{2}- or -NH- group present may be unsubstituted or substituted with one or more substituents selected from -Z-R\textsuperscript{6} (when other than hydrogen) and R\textsuperscript{10} moieties.

In certain compounds, J, M, T and U are each independently selected from -CH\textsubscript{2}- and -NH-; and Q is selected from a bond, -CH\textsubscript{2}- and -NH-.

The invention also includes compounds of the following Formulae:

or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

-Z-R\textsuperscript{6}

Z is a bond or a linker having 1 to 12 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)
\textsubscript{n}, -N(R\textsuperscript{8})-, hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}; wherein R\textsuperscript{8} is selected from R\textsuperscript{9}, -OR\textsuperscript{9}, -C(O)R\textsuperscript{9}, -C(O)OR\textsuperscript{9} and -S(O)R\textsuperscript{9}; and wherein R\textsuperscript{9} is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}; and -(CH\textsubscript{2})\textsubscript{k}-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}.

In one embodiment, Z is a bond or is selected from the following linkers:

- Z\textsuperscript{1};
- Z\textsuperscript{1}-Z\textsuperscript{2};
wherein Z₁, Z², Z³, Z⁴, Z⁵, Z⁶, Z⁷ and Z⁸ are each independently selected from -O-, -C(O)-, -S(O)ᵢ-, -N(R₈)ᵢ-, hydrocarbylene (e.g. C₈₋₆ alkylene or C₂₋₆ alkenylene) optionally substituted with 1, 2, 3, 4 or 5 R¹. and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R¹. More usually, Z is -Z₁⁻, -Z¹⁻Z²⁻ or -Z¹⁻Z²⁻Z³⁻. Z¹ is often -N(R₈)ᵢ-, -C(O), -O- or heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R¹.

In another embodiment, Z is a bond or a linker comprising 1, 2, 3 or 4 linkages selected from selected from -O-, -C(O)-, -S(O)ᵢ-, -N(R₈)ᵢ-, -CH₂⁻ and -CH=CH⁻. The linker typically comprises 1, 2 or 3 in-chain atoms. Thus, Z may be selected from -O-, -C(O)-, -S(O)ᵢ-, -N(R₈)ᵢ-, -CH₂⁻, -N(R₈)C(O)-, -N(R₈)S(O)ᵢ-, -C(O)N(R₈)ᵢ-, -S(O)ᵢN(R₈)ᵢ-, -N(R₈)S(O)ᵢN(R₈)ᵢ-, -CH₂CH₂⁻, -CH₂O⁻, -CH₂CH=CH⁻ and -OCH₂CH=CH⁻. R₈ is often hydrogen or C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4 or 5 R¹.

In a further embodiment, Z comprises at least one moiety selected from -N(R₈)ᵢ-, -C(O)- and -S(O)ᵢ-. Of mention are compounds comprising two or more of said moieties.

In a further embodiment, Z comprises at least one carbocyclylene or heterocyclylene moiety, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹. Of mention are compounds in which Z comprises at least one heterocyclylene moiety. In certain compounds, -Z-R⁶ is attached to the remainder of the compound via said carbocyclylene or heterocyclylene moiety.

In a further embodiment, Z is attached to the ring shown in formula (I) via a nitrogen atom. Thus, included in the invention are compounds in which Z is attached to said ring via an -N(R₈)ᵢ- moiety or via a nitrogen atom present in a heterocyclic moiety.
In a further embodiment, Z comprises an \(-\text{N}(\text{R}^8)\text{C}(\text{O})-\) moiety. In certain compounds, the group \(-Z-R^6\) is attached to the remainder of the compound via the nitrogen atom of said moiety.

In a further embodiment, Z is a linker selected from \(-\text{N}(\text{R}^8)\), \(-\text{N}(\text{R}^8)\text{C}(\text{O})-\), \(-\text{N}(\text{R}^8)\text{-C}_{1-6}\) alkylene- and \(-\text{N}(\text{R}^8)\text{C}(\text{O})\text{-C}_{1-6}\) alkylene-, wherein \(-Z-R^6\) is attached to the remainder of the compound via the nitrogen atom of said linker and wherein any \text{C}_{1-6} \) alkylene group is optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\). Typically, \text{R}^8 \) is selected from hydrogen, hydrocarbyl optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\) and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\). By way of example, \text{R}^8 \) may be selected from hydrogen, \text{C}_{1-6} \) alkyl (e.g. \text{C}_1, \text{C}_2, \text{C}_3 \) or \text{C}_4 \) alkyl) optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\); \(-(\text{CH}_2)_k\)-carbocyclyl (e.g. cyclopropyl, cyclopropylmethyl or benzyl) optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\), and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\).

In a further embodiment, Z is \(-\text{N}(\text{R}^8)\text{JC}(\text{O})-\), wherein \(-Z-R^6\) is attached to the remainder of the compound via the nitrogen atom of said linker. Typically, \text{R}^8 \) is selected from hydrogen, hydrocarbyl optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\); and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\). By way of example, \text{R}^8 \) may be selected from hydrogen, \text{C}_{1-6} \) alkyl (e.g. \text{C}_1, \text{C}_2, \text{C}_3 \) or \text{C}_4 \) alkyl) optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\); \(-(\text{CH}_2)_k\)-carbocyclyl (e.g. cyclopropyl, cyclopropylmethyl or benzyl) optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\), and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\).

In a further embodiment, Z is carbocyclylene or heterocyclylene, either of which is optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\). In a further embodiment, Z is heterocyclylene optionally substituted with \(1, 2, 3, 4\) or \(5 \text{ R}^{10}\). Of mention are compounds in which the heterocyclylene group comprises one or more (e.g. \(1, 2, 3\) or \(4\)) ring nitrogen atoms and optionally one or more ring \(-\text{C}(\text{O})\)- moieties.

In a further embodiment, Z comprises (e.g. is) a moiety selected from piperidinylene; pyrrolidin-2-onyl[1,3]oxazinan-2-onylene; tetrahydro-pyrimidin-2-onylene; 5,6,7,8-tetrahydro-naphthalenylene; piperazine-2,5-dionylene; isoindole-1,3-dionylene; 1,4-dihydro-2H-isooquinolin-3-onylene; 2,3-dihydro-isoindol-2-onylene; 3,4-dihydro-2H-isoquinolin-1 -onylene; 2H-pyridazin-3-onyiene; oxazoidin-2-onyiene; imidazolidin-2-onylene; hexahydro-pyrido[1,2-
a)pyrazine-1,4-dionylene; hexahydro-pyrrolo-[1,2-a]pyrazin-1,4-dionylene; 5,6,7,8-tetrahydro-
pyrido[4,3-d]pyrimidinylene; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene; 5,6-dihydro-
8H-[1,2,4]triazolo[1,5-a]pyrazinylene; 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylene;
6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazin-8-onylene; 6-yl-dihydro-8H-pyrido[3,4-d]pyrimidin-
oneylene; 6,7-dihydro-4H-oxazolido[5,4-c]pyrimidinylene; 7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-
oneylene; 6H-pyrido[4,3-d]pyrimidin-5-onylene; 5,8-dihydro-6H-pyrido[3,4-d]pyrimidinylene;
7,8-dihydro-[1,2,4]triazolo[4,3-c]pyrimidinylene; and 7,8-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-
oneylene; any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

In a further embodiment, Z comprises (e.g. is) a moiety selected from 2H-pyridazin-3-
onylene; oxazolidin-2-onylene; imidazolidin-2-onylene; 3,4-dihydro-5H-[1,2,4]triazolo[4,3-a]
pyrazinylene; and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylene; any of which is
optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

In a further embodiment, Z comprises (e.g. is) a moiety selected from imidazolidin-2-onylene
and pyridazin-3-onylene, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

R⁶ is selected from hydrogen, except when Y and Z are each a bond; hydrocarbyl optionally
substituted with 1, 2, 3, 4 or 5 R¹⁰; and -(CH₂)ₖ-heterocyclyl optionally substituted with 1, 2,
3, 4 or 5 R¹⁰.

In one embodiment, R⁶ is hydrogen.

In another embodiment, R⁶ is hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. In
this case, R⁶ is often selected from Cᵢ₋₆ alkyl (e.g. Ci, C₂, C₃ or C₄ alkyl) or -(CH₂)ₖ-
carbocyclyl (e.g. -(CH₂)ₖ-cycloalkyl or -(CH₂)ₖ-aryl), either of which is optionally substituted
with 1, 2, 3, 4 or 5 R¹⁰. In particular, R⁶ may be Cᵢ₋₆ alkyl (e.g. C₁, C₂, C₃ or C₄ alkyl),
-(CH₂)ₖ-cycloalkyl (e.g. cyclopropyl or cyclopropylmethyl) or -(CH₂)ₖ-aryl (e.g. phenyl or
benzyl), any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

In a further embodiment, R⁶ is -(CH₂)ₖ-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5
R¹⁰. Typically, k is 0 or 1, more usually 0. The heterocyclyl group may be heterocycloalkyl
or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. The
heterocyclyl group may be monocyclic or bicyclic, usually monocyclic. Exemplary
heterocyclyl groups include oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thiényl, furýl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolínyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazínyl, pyrazolíndinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazalyl, isoxazolyl, pyridyl, pyrazínyl, pyrimidínyl, piperidyl, piperazínyl, pyridazínyl, motpholinyl, thiomorpholinyl, especially thiomorpholíno, indolínyl, isoindolyl, 3H-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purínyl, 4H-quinolízinyl, isoquinolínol, quinolýl; tetrahydroquinolínol, tetrahydroisoquinolínol, decahydroquinolínol, octahydroisoquinolínol, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazínyl, naphthrydínol, quinoxalínol, quinaldínol, cinnolínol, pteridínol, carbazolyl, β-carbolínol, phenanthridínol, acridínol, perímidínol, phenanthrolínol, furazányl, phenazínyl, phenothiazínol, phenoazínol, chromenyl, isochromanyl and chromanyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

In a further embodiment, R⁶ is 5,6-dihydro-8H-[1,2,4]triazololo[4,3-a]pyrazín-7-yl, which may be substituted at the 3- position by, for example, trifluoromethyl.

In a further embodiment, R⁶ is carbocyclýl or heterocyclýl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

In a further embodiment, R⁶ is aryl or heteroaryl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

In a further embodiment, R⁶ is aryl, in particular phenyl or naphthyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹⁰. In embodiments, R⁶ is phenyl optionally substituted with 1, 2, 3, 4 or 5 R¹⁰, wherein the or each R¹⁰ is, for example, hydroxy, halogen (for example, chlorine or fluorine); C₁, C₂, C₃ or C₄ alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C₁₋₃, C₂₃ or C₄ alkoxy, for example methoxy, ethoxy, propoxy, isoproxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms. For example, R⁶ may be phenyl optionally substituted with 1, 2, 3, 4 or 5 halogen (e.g. fluorine) atoms.
In a further embodiment, R$^6$ is heteroaryl (often monocyclic), for example, thienyl or benzothiophenyl, and is optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$, wherein the or each R$^{10}$ is, for example, hydroxy, halogen (for example, chlorine or fluorine); C$_1$, C$_2$, C$_3$ or C$_4$ alkyl, for example methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms, an example being trifluoromethyl; or C$_1$, C$_2$, C$_3$ or C$_4$ alkoxy, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, any of which is optionally substituted with 1, 2, 3 or 4 halogen (e.g. fluorine or chlorine) atoms.

In further embodiment, Z is a bond or a linker comprising 1, 2, 3 or 4 linkages selected from selected from -O-, -C(O)-, -S(O)$_2$-, -N(R$^8$)$_2$-, -CH$_2$- and -CH=CH$_2$-; and R$^6$ is hydrogen or is selected from C$_{1-6}$ alkyl, cycloalkyl, aryl (e.g. phenyl) and heterocyclyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$.

In a further embodiment, Z is selected from -O-, -O-C$_{1-6}$ alkenylene- and -O-C$_{1-6}$ alkenylene-; and R$^6$ is hydrogen or is selected from C$_{1-6}$ alkyl, cycloalkyl, aryl (e.g. phenyl) and heterocyclyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$.

In a further embodiment, -Z-R$^6$ is selected from R$^{14}$, -OR$^{14}$, -C(O)R$^{14}$, -C(O)OR$^{14}$, -C(O)N(R$^{15}$)R$^{16}$, -N(R$^{15}$)R$^{16}$, -N(R$^{15}$)C(O)R$^{14}$, -N(R$^{15}$)S(O),R$^{15}$, -S(O)$_2$R$^{15}$ and -S(O)$_2$N(R$^{15}$)R$^{16}$; wherein R$^{14}$ is hydrogen or is selected from hydrocarbyl and -(CH$_2$)$_k$-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$; and wherein R$^{15}$ and R$^{16}$ are each independently selected from R$^{9}$, -OR$^9$, -C(O)R$^9$, -C(O)OR$^9$ and -S(O)$_2$R$^{9}$; or R$^{15}$ and R$^{16}$ taken together with a nitrogen atom to which they are attached form heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$.

In a further embodiment, R$^{14}$, R$^{15}$ and R$^{16}$ are each independently selected from hydrogen; C$_{1-6}$ (e.g. C$_1$, C$_2$, C$_3$ or C$_4$) alkyl optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$; and -(CH$_2$)$_k$-aryl (e.g. phenyl or benzyl) optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$.

In a further embodiment, -Z-R$^6$ is hydroxy or aliphatic hydrocarbyloxy (e.g. C$_{1-6}$ alkoxy or C$_{2-6}$ alkenyloxy). In a particular embodiment, Z is -OCH$_2$CH=CH$_2$- and R$^6$ is a 5- to 10- (e.g. 5- or 6-) membered saturated or unsaturated cyclic group, in particular aryl (e.g. phenyl or napthyl), which is optionally substituted with 1, 2, 3, 4 or 5 R$^{10}$. 
In a further embodiment, -Z-R^6 comprises at least one carbocyclic or heterocyclic moiety, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10. In particular embodiments, -Z-R^6 comprises at least two such moieties, which may be the same or different. By way of example, the or each moiety may be independently selected from cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), aryl (e.g. phenyl or naphthyl) and heterocyclyl (e.g. [1,2,4]triazolo[4,3-a]pyrazinyl, piperidinyl, piprazinyl, pyrrolidinyl, furyl, pyrimidinyl, pyrazinyl, benzimidazolyl, 3,4-dihydroisoquinolinyl, azepanyl, diazepanyl, triazolyl, morpholinyl, pyrazolyl, pyradizinyl, benzofuryl, pyridinyl, isoxazolyl, thiadiazolyl, thiophenyl, imidazo[2,1-b][1,3]thiazolyl, 3,4,6,7-tetrahydro-5H-imida[4,5-c]pyridin-5-yl), any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

In a further embodiment, Z is a bond and R^6 is carbocyclic or heterocyclic, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10. In a particular embodiment, Z is a bond and R^6 is heterocyclc optionally substituted with 1, 2, 3, 4 or 5 R^10. Of mention are compounds in which R^6 comprises one or more (e.g. 1, 2, 3 or 4) ring nitrogen atoms and optionally one or more ring -C(=O)- moieties. In certain compounds, R^6 is attached to the remainder of the compound via a ring nitrogen atom.

In a further embodiment, Z is a bond and R^6 is selected from piperidinyl; pyrrolidin-2-onyl[1,3]oxazinan-2-ony1; tetrahydro-pyrimidin-2-ony1; 5,6,7,8-tetrahydro-naphthalenyl; piperazine-2,5-diony1; isoinodole-1,3-diony1; 1,4-dihydro-2H-isoquinolin-3-ony1; 2,3-dihydro-isooindol-2-ony1; 3,4-dihydro-2H-isooquinolin-1 -ony1; 2H-pyridazin-3-ony1; oxazolidin-2-ony1; imidazolidin-2-ony1; hexahydro-pyrido[1,2-a]pyrazine-1,4-diony1; hexahydro-pyrrolo-[1,2-a]pyrazin-1,4-diony1; 5,6,7,8-tetrahydro-pyrido [4,5-S]pyrimidinyl; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinyl; 5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazinyl; 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-ony1; 6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazin-8-ony1; 6,7-dihydro-5H-pyrido[3,4-d]pyrimidin-8-ony1; 6,7-dihydro-4H-oxazolo[5,4-c]pyridinyl; 7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-ony1; 6H-pyrido[4,3-d]pyrimidin-5-ony1; 5,8-dihydro-6H-pyrido[3,4-d]pyrimidinyl; 7,8-dihydro-[1,2,4]triazolo[4,3-c]pyrimidinyl; and 7,8-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-6-ony1; any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.
In a further embodiment, Z is a bond and R\(^6\) is selected from 2H-pyridazin-3-onyl; oxazolidin-2-onyl; imidazolidin-2-onyl; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinyl; and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onyl; any of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\).

In a further embodiment, Z is a bond and R\(^6\) is imidazolidin-2-onyl or pyrazin-3-onyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\).

In a further embodiment, Z is a linker selected from \(-N(R^8)\)-, \(-N(R^8)C(O)\)-, \(-N(R^8)C(O)\)-alkylene- and \(-N(R^8)C(O)\)-alkylene-, wherein \(-Z-R^6\) is attached to the remainder of the compound via the nitrogen atom of said linker and wherein any C\(_{1-6}\) alkylene group is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\); and R\(^6\) is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\). Of mention are compounds in which R\(^6\) is aryl (e.g. phenyl) or heterocyclyl (e.g. pyridinyl, benzimidazolyl, benzotriazolyl, indazolyl, pyridazinyl or pyrimidinyl), either of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\). In particular compounds, R\(^6\) phenyl or pyridinyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\). In other compounds, R\(^6\) is substituted by 1, 2, 3, 4 or 5 R\(^{10}\), at least one of which is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, cyano, amino, hydroxy, C\(_{1-6}\) alkyl and C\(_{1-6}\) alkoxy. By way of example, said at least one R\(^{10}\) may be selected from cycloalkyl (e.g. cyclopropyl), aryl (e.g. phenyl), heterocycloalkyl (e.g. piperidinyl) and heteroaryl (e.g. pyridinyl), any of which is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, cyano, amino, hydroxy, C\(_{1-6}\) alkyl and C\(_{1-6}\) alkoxy.

In a further embodiment, Z is \(-N(R^8)JC(O)\)-, wherein the group \(-Z-R^6\) is attached to the remainder of the compound via the nitrogen atom of said linker; and R\(^6\) is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\).

In a further embodiment, Z and R\(^6\) each independently comprise a carbocyclic or heterocyclic group, and are each optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\). Included are compounds of this type in which Z comprises (e.g. is) a heterocyclylene moiety optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\); and R\(^6\) is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R\(^{10}\). Of mention are compounds in which Z comprises (e.g. is) a moiety selected from 2H-pyridazin-3-onylene, oxazolidin-2-onylene,
imidazolidin-2-onylene, 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene and 6,7-dihydro-5H-
[1,2,4]triazolo[4,3-a]pyrazin-8-onylene, any of which is optionally substituted with 1, 2, 3, 4 or
5 R. Exemplary R6 groups include aryl (e.g. phenyl) and heteroaryl (e.g. pyridyl,
pyrimidinyl, indolyl, quinolinyl, pyrazolyl, triazolyl or thiophenyl) groups, either of which are
optionally substituted with 1, 2, 3, 4 or 5 R.

R7

R7 is present when m is 1, 2, 3, 4, 5 or 6 and may be an R moiety, wherein R is
independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR, -OR,
-C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -N(R)R, -R(R)R, -C(O)NR, -S(O)NR, -N(R)NR
and R; wherein R and R are each independently hydrogen or R; and R is selected
from hydrocarbyl and -(CH2)k-heterocyclyl, either of which is optionally substituted with 1, 2,
3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, Calkyl
and Calkoxy. Alternatively, an R moiety and Y taken together with the atom(s) to which
they are attached may form carbocyclyl or heterocyclyl, either of which is optionally
substituted with 1, 2, 3, 4 or 5 R; or two R moieties taken together may form a bridge
between the atoms to which they are attached, wherein the bridge is a hydrocarbylene or
-(CH2)i-O-(CH2)j - bridge, and wherein i and j are each independently 0, 1 or 2.

R7 may be attached to a ring carbon or nitrogen atom of the ring shown in Formula (I). When
R7 is attached to a ring nitrogen atom, it is usually selected from -C(O)R, -C(O)OR,
-S(O)R, -C(O)N(R)R, -S(O)N(R)R and R.

In one embodiment, R7 is independently selected from hydrogen, halogen (e.g. fluorine,
chlorine or bromine), hydroxy, cyano, amino, -C(O)OH, Calkyl, Calkoxy (e.g. C, C, C
or Calkoxy), -C(O)-Calkyl, -C(O)O-Calkyl, -S(O)alkyl, -NH(Calkyl) and -N(Calkyl),
wherein any Calkyl group present is optionally substituted with 1, 2, 3, 4 or 5
substituents independently selected from halogen, cyano, amino, hydroxy and Calkoxy.

In another embodiment, R7 is independently selected from halogen (e.g. fluorine or chlorine),
cyano, amino, hydroxy, Calkyl (e.g. C, C, C or Calkyl) and Calkoxy (e.g. C, C, C
or Calkoxy), any Calkyl group present is optionally substituted with 1, 2, 3, 4 or 5
substituents independently selected from halogen, cyano, amino, hydroxy and Calkoxy.
In a further embodiment, m is 0, 1 or 2.

In a further embodiment, m is 0 or 1.

In a further embodiment, m is 1.

In a further embodiment, m is 0.

$R^{10}$

Each $R^{10}$ is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, $\text{=NR}^{11}$, $\text{-OR}^{11}$, $\text{-C(O)R}^{11}$, $\text{-C(O)OR}^{11}$, $\text{-OC(O)R}^{11}$, $\text{-N(R}^{11})\text{R}^{12}$, $\text{-C(O)N(R}^{11})\text{R}^{12}$, $\text{-SO}^{1}\text{R}^{13}$ and $\text{R}^{13}$; wherein $R^{11}$ and $R^{12}$ are each independently hydrogen or $R^{13}$; and $R^{13}$ is selected from hydrocarbyl and $-(\text{CH}_2)_k$ heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C$_{1-6}$ alkyl and C$_{1-6}$ alkoxy.

Typically, each $R^{10}$ is independently selected from halogen (e.g. fluorine, chlorine or bromine), hydroxy, cyano, amino, $\text{-C(O)OH}$, C$_{1-6}$ alkyl, C$_{1-6}$ alkoxy (e.g. C$_1$, C$_2$, C$_3$ or C$_4$ alkoxy), $\text{-C(O)-C}_{1-6}$ alkyl, $\text{-C(O)O-C}_{1-6}$ alkyl, $\text{-SO}^{1}\text{C}_{1-6}$ alkyl, $\text{-NH(C}_{1-6}$ alkyl) and $\text{-N(C}_{1-6}$ alkyl)$_2$ wherein any C$_{1-6}$ alkyl group present is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy and C$_{1-6}$ alkoxy.

For the avoidance of doubt, where a group is substituted with more than one $R^{10}$, each $R^{10}$ is independently selected from the range of substituents specified. The same applies to compounds of the invention comprising more than one $R^{10}$ substituent; each $R^{10}$ is selected independently of any other $R^{10}$ substituent present in the compound. As previously indicated, where $R^{10}$ is halo, particularly fluoro, any number of hydrogens may in principle be replaced.
Of mention is a compound of the following Formula:

\[
Y - Z - R^6
\]

\[\text{H}_2\text{N} - (R^7)_m - X - R^5\]

or a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
Y - Z - R^6
\]

\[\text{H}_2\text{N} - (R^7)_m - X - \text{phenyl} - (R^{10})_p\]

wherein \( p \) is as defined elsewhere herein;

or a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:
or a pharmaceutically acceptable salt or prodrug thereof.

Of particular mention is a compound of the following Formula:

\[
\begin{align*}
&\text{H}_2\text{N} \\
&\text{X-} \text{R}^5
\end{align*}
\]

or a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
\begin{align*}
&\text{H}_2\text{N} \\
&\text{X-} \text{R}^{10}_p
\end{align*}
\]

or a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
\begin{align*}
&\text{H}_2\text{N} \\
&\text{X-} \text{R}^{10}_p
\end{align*}
\]
or a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
\begin{array}{c}
\text{R}^6 \text{Z} \\
\text{A} \\
\text{H}_2\text{N} \\
\text{X-}\text{R}^5
\end{array}
\]

\[(\text{XXXL})\]

wherein A, D, E, G and q are as defined elsewhere herein;

or a pharmaceutically acceptable salt or prodrug thereof.

The invention therefore includes compounds of the following Formulae:

\[(\text{XLI})\]  \[(\text{XLII})\]  \[(\text{XLIII})\]
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

wherein \( p \) is as defined elsewhere herein;

or a pharmaceutically acceptable salt or prodrug thereof.

The invention therefore includes compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:
or a pharmaceutically acceptable salt or prodrug thereof.

The invention therefore includes compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
\begin{align*}
\text{R}^6 - \text{Z} & \text{J} \\
\text{H}_2\text{N} & \text{X} - \text{R}^5 \\
\end{align*}
\]

(LXI)

wherein J, M, Q, T, U and t are as defined elsewhere herein;

or a pharmaceutically acceptable salt or prodrug thereof.

The invention therefore includes compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
\begin{align*}
R^6 & \quad Z & \quad M & \quad Q & \quad T & \quad (R^{10})_t \\
& \quad J & \quad U \quad & \quad & \quad & \\
& \quad H_2N & \quad X & \quad (R^{10})_p \\
\end{align*}
\]

wherein \( p \) is as defined elsewhere herein;

or a pharmaceutically acceptable salt or prodrug thereof.

The invention therefore includes compounds of the following Formulae:
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

Also of mention is a compound of the following Formula:

\[
\begin{align*}
R^6 &- Z - J - T(R^{10})_t \\
&\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ Quad
or, in each case, a pharmaceutically acceptable salt or prodrug thereof.

With regard to Formulae (XXXI) to (LXX), Z may be a bond or a linker comprising 1 to 12 in-chain atoms. For example, Z may comprise 1, 2, 3 or 4 linkages selected from selected from -O-, -C(O)-, -S(O)ₙₙ, -N(R₈)-, -CH₂- and -CH=CH-; and R₆ may be hydrogen or selected from Cₙ₋₆ alkyl, cycloalkyl, aryl (e.g. phenyl) and heterocycl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹₀.

In further embodiments of said formulae, Z is selected from -O-, -O-C₁₋₆ alkylenes- and -O-C₁₋₆ alkenylene-; and R₆ is hydrogen or is selected from C₁₋₆ alkyl, cycloalkyl, aryl (e.g. phenyl) and heterocycl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R¹₀.

In further embodiments, Z comprises at least one moiety selected from -N(R₈)-, -C(O)- and -S(O)₂. Of mention are compounds comprising two or more of said moieties.

In further embodiments, Z comprises at least one carbocyclene or heterocyclylene moiety, either of which is optionally substituted with 1, 2, 3, 4 or 5 R¹₀. Of mention are compounds in which Z comprises at least one heterocyclylene moiety. In certain compounds, -Z-R₆ is attached to the remainder of the compound via said carbocyclene or heterocyclylene moiety.
In further embodiments, Z is attached to the ring shown in formula (I) via a nitrogen atom. Thus, included in the invention are compounds in which Z is attached to said ring via an \(-\text{N}(\text{R}^8)\)- moiety or via a nitrogen atom present in a heterocyclic moiety.

In further embodiments, Z comprises an \(-\text{N}(\text{R}^8)\text{C(O)}-\) moiety. In certain compounds, the group \(-\text{Z-R}^6\) is attached to the remainder of the compound via the nitrogen atom of said moiety.

In further embodiments, Z is a linker selected from \(-\text{N}(\text{R}^8)-\), \(-\text{N}(\text{R}^8)\text{C(O)}-\), \(-\text{N}(\text{R}^8)\text{C}_{1,6}\) alkylene- and \(-\text{N}(\text{R}^8)\text{C(O)}-\text{C}_{1,6}\) alkylene-, wherein \(-\text{Z-R}^6\) is attached to the remainder of the compound via the nitrogen atom of said linker and wherein any \(\text{C}_{1,6}\) alkylene group is optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\). Typically, \(\text{R}^8\) is selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\), and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\). By way of example, \(\text{R}^8\) may be selected from hydrogen, \(\text{C}_{1,6}\) alkyl (e.g. \(\text{C}_1, \text{C}_2, \text{C}_3\) or \(\text{C}_4\) alkyl) optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\), \(-(\text{CH}_2)_k\)-carbocyclcyl (e.g. cyclopropyl, cyclopropymethyl or benzyl) optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\), and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\).

In further embodiments, Z is \(-\text{N}(\text{R}^8)\text{C(O)}-\), wherein \(-\text{Z-R}^6\) is attached to the remainder of the compound via the nitrogen atom of said linker. Typically, \(\text{R}^8\) is selected from hydrogen, hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\); and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\). By way of example, \(\text{R}^8\) may be selected from hydrogen, \(\text{C}_{1,6}\) alkyl (e.g. \(\text{C}_1, \text{C}_2, \text{C}_3\) or \(\text{C}_4\) alkyl) optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\), \(-(\text{CH}_2)_k\)-carbocyclcyl (e.g. cyclopropyl, cyclopropymethyl or benzyl) optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\), and \(-(\text{CH}_2)_k\)-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\).

In further embodiments, Z is carbocyclcylene or heterocyclcylene, either of which is optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\).

In further embodiments, Z is heterocyclcylene optionally substituted with 1, 2, 3, 4 or 5 \(\text{R}^{10}\). Of mention are compounds in which the heterocyclcylene group comprises one or more (e.g. 1, 2, 3 or 4) ring nitrogen atoms and optionally one or more ring -\text{C(O)}- moieties.
In further embodiments, Z comprises (e.g. is) a moiety selected from piperidinylene; pyrrolidin-2-onyl[1,3]oxazinan-2-onylene; tetrahydro-pyrimidin-2-onylene; 5,6,7,8-tetrahydro-naphthalenylene; piperazine-2,5-dionylene; isoindole-1,3-dionylene; 1,4-dihydro-2H-isoquinolin-3-onylene; 2,3-dihydro-isoindol-2-onylene; 3,4-dihydro-2H-isoquinolin-1-onylene; 2H-pyridazin-3-onylene; oxazolidin-2-onylene; hexahydro-pyrido[1,2-a]pyrazine-1,4-dionylene; hexahydro-pyrrolo-[1,2-a]pyrazin-1,4-dionylene; 5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidinylen; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene; 5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazinylene; 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylene; 6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazin-8-onylene; 6,7-dihydro-5H-pyrido[3,4-d]pyrimidinylen; 6,7-dihydro-4H-oxazolo[5,4-c]pyridinylen; 7,8-dihydro-6H-pyrido[4,3-d]pyrimidinylen; 6H-pyrido[4,3-d]pyrimidin-5-onylen; 5,8-dihydro-6H-pyrido[3,4-d]pyrimidinylen; 7,8-dihydro-[1,2,4]triazolo[4,3-c]pyrimidinylen; and 7,8-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-6-onylen; any of which is optionally substituted with 1, 2, 3, 4 or 5 R10.

In further embodiments, Z comprises (e.g. is) a moiety selected from 2H-pyridazin-3-onylen; oxazolidin-2-onylen; imidazolidin-2-onylen; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylen; any of which is optionally substituted with 1, 2, 3, 4 or 5 R10.

In further embodiments, Z comprises (e.g. is) a moiety selected from imidazolidin-2-onylen and pyridazin-3-onylen, either of which is optionally substituted with 1, 2, 3, 4 or 5 R10.

In further embodiments, -Z-R6 is selected from R14, -OR14, -C(O)R14, -C(O)OR14, -C(O)N(R15)R16, -N(R15)R16, -N(R15)C(O)R14, -N(R15)SO2R14, -SO2(R15)R16 and -SO2(R15)N(R15)R16; wherein R14 is hydrogen or is selected from hydrocarbyl and -(CH2)n-heterocycl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R10; and wherein R15 and R16 are each independently selected from R9, -OR9, -C(O)R9, -C(O)OR9 and -SO2R9; or R15 and R16 taken together with a nitrogen atom to which they are attached form heterocycl optionally substituted with 1, 2, 3, 4 or 5 R10.

In further embodiments, R14, R15 and R16 are each independently selected from hydrogen; C1-6 (e.g. C1, C2, C3 or C4) alkyl optionally substituted with 1, 2, 3, 4 or 5 R10; and -(CH2)n-aryl (e.g. phenyl or benzyl) optionally substituted with 1, 2, 3, 4 or 5 R10.
In further embodiments, -Z-R^6 is hydroxy or aliphatic hydrocarbyloxy (e.g. C_{1-6} alkoxy or C_{2-6} alkenyloxy). In a particular embodiment, Z is -OCH_2CH=CH- and R^6 is a 3- to 10- (e.g. 5- or 6-) membered saturated or unsaturated cyclic group, in particular aryl (e.g. phenyl or naphthyl), which is optionally substituted with 1, 2, 3, 4 or 5 R^{10}.

In further embodiments, -Z-R^6 comprises at least one carbocyclic or heterocyclic moiety, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^{10}. In particular embodiments, -Z-R^6 comprises at least two such moieties, which may be the same or different. By way of example, the or each moiety may be independently selected from cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), aryl (e.g. phenyl or naphthyl) and heterocyclyl (e.g. [1,2,4]triazolo[4,3-a]pyrazinyl, piperedinyl, pyrrolidinyl, furyl, pyrimidinyl, pyrazinyl, benzimidazolyl, 3,4-dihydroisoquinolinyl, azepanly, diazepanly, triazolyl, morpholinyl, pyrazolyl, pyradinyl, benzofuryl, pyridinyl, isoxazolyl, thiadiazolyl, thiophenyl, imidazo[2,1-b][1,3]thiazolyl, 3,4,6,7-tetrahydro-5H-imida[4,5-c]pyridin-5-yl), any of which is optionally substituted with 1, 2, 3, 4 or 5 R^{10}.

In further embodiments, Z is a bond and R^6 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^{10}. In a particular embodiment, Z is a bond and R^6 is heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{10}. Of mention are compounds in which R^6 comprises one or more (e.g. 1, 2, 3 or 4) ring nitrogen atoms and optionally one or more ring -C(O)- moieties. In certain compounds, R^6 is attached to the remainder of the compound via a ring nitrogen atom.

In further embodiments, Z is a bond and R^6 is selected from piperidinyl; pyrrolidin-2-onyl[1,3]oxazinan-2-onyl; tetrahydro-pyrimidin-2-onyl; 5,6,7,8-tetrahydro-naphthalenyl; piperazine-2,5-dionyl; isoxindole-1,3-dionyl; 1,4-dihydro-2H-isoquinolin-3-onyl; 2,3-dihydro-isoindol-2-onyl; 3,4-dihydro-2H-isoquinolin-1-onyl; 2H-pyridazin-3-onyl; oxazolidin-2-onyl; imidazolidin-2-onyl; hexahydro-pyrido[1,2-a]pyrazine-1,4-dionyl; hexahydro-pyrrolo[1,2-a]pyrazin-1,4-dionyl; 5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidinyl; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinyl; 5,6-dihydro-8H-[1,2,4]triazolo[1,5-a]pyrazinyl; 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onyl; 6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazin-8-onyl; 6,7-dihydro-5H-pyrido[3,4-d]pyrimidin-8-onyl; 6,7-dihydro-4H-oxazolo[5,4-c]pyridinyl; 7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-onyl; 6H-pyrido[4,3-d]pyrimidin-5-onyl; 5,8-dihydro-6H-pyrido[3,4-d]pyrimidinyl; 7,8-dihydro-[1,2,4]triazolo[4,3-c]pyrimidinyl; and 7,8-dihydro-
[1,2,4]triazolo[4,3-a]pyrazin-6-onyl; any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

In further embodiments, Z is a bond and R^6 is selected from 2H-pyridazin-3-onyl; oxazolidin-2-onyl; imidazolidin-2-onyl; 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinyl; and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onyl; any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

In further embodiments, Z is a bond and R^6 is imidazolidin-2-onyl or pyrazin-3-onyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

In further embodiments, Z is a linker selected from -N(R)^6-, -N(R)^6C(O)-, -N(R)^6C=O, alkylene- and -N(R)^6C=O-C^16_alkylene-, wherein -Z-R^6 is attached to the remainder of the compound via the nitrogen atom of said linker and wherein any C^16_alkylene group is optionally substituted with 1, 2, 3, 4 or 5 R^10; and R^6 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10. Of mention are compounds in which R^6 is aryl (e.g. phenyl) or heterocyclyl (e.g. pyridinyl, benzimidazolyl, benzo triazolyl, indazolyl, pyridazinyl or pyridinyl), either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10. In particular compounds, R^6 phenyl or pyridinyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10. In other compounds, R^6 is substituted by 1, 2, 3, 4 or 5 R^10, at least one of which is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, cyano, amino, hydroxy, C^16_alkyl and C^16_alkoxy. By way of example, said at least one R^10 may be selected from cycloalkyl (e.g. cyclopropyl), aryl (e.g. phenyl), heterocycloalkyl (e.g. piperidinyl) and heteroaryl (e.g. pyridinyl), any of which is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, cyano, amino, hydroxy, C^16_alkyl and C^16_alkoxy.

In further embodiments, Z is -N(R)^6C(O)-, wherein the group -Z-R^6 is attached to the remainder of the compound via the nitrogen atom of said linker; and R^6 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

In further embodiments, Z and R^6 each independently comprise a carbocyclyl or heterocyclyl group, and are each optionally substituted with 1, 2, 3, 4 or 5 R^10. Included are compounds of this type in which Z comprises (e.g. is) a heterocyclylene moiety optionally substituted with
1, 2, 3, 4 or 5 R\textsuperscript{10}; and R\textsuperscript{6} is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. Of mention are compounds in which Z comprises (e.g. is) a moiety selected from 2H-pyridazin-3-onylene, oxazolidin-2-onylene, imidazolidin-2-onylene, 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylene, any of which is optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}. Exemplary R\textsuperscript{6} groups include aryl (e.g. phenyl) and heteroaryl (e.g. pyridyl, pyrimidinyl, indolyl, quinolinyl, pyrazolyl, triazolyl or thiophenyl) groups, either of which are optionally substituted with 1, 2, 3, 4 or 5 R\textsuperscript{10}.

In further embodiments of the above formulae, when p is 1, 2, 3, 4 or 5, at least one R\textsuperscript{10} is halogen or C\textsubscript{1-6} alkyl. In particular embodiments, the or each R\textsuperscript{10} is independently halogen or C\textsubscript{1-6} alkyl.

In further embodiments, when p is 1, 2, 3, 4 or 5, at least one R\textsuperscript{10} is halogen. In particular embodiments, the or each R\textsuperscript{10} is halogen.

In further embodiments, when p is 1, 2, 3, 4 or 5, at least one R\textsuperscript{10} is fluorine or chlorine. In particular embodiments, the or each R\textsuperscript{10} is independently fluorine or chlorine.

In further embodiments, p is 0, 1, 2 or 3. In particular embodiments, p is 0, 1 or 2.

Examples of compounds of the invention include those shown below. It will of course be appreciated that, where appropriate, each compound may be in the form of the free compound, an acid or base addition salt, or a prodrug. Where a nitrogen atom forming only two bonds is shown, this represents NH.
DI37

DI38

DI39

DI40

DI41

DI42

DI43

DI44

DI45

DI46

DI47

DI48

DI49

DJ1

DJ2

DJ3
Compounds of the invention may be in the form of pharmaceutically acceptable salts. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., US, 1985, p. 1418, the disclosure of which is hereby incorporated by reference; see also Stahl et al, Eds, "*Handbook of Pharmaceutical Salts Properties Selection and Use*", Verlag Helvetica Chimica Acta and Wiley-VCH, 2002.

The disclosure thus includes pharmaceutically-acceptable salts of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof, for example the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g. from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate,
maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The invention includes prodrugs for the active pharmaceutical species of the invention, for example in which one or more functional groups are protected or derivatised but can be converted in vivo to the functional group, as in the case of esters of carboxylic acids convertible in vivo to the free acid, or in the case of protected amines, to the free amino group. The term "prodrug," as used herein, represents in particular compounds which are rapidly transformed in vivo to the parent compound, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; H Bundgaard, ed, Design of Prodrugs, Elsevier, 1985; and Judkins, et al. Synthetic Communications, 26(23), 4351-4367 (1996), each of which is incorporated herein by reference.

Prodrugs therefore include drugs having a functional group which has been transformed into a reversible derivative thereof. Typically, such prodrugs are transformed to the active drug by hydrolysis. As examples may be mentioned the following:

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Reversible derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acid</td>
<td>Esters, including e.g. acyloxyalkyl esters, amides</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Esters, including e.g. sulfates and phosphates as well as carboxylic acid esters</td>
</tr>
<tr>
<td>Amine</td>
<td>Amides, carbamates, imines, enamines,</td>
</tr>
</tbody>
</table>
Carbonyl (aldehyde, imines, oximes, acetals/ketals, enol esters, ketone) oxazolidines and thiazoxolidines

Prodrugs also include compounds convertible to the active drug by an oxidative or reductive reaction. As examples may be mentioned:

**Oxidative activation**
- N- and O- dealkylation
- Oxidative deamination
- N-oxidation
- Epoxidation

**Reductive activation**
- Azo reduction
- Sulfoxide reduction
- Disulfide reduction
- Bioreductive alkylation
- Nitro reduction.

Also to be mentioned as metabolic activations of prodrugs are nucleotide activation, phosphorylation activation and decarboxylation activation. For additional information, see "The Organic Chemistry of Drug Design and Drug Action", R B Silverman (particularly Chapter 8, pages 497 to 546), incorporated herein by reference.


Thus, it will be appreciated by those skilled in the art that, although protected derivatives of compounds of the disclosure may not possess pharmacological activity as such, they may be administered, for example parenterally or orally, and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives are therefore examples of "prodrugs". All prodrugs of the described compounds are included within the scope of the disclosure.
Some groups mentioned herein (especially those containing heteroatoms and conjugated bonds) may exist in tautomeric forms and all these tautomers are included in the scope of the disclosure. More generally, many species may exist in equilibrium, as for example in the case of organic acids and their counterpart anions; a reference herein to a species accordingly includes reference to all equilibrium forms thereof.

The compounds of the disclosure may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. All diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the disclosure. Where a single enantiomer or diastereomer is disclosed, the disclosure also covers the other enantiomers or diastereomers, and also racemates; in this regard, particular reference is made to the specific compounds listed herein.

Geometric isomers may also exist in the compounds of the present disclosure. The present disclosure contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond and designates such isomers as of the Z or E configuration, wherein the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon—carbon double bond.

The disclosure therefore includes all variant forms of the defined compounds, for example any tautomer or any pharmaceutically acceptable salt, ester, acid or other variant of the defined compounds and their tautomers as well as substances which, upon administration, are capable of providing directly or indirectly a compound as defined above or providing a species which is capable of existing in equilibrium with such a compound.
Synthesis

By way of illustration, a compound of the invention may be prepared according to any of the following general reaction schemes:
Scheme A

$t\text{-butyl acrylate, Triton B}$

$t\text{BuOH, reflux, 5h}$

$t\text{BuOK, THF}$

reflux, 5h

$\text{NaCl, DMSO, } H_2O$

$150^\circ C, 5h$

$\text{NaBH}_4, \text{THF}$

-78$^\circ C, 1h$

$\text{BH}_3, \text{THF}$

reflux, overnight

Scheme B

$\text{MeI, 4 eq NaH, THF, rt}$

$\text{LiAlH}_4, \text{THF, 50^\circ C, 1hr}$

$H_2N$
Scheme C

1.5 eq NaBH(OAc)₃
DCE, rt

LiAlH₄,
THF, 50°C
Scheme D
Scheme DA
Scheme DB
Scheme DD
Scheme DE
Scheme DF
Scheme DG
Scheme DI
Scheme DJ
Scheme E
Scheme EA
Scheme F

Scheme G
Scheme M

X = C=O or SO₂
Scheme N

Scheme O
Scheme P

Scheme Q
Scheme R

Scheme S
Scheme T
Scheme V
Scheme W
Scheme WA
Scheme WB
Scheme WC
Scheme WD
Scheme WE
Scheme WF
Scheme WG
Scheme WH
Scheme W1
Scheme WJ
Scheme WK
It will be understood that the processes detailed above and elsewhere herein are solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.
Administration & Pharmaceutical Formulations

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route, as an oral or nasal spray or via inhalation. The compounds may be administered in the form of pharmaceutical preparations comprising prodrug or active compound either as a free compound or, for example, a pharmaceutically acceptable non-toxic organic or inorganic acid or base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Typically, therefore, the pharmaceutical compounds of the invention may be administered orally or parenterally ("parenterally" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion) to a host to obtain an protease-inhibitory effect. In the case of larger animals, such as humans, the compounds may be administered alone or as compositions in combination with pharmaceutically acceptable diluents, excipients or carriers.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require inhibition of DPP-IV enzyme activity, an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg
per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may
be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50
mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg
per day. For oral administration, the compositions are preferably provided in the form of
tables containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0,
15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0,
800.0, 900.0 and 1000.0 milligrams of the active ingredient for the symptomatic adjustment
of the dosage to the patient to be treated. The compounds may be administered on a
regimen of 1 to 4 times per day, preferably once or twice per day. The dosage regimen may
be adjusted to provide the optimal therapeutic response.

According to a further aspect of the invention there is thus provided a pharmaceutical
composition including a compound of the invention, in admixture with a pharmaceutically
acceptable adjuvant, diluent or carrier.

Pharmaceutical compositions of this invention for parenteral injection suitably comprise
pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions,
suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable
solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous
carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol,
propylene glycol, polyethylene glycol and the like), and suitable mixtures thereof, vegetable
oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can
be maintained, for example, by the use of coating materials such as lecithin, by the
maintenance of the required particle size in the case of dispersions and by the use of
surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents,
emulsifying agents and dispersing agents. Prevention of the action of microorganisms may
be ensured by the inclusion of various antibacterial and antifungal agents, for example,
paraben, chlorobutanol or phenol sorbic acid. It may also be desirable to include isotonic
agents such as sugars or sodium chloride, for example. Prolonged absorption of the
injectable pharmaceutical form may be brought about by the inclusion of agents (for example
aluminum monostearate and gelatin) which delay absorption.
In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are suitably made by forming microencapsule matrices of the drug in biodegradable polymers, for example poly(lactide-co-glycolide). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also be prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is typically mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or one or more: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginites, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycol, for example.
Suitably, oral formulations contain a dissolution aid. The dissolution aid is not limited as to its identity so long as it is pharmaceutically acceptable. Examples include nonionic surface active agents, such as sucrose fatty acid esters, glycerol fatty acid esters, sorbitan fatty acid esters (e.g. sorbitan trioleate), polyethylene glycol, polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, methoxypolyoxyethylene alkyl ethers, polyoxyethylene alkylphenyl ethers, polyethylene glycol fatty acid esters, polyoxyethylene alkylamines, polyoxyethylene alkyl thioethers, polyoxyethylene polyoxypropylene copolymers, polyoxyethylene glycerol fatty acid esters, pentaerythritol fatty acid esters, propylene glycol monofatty acid esters, polyoxyethylene propylene glycol monofatty acid esters, polyoxyethylene sorbitol fatty acid esters, fatty acid alkylolamides, and alkylamine oxides; bile acid and salts thereof (e.g. chenodeoxycholic acid, cholic acid, deoxycholic acid, dehydrocholic acid and salts thereof, and glycine or taurine conjugate thereof); ionic surface active agents, such as sodium laurylsulfate, fatty acid soaps, alkylsulfonates, alkylphosphates, ether phosphates, fatty acid salts of basic amino acids; triethanolamine soap, and alkyl quaternary ammonium salts; and amphoteric surface active agents, such as betaines and aminocarboxylic acid salts.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, and/or in delayed fashion. Examples of embedding compositions include polymeric substances and waxes.

The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

The active compounds may be in finely divided form, for example it may be micronised.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl
carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents. Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.
Advantageously, the compounds of the invention may be orally active, have rapid onset of activity and low toxicity.

The compounds of the invention may have the advantage that they are more efficacious, less toxic, longer acting, have a broader range of activity, more potent, produce fewer side effects, more easily absorbed than, or have other useful pharmacological properties over, compounds known in the prior art.

*Combination therapies*

Compounds of the invention may be administered in combination with one or more additional therapeutic agents. Accordingly, the invention provides a pharmaceutical composition comprising an additional agent. The invention also provides a product comprising a compound of the invention and an agent; as a combined preparation for simultaneous, separate or sequential use in therapy.

In particular, a composition or product of the invention may further comprise a therapeutic agent selected from anti-diabetic agents, hypolipidemic agents, anti-obesity or appetite-regulating agents, anti-hypertensive agents, HDL-increasing agents, cholesterol absorption modulators, Apo-A1 analogues and mimetics, thrombin inhibitors, aldosterone inhibitors, inhibitors of platelet aggregation, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, chemotherapeutic agents, and 5-HT₃ or 5-HT₄ receptor modulators; or pharmaceutically acceptable salts or prodrugs thereof.

Examples of anti-diabetic agents include insulin, insulin derivatives and mimetics; insulin secretagogues, for example sulfonylureas (e.g. glipizide, glyburide or amaryl); insulinotropic sulfonylurea receptor ligands, for example meglitinides (e.g. nateglinide or repaglinide); insulin sensitisers, for example protein tyrosine phosphatase-1B (PTP-1B) inhibitors (e.g. PTP-112); GSK3 (glycogen synthase kinase-3) inhibitors, for example SB-517955, SB-4195052, SB-216763, NN-57-05441 or NN-57-05445; RXR ligands, for example GW-0791 or AGN-194204; sodium-dependent glucose cotransporter inhibitors, for example T-1095; glycogen phosphorylase A inhibitors, for example BAY R3401; biguanides, for example metformin; alpha-glucosidase inhibitors, for example acarbose; GLP-1 (glucagon like peptide-1), GLP-I analogues and mimetics, for example exendin-4; DPPIV (dipeptidyl...
peptidase IV) inhibitors, for example DPP728, LAF237 (vildagliptin), MK-0431, saxagliptin or GSK23A; AGE breakers; and thiazolidone derivatives, for example glitazone, pioglitazone, rosiglitazone or (R)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonfyl}-2,3-dihydro-1H-indole-2-carboxylic acid (compound 4 of Example 19 of WO 03/043985) or a non-glitazone type PPAR- agonist (e.g. GI-262570); or pharmaceutically acceptable salts or prodrugs thereof.

Examples of hypolipidemic agents include 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, for example lovastatin, pravastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin or rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) ligands; LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid; and aspirin; or pharmaceutically acceptable salts or prodrugs thereof.

Examples of anti-obesity/appetite-regulating agents include phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine and cannabinoid receptor antagonists; or pharmaceutically acceptable salts or prodrugs thereof.

Examples of anti-hypertensive agents include loop diuretics, for example ethacrynic acid, furosemide or torsemide; diuretics, for example thiazide derivatives, chlorothiazide, hydrochlorothiazide or amiloride; angiotensin converting enzyme (ACE) inhibitors, for example benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril ortrandolapril; Na-K-ATPase membrane pump inhibitors, for example digoxin; neutralendopeptidase (NEP) inhibitors, for example thiorphan, terteo-thiorphan or SQ29072; ECE inhibitors, for example SLV306; dual ACE/NEP inhibitors, for example omapatrilat, sampatrilat or fasidotril; angiotensin II antagonists, for example candesartan, eprosartan, irbesartan, losartan, telmisartan or valsartan; renin inhibitors, for example aliskiren, terlakiren, ditekiren, RO-66-1 132 or RO-66-1168; b-adrenergic receptor blockers, for example acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol or timolol; inotropic agents, for example digoxin, dobutamine or milrinone; calcium channel blockers, for example amiodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine,
nifedipine, nisoldipine or verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors; or pharmaceutically acceptable salts or prodrugs thereof.

Examples of cholesterol absorption modulators include Zetia® and KT6-971, or pharmaceutically acceptable salts or prodrugs thereof.

Examples of aldosterone inhibitors include anastrazole, fadrazole and eplerenone, or pharmaceutically acceptable salts or prodrugs thereof.

Examples of inhibitors of platelet aggregation include aspirin or clopidogrel bisulfate, or pharmaceutically acceptable salts or prodrugs thereof.

Examples of chemotherapeutic agents include compounds decreasing the protein kinase activity, for example PDGF receptor tyrosine kinase inhibitors (e.g. imatinib or 4-methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide), or pharmaceutically acceptable salts or prodrugs thereof.

Examples of 5-HT₃ or 5-HT₄ receptor modulators include tegaserod, tegaserod hydrogen maleate, cisapride or cilansetron, or pharmaceutically acceptable salts or prodrugs thereof.

The weight ratio of the compound of the present invention to the further active ingredient(s) may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000: 1 to about 1: 1000, preferably about 200: 1 to about 1: 200.

Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).
Use

Compounds of the invention may be useful in the therapy of a variety of diseases and conditions.

In particular, compounds of the invention may be useful in the treatment or prevention of a disease or condition selected from non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, osteoporosis, heart failure, impaired glucose metabolism or impaired glucose tolerance, neurodegenerative diseases (for example Alzheimer's disease or Parkinson disease), cardiovascular or renal diseases (for example diabetic cardiomyopathy, left or right ventricular hypertrophy, hypertrophic medial thickening in arteries and/or in large vessels, mesenteric vasculature hypertrophy or mesangial hypertrophy), neurodegenerative or cognitive disorders, hyperglycemia, insulin resistance, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), pancreatitis, retinopathy, nephropathy, neuropathy, syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), type 2 diabetes, growth hormone deficiency, neutropenia, neuronal disorders, tumor metastasis, benign prostatic hypertrophy, gingivitis, hypertension and osteoporosis.

The compounds may also be useful in producing a sedative or anxiolytic effect, attenuating post-surgical catabolic changes or hormonal responses to stress, reducing mortality and morbidity after myocardial infarction, modulating hyperlipidemia or associated conditions; and lowering VLDL, LDL or Lp(a) levels.
Examples

The following Examples illustrate the invention.

Example A1

4-Aminomethyl-4-(2.5-difluoro-phenyl)-cyclohexanol

This compound was prepared according to Scheme A:

A) 4-(2.5-Difluoro-phenyl)-4-cyano-heptanedioic acid di-tert-butyl ester

A solution of 2,5-difluorobenzyl cyanide (2.00g, 13.06mmol) and tert-butyl acrylate (9.86ml, 67.92 mmol) in NBuOH (20ml) was heated at 60°C. The heat was quickly removed and a solution of Triton B (1.98ml of 40% MeOH solution diluted with 10ml of fBuOH, 4.4mmol) was added in one portion. The mixture was stirred at reflux for 5h then cooled to RT. The mixture was diluted with Et₂O (300ml) and washed successively with 2M aqueous HCl solution (150ml) and brine (150ml). The organic layer was dried over Na₂SO₄, filtered, then evaporated. The crude material was purified by silica gel chromatography (gradient elution, hexane/TBME 95:5 to 3:7) to provide the title compound (3.44g).

MS: 427.6 [M+H₂O]⁺
HPLC (SunFire TM (4.6x20mm) C18, 3.5µm, 3ml/min, linear gradient MeCN in H₂O (0.1%TFA) 5 to 100% in 4min then 0.5min 100%): Rt = 3.18min

B) 5-(2.5-difluoro-phenyl)-5-cyano-2-oxo-cyclohexanecarboxylic acid di-tert-butyl ester

A solution of 4-(2.5-difluoro-phenyl)-4-cyano-heptanedioic acid di-tert-butyl ester (3.13g, 7.49 mmol) in THF (60 ml) was treated with f-BuOK (1.73g 15.0 mmol) at RT then the mixture was refluxed for 5h. The reaction was then cooled to 0 °C in ice-bath, acidified by addition of AcOH-H₂O (2.14ml in 20ml) and diluted with Et₂O (150ml). The organic layer was separated then washed successively with 1M Na₂CO₃ aqueous solution (2 x 50ml), water (2x50ml), and brine (50ml). The organic layer was dried over Na₂SO₄, filtered, and evaporated to obtain the title compound as a crude (2.91 g).

MS: 336.2 [M+H]⁺, 353.2 [M+H₂O]⁺
HPLC (SunFire TM (4.6x20mm) C18, 3.5µm, 3ml/min, linear gradient MeCN in H₂O (0.1%TFA) 5 to 100% in 4min then 0.5min 100%): Rt = 2.95min

C) 1-(2,5-Difluoro-phenyl)-oxo-cyclohexanecarbonitrile

A mixture of 5-(2,5-difluoro-phenyl)-5-cyano-2-oxo-cyclohexanecarboxylic acid tert-butyl ester (crude 2.91 g, ca. 7.49 mmol) and NaCl (2.63 g, 44.9 mmol) in DMSO (60 ml) and water (4 ml) was heated at 150 ºC for 5h. The reaction was then cooled to RT, diluted with Et₂O (500 ml) and washed with 1N aqueous HCl (2x200 ml) and brine (50 ml). The organic layer was dried over Na₂SO₄, filtered and evaporated. The remaining oil was purified with silica gel chromatography (gradient elution, hexane:TBME 95:5 to 1:1) to provide a mixture containing the title compound. This mixture was sublimed in a Kugelrohr apparatus (140 ºC, 0.017 mbar) to yield the pure title compound as a colorless solid (554 mg).

HPLC (SunFire TM (4.6x20mm) C18, 3.5µm, 3ml/min, linear gradient MeCN in H₂O (0.1%TFA) 5 to 100% in 4min then 0.5min 100%): Rt = 1.74min

D) 1-(2,5-Difluoro-phenyl)-4-hydroxy-cyclohexanecarbonitrile

To a solution of 1-(2,5-difluoro-phenyl)-4-oxo-cyclohexanecarbonitrile (150 mg, 0.625 mmol) in dry THF (2 ml) was added at -78 ºC NaBH₄ (49 mg, 1.25 mmol), and the reaction was stirred at -78 ºC for 1 hr before carefully quenched by MeOH. EtOAc was added and the phases are separated. The aqueous phase was further extracted twice with EtOAc. The combined organic phase was washed once with brine, dried over Na₂SO₄, filtered and evaporated. The crude product was purified with silica gel chromatography (gradient elution, hexane-CH₂Cl₂ (1:1)/TBME 95/5 to 6/4) to yield the title compound (114 mg, 0.48 mmol).

MS: 256.26 [M+H₂O]+

TLC (silica gel, hexane:CH₂Cl₂:TBME 1:1:2): Rf = 0.35

E) 4-Aminomethyl-4-(2,5-difluoro-phenyl)-cyclohexanol

To a solution of 1-(2,5-difluoro-phenyl)-4-hydroxy-cyclohexanecarbonitrile (50 mg, 0.21 mmol) in dry THF (1 ml) was added BH₃ (1 M solution in THF, 2.1 ml, 2.1 mmol), and the reaction flask was sealed and heated at 70 ºC for 20 h. After cooled to RT, the reaction was
carefully quenched by addition of MeOH then evaporated. The crude product was purified by preparative HPLC to yield the title compound as a TFA salt (19.4mg, 0.055mmol). MS: 242.3 [M+H]+

HPLC (SunFire TM (4.6x20mm) C18, 3.5µm, 3ml/min, linear gradient MeCN in H₂O (0.1%TFA) 5 to 100% in 4min then 0.5min 100%): Rt = 0.87min

Example A2
4-Aminomethy-4-phenyl-cyclohexanol

The title compound was prepared analogously as described in example A1 using Benzylcyanide instead of 2,5-difluorobenzyl cyanide. MS: 206 [M+H]⁺

Example B1
C-ri-f 2,S-Difluoro-phenylM-methoxy-cyclohexyl-methylamine

This compound was prepared according to Scheme B:

A) 1-(2,5-Difluoro -phenylM-methoxy-cyclohexanecarbonitrile

To NaH (67mg, 60% in mineral oil, 1.68 mmol, washed with hexane, suspended in dry THF 1ml) were added 1-(2,5-difluoro-phenyl)-4-hydroxy-cyclohexanecarbonitrile (100mg, 0.421 mmol) in dry THF (1ml) and MeI (0.105ml, 1.68mmol). The reaction was stirred at rt for 2hrs then carefully quenched with sat. NH₄Cl aq., and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried over Na₂SO₄ and evaporated in vacuo to give 87mg of the title compound as a pale yellow solid.

TLC (silicagel, cyclohexane:acetone 3:2): Rf = 0.57.

B) C-f1-(2,5-Difluoro-phenyl)-4-methoxy-cyclohexyl-methylamine

To a solution of 1-(2,5-difluoro-phenyl)-4-methoxy-cyclohexanecarbonitrile (87mg, 0.346mmol) in dry THF (1ml) was added LiAlH₄ (22.6mg, 0.578mmol), and the reaction was stirred at 50°C for 1 hr. After carefull quench with sat. NH₄Cl aq., the mixture was extracted three times with ethyl acetate, and the combined organic phase was washed with brine,
dried over Na₂SO₄ and evaporated. The residual oil was taken up in MeOH-MeCN (1:1) and loaded over 6ml SCX column filled with benzenesulfonic acid (500mg), eluted with ethyl acetate and methanol. Finally the amine was washed off with 2M ammonia in methanol. Evaporation of the amine solution in vacuo gives a white solid which was further purified by preparative HPLC to afford pure title compound as a white solid (10mg).

MS: 256.1 [M +H]⁺

HPLC(WATERS Symmetry C18, linear gradient MeCN in H₂O (0.1% formic acid) 20% (0-1min), 20-100% (1-6min), 100% (6-8.5min)): Rt = 3.42min

**Example B2**

**C-f1-Phenyl-4-((£)-3-phenyl-allyloxy)-cyclohexyn-methylamine**

The title compound was prepared analogously as described in example B2 step A) using commercially available 4-cyano-4-phenyl-cyclohexanone and ((£)-3-bromo-propenyl)-benzene instead of 1-(2,5-difluoro-phenyl)-4-hydroxy-cyclohexanecarbonitrile and MeI, respectively.

MS: 322.15 [M+H]⁺

**Example B3**

**1-Fc/s-1-(3-Chlorophenyl)-4-methoxycyclohexynmethanamine hydrochloride**

This compound was prepared by adaptation of the route shown in Scheme B.

A) c/s-1-(3-Chlorophenyl)-4-hydroxy-cyclohexanecarbonitrile

1-(3-Chlorophenyl)-4-oxo-cyclohexanecarbonitrile (530mg, 2.3mmol) was dissolved in tetrahydrofuran (7mL) and cooled to -78°C under an atmosphere of nitrogen. Sodium borohydride (170mg, 4.5mmol) was added and the reaction mixture was stirred at -78°C for 1.5hours. The reaction was quenched by the addition of methanol (10mL) and diluted with ethyl acetate (20mL). The layers were separated and the aqueous layer was extracted with a more ethyl acetate (20mL). The combined organic phases were washed with water (2 x 20mL) and brine (2 x 20mL), dried (MgSO₄), and concentrated to a yellow gum. The gum was purified by flash chromatography (Silica, eluting with 20% ethyl acetate in cyclohexane) to afford the title compound as a white sticky solid.
MS (ES⁺): 236 [M+H]⁺.

TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% \( \text{CH}_3\text{CN}+0.1\% \text{Formic acid/H}_2\text{O}+0.1\% \) Formic acid for 5 min, flow 2.0 ml/min]: 3.04 min.

B) c/s-1-(3-Chlorophenyl)-4-methoxy-cyclohexanecarbonitrile

Sodium hydride (50mg of a 60% dispersion in mineral oil, 1.25mmol) was suspended in tetrahydrofuran (5ml) and cooled to 0°C under an atmosphere of nitrogen. A solution of cis-1-(3-chlorophenyl)-4-hydroxy-cyclohexanecarbonitrile (140mg, 0.60mmol) in tetrahydrofuran (2mL) was added. The mixture was stirred at 0-5°C for 45mins. Iodomethane (130µL, 2.0mmol) in tetrahydrofuran (1mL) was then added and the reaction mixture was stirred at room temperature for 2hours. Further quantities of sodium hydride (50mg of a 60% dispersion in mineral oil, 1.25mmol) and iodomethane (130µL, 2.0mmol) were added and the reaction stirred for a 1hour. Water (2OmL) was added cautiously and the reaction mixture was extracted with ethyl acetate (3x15ml). The combined extracts were dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated in vacuo to leave a yellow gum. The gum was purified by flash chromatography (Silica, eluting sequentially with pentane, pentanediethyl ether 6:1, then 2:1, then 1:1, and finally diethyl ether) to afford the title compound as a colourless oil.

\(^1\)Hnmr [400 MHz, CDC\(_3\), tetramethylsilane as internal standard], \( \delta \) 1.74-1.88 (4H, m), 2.17-2.29 (4H, m), 3.23 (1H, m), 3.41 (3H, s), 7.28-7.36 (2H, m), 7.40 (1H, m), and 7.46 (1H, br.s).

C) 1-fc/s-1-O-Chlorophenyl-N^1-methoxy-cyclohexynmethanamine hydrochloride

A solution of borane-tetrahydrofuran complex (1.4mL), 1.4mmol of a 1M solution in tetrahydrofuran) was added to a solution of 1-(3-chlorophenyl)-4-methoxyoxy-cyclohexanecarbonitrile (99mg, 0.35mmol) in tetrahydrofuran (5mL) and the resulting mixture was heated at reflux under a nitrogen atmosphere for 5hours. The mixture was treated with 6N aq. Hydrochloric acid (5mL) and methanol (2mL) and refluxed for 2hours. The cooled reaction mixture was basified with 1M aq. sodium hydroxide and extracted with dichloromethane (3x10mL). The combined organic phases were dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated in vacuo to leave a colourless oil. The oil was purified on anion-exchange column (SCX cartridge (5g) eluting sequentially with dichloromethane, dichloromethane:methanol 1:1, dichloromethane:methanol 1:1 with 5% ammonia).
Evaporation of the appropriate fractions gave a gum which was further purified by flash chromatography (silica (10g), eluting with dichloromethane: ethanol: ammonia, 200: 8: 1 then 100: 8: 1) to give a colourless oil. The oil was dissolved in methanol (2ml), treated with 1M hydrochloric acid (2ml), and concentrated in vacuo to afford the title compound as a white solid.

MS (ES)⁺: 254, 256 [M+H]⁺.

**Example B4**

1-fc/s-1-(3-Chlorophenyl)-4-(3-phenylpropoxy) cyclohexymethanamine hydrochloride

The title compound was prepared analogously as described in Example B3 using (3-bromopropyl)-benzene and sodium iodide instead of iodomethane.

MS (ES)⁺: 358, 360 [M+H]⁺.

**Example B5**

1-rc/s-4-(Benzyloxy)-1-O-chlorophenvDcyclohexymethanamine hydrochloride

The title compound was prepared analogously as described in Example B3 using benzyl bromide instead of iodomethane.

MS (ES)⁺: 330, 332 [M+H]⁺.

**Example B6**

A mixture of i-rc/s^-methoxy-i-O-methylphenvDcvclohexyllmethanamine hydrochloride and 1-frans-4-methoxy-1-O-methylphenvhcvclohexyllumethanamine hydrochloride

This compound was prepared by adaptation of the routes shown in Schemes A and B.
The title compounds were prepared analogously as described in Examples A1 and B3 using (meta-tolyl)-acetonitrile instead of 2,5-difluorobenzyl cyanide. The title compounds were obtained as a mixture of diastereoisomers.


Tₚ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.50 and 5.45 min.

Example B7

1-trans-1-O-ChlorophenylM-methoxycyclohexylmethanamine hydrochloride

The title compound was prepared by adaptation of the route depicted in Scheme B.

A) Isonicotinic acid ffrans-4-(3-chlorophenyl)-4-cyano-cyclohexyll ester

Diethylazodicarboxylate (270 µL) was added to a stirred suspension of c/s-1-(3-chlorophenyl)-4-hydroxy-cyclohexanecarbonitrile (400mg, 1.70mmol), isonicotinic acid (935mg, 7.59mmol) and triphenylphosphine (2.2g, 8.37mmol) in toluene (15mL) under nitrogen and stirring was continued for 18 hours. The reaction mixture was partitioned between sodium bicarbonate (8%, 20mL) and ethyl acetate (3x10mL). The combined organic phases were washed with sodium bicarbonate (8%, 20ml) and water, dried (Na₂SO₄) and concentrated in vacuo to leave a colourless oil. The oil was purified by ion exchange chromatography (SCX cartridge (50g) eluting sequentially with dichloromethane, dichloromethanemethanol 1:1, and dichloromethane:methanol 1:1 with 5% ammonia) and then by flash chromatography (silica, 20g eluting with dichloromethane:ethanol:ammonia, 400:8:1 to 200:8:1) to give an oil. Final purification (silica 10g eluting sequentially with pentane, pentane:diethyl ether 9:1, pentane:diethyl ether 4:1 and pentane:diethyl ether 1:1) gave the title compound as a colourless oil.


Tₚ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.70 min.

B) trans-i-(3-Chlorophenyl)-4-hydroxy-cyclohexanecarbonitrile
A mixture of isonicotinic acid [trans-4-(3-chlorophenyl)-4-cyano-cyclohexyl] ester (254mg, 0.70mmol) and 1 M aq. lithium hydroxide (3ml) in tetrahydrofuran (3ml) was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (20ml), extracted with ethyl acetate (2x20ml) and the extracts were washed with 2 M aq. sodium carbonate (20ml) and brine (10ml). After drying (Na$_2$SO$_4$) and concentrating in vacuo, the title compound was obtained as a colourless oil.

MS (ES$^+$): 236 [M+H]$^+$. 

$T_R$ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1% Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.17 min.

C) 1-fran/s-1-O-ChlorophenylM-methoxy-cyclohexylmethanamine hydrochloride

The title compound was prepared analogously as described in Example B3 using trans-1-(3-chlorophenyl)-4-hydroxy-cyclohexanecarbonitrile instead of cis-1-(3-chlorophenyl)-4-hydroxy-cyclohexanecarbonitrile.


$T_R$ [HPLC, Higgins Clopeus δ micron C18; 5-95% CH$_3$CN+0.1% Formic acid/H$_2$O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 5.12 min.

Example B8

1-rc/s-4-Methoxy-1-(2,4,5-trifluorophenyl)cyclohexyllmethanamine hydrochloride

The title compound was prepared by adaptation of the route depicted in Scheme B.

A) 4-Cyano-4-(2,4,5-trifluorophenyl)-heptanedioic acid dimethyl ester.

A solution of Triton B (2.7mL, 5.9mmol of a 40% solution in methanol) in t-butanol (2mL) was added in one portion to a heated (80°C) solution of the 2,4,5-trifluorophenyl-acetonitrile (3.0g, 17.54mmol) and methyl acrylate (6.3mL, 70.0mmol) in t-butanol (6mL) and the resulting mixture was heated at reflux for 5 h. The reaction mixture was partitioned between 1N hydrochloric acid (40mL) and diethyl ether (2x30mL) and the organic phases were washed with brine (20mL) and blown down. The residue was purified by flash chromatography (silica (50g), eluting sequentially with pentane, pentane:diethyl ether 9:1,
pentane:diethyl ether 3:1 and pentane:diethyl ether 1:1) to give the title compound as a colourless oil.

TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.46 min.

B) 5-Cvano-2-oxo-5-(2,4,5-trifluorophenyl)-cyclohexanecarboxylic acid methyl ester.

4-Cyano-4-(2,4,5-trifluorophenyl)-heptanedioic acid dimethyl ester (2.65g, 7.7mmol), potassium tert butoxide (1.73g, 15.4mmol) and 1,2,4,5-tetrafluorobenzene (1.72mL, 15.4mmol) were suspended in dry tetrahydrofuran (50mL) and the mixture was heated at reflux overnight under an atmosphere of nitrogen. After cooling to room temperature, glacial acetic acid (2.21 mL) in water (30mL) was added to the reaction mixture which was extracted with diethyl ether (2 x 30mL). The organic phases were washed with 1M aq. sodium carbonate (2 x 30mL), water (2 x 30mL) and brine (2 x 30mL), dried (MgSO$_4$), and concentrated to give an amber coloured gum. The gum was purified by chromatography (silica (50g), eluting with 5% ethyl acetate in cyclohexane) to give the title compound as a white solid.

MS (ES$^+$): 312 [M+H]$^+$. 

TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.74 min.

C) 4-Oxo-i-(2,4,5-trifluorophenyl)-cyclohexanecarbonitrile

A mixture of 5-cyano-2-oxo-5-(2,4,5-trifluorophenyl)-cyclohexanecarboxylic acid methyl ester (950mg, 3.1mmol), 10% aq. sulphuric acid (10mL) and glacial acetic acid (22mL) was heated at 110°C overnight. After cooling to room temperature, the reaction mixture was diluted with water (20mL) and extracted into ethyl acetate (20mL). The organic layer was washed with water (2 x 20mL), sat. aq. sodium bicarbonate (20mL) and brine (20mL), and dried (MgSO$_4$). Concentration in vacuo afforded the title as a pale yellow solid.

TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.17 min.

D) 1-fc/s-4-Methoxy-1-(2,4,5-trifluorophenyl)cyclohexylnitromethanamine hydrochloride
The title compound was prepared analogously as described in Example B3 using 4-oxo-1-(2,4,5-trifluorophenyl)-cyclohexanecarbonitrile instead of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile.

MS (ES\(^+\)): 274 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.90 min.

**Example B9**

C-(4-Methoxy-1-phenyl-cyclohexyl)-methylamine

The title compound was prepared analogously as described in Example B1 using 1-phenyl-4-hydroxy-cyclohexanecarbonitrile instead of 1-(2,5-Difluoro-phenyl)-4-hydroxy-cyclohexanecarbonitrile.

MS (ES\(^+\)): 220 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.32 min.

**Example B10**

C-n-PhenvM-O-phenyl-propoxyj-cyclohexyn-methylamine

The title compound was prepared analogously as described in Example B9 using (3-Bromo-propyl)-benzene instead of methyl iodide.

MS (ES\(^+\)): 324 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 7.15-7.40 min.

**Example B11**

C-M-Benzylolxy-i-phenyl-cyclohexyD-methylamine

The title compound was prepared analogously as described in Example B9 using benzyl bromide instead of methyl iodide.

MS (ES\(^+\)): 296 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.32 min.
Example B12
C-ri-(2-Chloro-phenyl)-4-methoxy-cyclohexyn-methylamine

The title compound was prepared analogously as described in Example A1 and B1 using 2-chlorobenzyl cyanide instead of 2,5-difluorobenzyl cyanide.
MS (ES⁺): 254 [M+H⁺].
HPLC (YMC, 10 min method, gradient water / ACN 0-100%): 3.95 min.

Example B13
C-M-(4-Chloro-phenyl)-4-methoxy-cyclohexyl-methylamine

The title compound was prepared analogously as described in Example A1 and B1 using 4-chlorobenzyl cyanide instead of 2,5-difluorobenzyl cyanide.
MS (ES⁺): 254 [M+H⁺].
HPLC (YMC, 10 min method, gradient water / ACN 0-100%): 3.57 min.

Example C1
C-H A-trans-1-Phenyl-4-(3-trifluoromethyl-5,6-dihydro-8H-f1.2.41triazolof4,3-alpyrazin-7-yl)-cyclohexyl-methylamine

This compound was prepared according to Scheme C:

A) 1A-trans-1-Phenyl-4-(3-trifluoromethyl-5,6-dihydro-8H-f 1.2.41triazolof4,3-alpyrazin-7-yl)-cyclohexanecarbonitrile

To a solution of 4-oxo-1-phenyl-cyclohexanecarbonitrile (100mg, 0.50 mmol) in 1,2-dichloroethane (1ml) were successively added S-trifluoromethyl-S,β,7,δ-tetrahydro-
[1,2,4]triazolo[4,3-alpyrazine (106mg, 0.55 mmol), sodium triacetoxyborohydride (168mg, 0.75 mmol), and acetic acid (29 µl, 0.50 mmol). The reaction was stirred at RT for 2hrs
before diluted with EtOAc and quenched with water. The resulting mixture was extracted
twice with EtOAc, and the combined organic phase was washed once with brine, dried over
Na₂SO₄, and evaporated to provide pale yellow solid. Purification by preparative HPLC
yielded the title compound (100mg) along with its stereoisomer 1,4-c/s-1-Phenyl-4-(3-
trifluoromethyl-S.e-dihydro- δH-II^\text{N} Jtriazolo[4. a-alpyrazin-y-yO-cyclohexanecarbonitrile (18mg), both as white solids.

MS: 376.0 [M +H]^+

B) C-H.4-frans-1-Phenyl-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclohexyl-methylamine

To a solution of 1,4-frans-1-Phenyl-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7)-yl)-cyclohexanecarbonitrile (45mg, 0.12mmol) in dry THF (1ml) was added LiAlH₄ (9.4mg, 0.24mmol), and the reaction was stirred at 50°C for 3h. Another 10mg of LiAlH₄ was added and the stirring continues further at 60°C for 2h. After careful quench with sat. aqueous NH₄Cl solution, the mixture was extracted twice with EtOAc, and the combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated to give the title compound (24mg) as an yellow solid.

MS: 380.2 [M +H]^+

**Example D1**

1-(c/s-1-(3-Chlorophenyl)-4-r3-(trifluoromethyl)-5,6-dihvdrori .2.41triazolog4.3-alpyrazin-7(8H)-vcvclohexyl>methanamine dihvdrochloride

This compound was prepared according to Scheme D:

A) 4-(3-Chloro-phenyl)-4-cvano-heptanedioic acid dimethyl ester.

A solution of Triton B (10mL of a 40% solution in methanol) in t-butanol (10mL) was added portionwi to a heated (80°C) solution of the 3-chlorophenylacetoniure (11.65g, 0.077mol) and methyl acrylate (19mL, 0.21 mol) in t-butanol (20ml) at a rate to maintain a controllable reflux. When the addition wa complete, the reaction mixture was heated at reflux for 2h. After cooling, the reaction mixture was partitioned between 1N hydrochloric acid (70mL) and diethyl ether (3x30mL) and then the organic phases were washed with brine (20mL) and concentrated. The residue was recrystallised from dieth; ether: pentane 1:1 to give the title compound as a white solid, m.p. 78.5-80°C.

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.57min.
\(^1\)Hnmr [400 MHz, CDCl\(_3\), tetramethylsilane as internal standard], \(\delta\) 2.13 (2H, m), 2.28 (2H, m), 2.38 (2H, m), 2.51 (2H, m), 3.63 (6H, s), 7.28-7.42 (4H, m).

B) 5-(3-Chlorophenyl)-5-cyano-2-oxo-cyclohexanecarboxylic acid methyl ester.

Potassium tert-butoxide (4.8g, 43.0mmol) was added in one portion to a stirred solution of 4-(3-chloro-phenyl)-4-cyano-heptanedioic acid dimethyl ester (6.23g, 19.3mmol) in anhydrous tetrahydrofuran (80mL). The resulting mixture was stirred at reflux for 5h. The reaction mixture was cooled (0°C) and treated with a solution of acetic acid (4.5mL) in water (30mL). The mixture was extracted with diethyl ether (70mL) and the organic phase was washed with aqueous sodium carbonate solution (2N, 80mL), water (2x40mL) and then dried (Na\(_2\)SO\(_4\)). After concentration in vacuo, the title product was obtained as a white solid.

MS (ES\(^+\)): 290 and 292 [M-H]\.  
T\(_R\) [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.95min.

C) 1-(3-Chlorophenyl)-4-oxo-cyclohexanecarbonitrile.

A mixture of 5-(3-chlorophenyl)-5-cyano-2-oxo-cyclohexanecarboxylic acid methyl ester (8.0g, 27.4mmol) and 10% aqueous sulphuric acid (40mL) in acetic acid (80mL) was heated overnight at 110°C. After cooling to room temperature, the reaction mixture was diluted with water (200mL) and extracted into EtOAc (70mL x3) The combined organic phases were washed with sodium bicarbonate solution (8%, 3x50mL), water (2x50mL) and brine (20mL), and then dried (Na\(_2\)SO\(_4\)). After concentration the title compound was obtained as an orange oil.

MS (ES\(^+\)): 234 [M+H]\^.  
T\(_R\) [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.32min.

D) 8-(3-Chlorophenyl)-1,4-dioxa-spiro4.5decan-8-carbonitrile.

Para-Toluenesulphonic acid (0.37g, 1.95mmol) and ethylene glycol (48mL) were added to a solution of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile (22.3 g, 95.4mmol) in toluene (250mL) and the mixture was heated at 140-143°C for 6 hours using a Dean and Stark
apparatus to remove excluded water. After cooling to room temperature, the toluene was removed by evaporation to give a pale yellow oil. The oil was dissolved in diethyl ether (300 mL) and the solution washed with water (2 × 150 mL). The aqueous layers were combined and back extracted with diethyl ether (200 mL). The combined organics were washed with brine (100 mL), dried (MgSO₄), and evaporated to give the title product as a pale yellow oil, which solidified on standing to give a colourless wax.

Tₚ[R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1% Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.78min.

¹Hnmr [400 MHz, CDCl₃, tetramethylsilane as internal standard], δ 1.87 (2H, m), 2.05-2.20 (6H, m), 3.99 (4H, m), 7.28-7.36 (2H, m), 7.42 (1H, m), and 7.49 (1H, br.s).

E) C-f8-(3-Chlorophenyl)-1.4-dioxo-spiro[4.5]dec-8-vn-methylamine

A solution of the 8-(3-chlorophenyl)-1.4-dioxo-spiro[4.5]decane-8-carbonitrile (6.0g, 21.6mmol) in tetrahydrofuran (15mL) was added dropwise to a stirred suspension of lithium aluminium hydride (2.0g, 52.7mmol) in tetrahydrofuran (5mL). The reaction was stirred at room temperature for 1 hour then cautiously quenched with saturated aqueous Rochelle’s salt (30mL) and extracted into ethyl acetate (3×40mL). The combined organics were washed with water and brine, dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (Silica cartridge (25g) using gradient elution with dichloromethane:ethanol:ammonia from 400:8:1 to 100:8:1) to give a colourless oil. The oil was further purified (SCX cartridge (25g) eluting with dichloromethane then dichloromethane:methanol 1:1, then dichloromethane: methanol 1:1 with 5% ammonia) to give the title compound as a cream solid.


Tₚ[R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1% Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 1.93min.

F) f8-(3-Chlorophenyl)-1.4-dioxo-spiro[4.5]dec-8-ylmethyl1-carbamic acid tert-butyl ester.

Tert-Butyloxycarbonyl anhydride (3.6g, 16.5mmol) was added to a stirred solution of C-[8-(3-chlorophenyl)-1.4-dioxo-spiro[4.5]dec-8-yl]-methylamine (3.9g, 13.8mmol) and triethylamine (7mL) in tetrahydrofuran (40mL) and the mixture was stirred for 18h. The mixture was partitioned between 1N hydrochloric acid (20mL) and extracted with ethyl acetate (3×10mL).
The combined organic phases were washed with water (20mL) and brine (10mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to give a brown oil. The oil was purified by flash chromatography (silica cartridge (50g) eluting sequentially with pentane, pentane:diethylether (4:1), pentane:diethylether (1:1) and diethyl ether) to give the title compound as a yellow oil.

MS (ES$^+$): 382 [M+H]$^+$.  
$T_R$ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.96min.

G) 1-(3-Chlorophenyl)-4-oxo-cyclohexylmethylRarbarrtic acid tert-butyl ester.

Pyridinium para-toluene sulphonate (1.16g, 4.62mmol) was added to a stirred solution of the [8-(3-chlorophenyl)-1,4-dioxa-spiro[4.5]dec-8-ylmethyl]-carbamic acid tert-butyl ester (1.10g, 23.0mmol) in a mixture of acetone (120mL) and water (12mL). The resulting solution was then heated to gentle reflux for 16h. A further aliquot of pyridinium para-toluene sulphonate (1.16g, 4.62mmol) was added and the mixture was heated for an additional 20h. After cooling, the volatiles were evaporated to give a yellow solid, which was purified by column chromatography (Silica cartridge (330g), using gradient elution with 10-30% ethyl acetate in cyclohexane) to give the title compound as a white solid.

$T_R$ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.62min.

H) ((c/s-1-(3-Chlorophenyl)-4-f3-(trifluoromethyl)-5,6-dihvdrof1.2.4triazolo[4.3-a1pyrazin-7(8H)-yl1cvclohexyl)methyl)-carbamic acid tert-butyl ester and ((^ra/7s-1-(3-chlorophenyl)-4-f3-(trifluoromethyl)-5,6-dihvdrof1.2.4triazolo[4.3-a1pyrazin-7(8H)-vnvclohexyl) methyl)-carbamic acid tert-butyl ester

Sodium triacetoxyborohydride (316mg, 1.49mmol) was added to a solution of [1-(3-chlorophenyl)-4-oxo-cyclohexylmethyl]-carbamic acid tert-butyl ester (360mg, 1.07mmol) and 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (286.4mg, 1.49mmol) in 1,2-dichloroethane and the mixture was stirred at room temperature for 24h. The reaction was quenched with water and the product was extracted with ethyl acetate. The organic extracts were washed with water, dried and concentrated in vacuo to give a yellow oil. The oil
was purified by flash chromatography (silica, eluting with 1:33:66 2M ammonia in methanol:ethyl acetate:cyclohexane) to afford the individual title compounds as white solids.

**Cis** diastereoisomer:

MS (ES\(^+\)): 514[M+H]\(^+\).

\(T_R\) [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.70 min.

**Trans** diastereoisomer:

MS (ES\(^+\)): 514[M+H]\(^+\).

\(T_R\) [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.57 min.

i) Mcis-i-O-chlorophenyl\(^+\)-fS-ftrifluoromethyl\(-\)S.e-dihydrof\(^+\)itriazoloK.S-alpyrazin-7(8H)-yl1cyclohexyl)methanamine dihydrochloride.

Trifluoroacetic acid (1mL) was added to a solution of ([c/s-1-(3-chlorophenyl)-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]cyclohexyl]methyl)-carbamic acid tert-butyl ester (93mg, 0.181mmol) in dichloromethane (10mL) and the reaction stirred at room temperature for 90mins. The reaction mixture was concentrated in vacuo and the residue was purified (SCX cartridge eluting sequentially with dichloromethane, methanol and 0.5M ammonia in methanol). Fractions containing the product were concentrated in vacuo to give the free base of the title compound, which was dissolved in dichloromethane and treated with excess 1M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

MS (ES\(^+\)): 414 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clineus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 5.96 min.

**Example D2**

\(1\textbf{trans-1}-(3\text{-Chlorophenyl})-4\text{-r3-(trifluoromethyl)-5,6-dihvdror}i\textbf{.241triazolor4.3-alpyrazin}^\text{SHWncvlohexyDrnethanaminedihvdrochloride}\)

The title compound was prepared analogously as described in Example D1, step I from ([trans-1-(3-chlorophenyl)-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]cyclohexyl]methyl)-carbamic acid tert-butyl ester.
Example D3

\( \text{1-\{c/s-\text{f4-(4-benzylpiperidin-1-vD-1-phenylcyclohexyl) \text{methanamine dihydrochloride}\} and 1-\{\text{trans-r4-(4-benzylpiperidin-1-vh-1-phenylcyclohexyl) \text{methanamine dihydrochloride}\} } \)

The title compounds were prepared analogously as described in Example D1 using phenylacetonitrile instead of 3-chlorophenylacetonitrile and 4-benzylpiperidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^{+}\)): 363 [M+H]

\( T_R \) [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.12 min.

Example D4

\( \text{1-\{c/s-\text{r4-(4-Benzylpiperazin-1-vO-1-phenylcyclohexyl) \text{methanamine dihydrochloride}\} and 1-\{\text{trans-r4-(4-benzylpiperazin-1-vh-1-phenylcyclohexyl) \text{methanamine dihydrochloride}\} } \)

The title compounds were prepared analogously as described in Example D1 using phenylacetonitrile instead of 3-chlorophenylacetonitrile and 1-benzylpiperazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^{+}\)): 364 [M+H]

\( T_R \) [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.59 min.

Example D5

\( \text{1-\{c/s-ri-Phenyl-4-(4-phenylpiperazin-1-yl)cyclohexyn)methanamine dihydrochloride and 1-\{\text{trans-H-phenyl-4-(4-phenylpiperazin-1-yl)cyclohexyn)methanamine dihydrochloride}\} } \)
The title compounds were prepared analogously as described in Example D1 using phenylacetonitrile instead of 3-chlorophenylacetonitrile and 1-phenylpiperazin instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

TR [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.32 and 4.43 min.

**Example D6**

1-1c′/s-r4-(4-tert-Butylpiperidin-1-v0-1-phenylcyclohexyl)methanamine and \(\Lambda^{\text{trans}}\)-(4-tert-butylpiperidin-1-yl)-1-phenylcyclohexyl)methanamine

The title compounds were prepared analogously as described in Example D1 using phenylacetonitrile instead of 3-chlorophenylacetonitrile and 4-tert-butylpiperidin instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

TR [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.95 and 5.10 min.

**Example D7**

1-{c/s-r4-(4-Methylpiperidin-1-v0-1-phenylcyclohexyl)lilmethanamine dihydrochloride and 1-\{(trans-f4-(4-methylpiperidin-1-yl)-1-phenylcyclohexyn)methanamine dihydrochloride}

The title compounds were prepared analogously as described in Example D1 using phenylacetonitrile instead of 3-chlorophenylacetonitrile and 4-tert-butylpiperidin instead of S-trifluoromethyl-S,\(\beta\),\(\delta\)-tetrahydro-\(\Pi^\beta\)triazolo [4,S-alpyrazine, and were isolated as a mixture of diastereoisomers.

TR [HPLC, Higgins Cliqueus Smicron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.25 and 3.57 min.
Example D8

1'-lc/s-f4-(4-Benzylpiperidin-1-yl)-1-O-chlorophenylcyclohexylmethanamine dihydrochloride and 1-(trans-f4-f4-benzylpiperidin-1-yl)-1-(3-chlorophenyl)cyclohexylmethanamine dihydrochloride

The title compounds were prepared analogously as described in Example D1 using 4-benzylpiperidine instead of S-trifluoromethyl-S.ej. δ-tetrahydro-1H^[triazoloKPS-alpyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^+\)): 397, 399 [M+H]\(^+\).

T\(_R\) [HPLC, Higgins Cilpeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.75 and 4.87 min.

Example D9

1'-c/s-f4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-1.4'-bipiperidin-2-one dihydrochloride and 1'-lftrans^-faminomethylM-O-chlorophenvDcyclohexynVI,^-bipiperidin-2-one dihydrochloride.

The title compounds were prepared analogously as described in Example D1 using \([1,4\]"bipiperidinyl-2-one instead of S-trifluoromethyl-S.ej. δ-tetrahydro-1H^[triazoloKPS-alpyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^+\)): 404, 406 [M+H]\(^+\).

T\(_R\) [HPLC, Higgins Cilpeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.31 min.

Example D10

1-{1-rc/s-r4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexynpiperidin-4-vn)pyrrolidin-2-one dihydrochloride and 1'-lftrans-(aminomethylO-4-(3-chlorophenyl)cyclohexynpiperidirHt-ylDpyrrolidin-2-one dihydrochloride.

The title compounds were prepared analogously as described in Example D1 using 1-piperidin-4-yl-pyrrolidin-2-one instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^+\)): 390, 392 [M+H]\(^+\).
The title compounds were prepared analogously as described in Example D1 using 4-imidazol-1-yl-piperidine instead of S-trifluoromethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES⁺): 373, 375 [M+H]⁺.

The title compounds were prepared analogously as described in Example D1 using piperidine-3-carboxamide instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


The title compounds were prepared analogously as described in Example D1 using piperazine-1-v pvclohexyn>methanamine hydrochloride and 1-(frans-ri-(3-chlorophenyl)-4-(2-phenylethyl)piperazin-1-yl)cvclohexyn>methanamine hydrochloride and 1-(frans-ri-(3-chlorophenyl)-4-(2-phenylethyl)piperazin-1-v pvclohexyn>methanamine hydrochloride and 1-(frans-ri-(3-chlorophenyl)-4-(2-phenylethyl)piperazin-1-ylicvclohexyrDmethanamine hydrochloride
The title compounds were prepared analogously as described in Example D1 using 1-phenethyl-piperazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


TR [HPLC, Higgins Clupeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.91 and 4.41 min.

**Example D14**

1-(c/s-f1-O-Chlorophenyl)-4-r4-(2-furoyl)piperazin-1-yicyclohexylmethanamine hydrochloride and 1-ftrans-M-(3-chlorophenyl)-4-f4-(2-furoyl)piperazin-1-yicyclohexylmethanamine hydrochloride.

The title compounds were prepared analogously as described in Example D1 using 1-(2-furoyl)-piperazine instead of S-trifluoromethyl-S,β,7,β-tetrahydro-Il^4^triazolo^4^S-a]pyrazine, and were isolated as a mixture of diastereoisomers.


TR [HPLC, Higgins Clupeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 2.88 and 3.53 min.

**Example D15**

1-(c/s-M-(3-Chlorophenyl)-4-(4-pyrimidin-2-yl)piperazin-1-vicyclohexylDmethanamine dihydrochloride and 1-ftrans-M-(3-chlorophenyl)-4-(4-pyrimidin-2-yl)piperazin-1-vicyclohexylDmethanamine dihydrochloride.

The title compounds were prepared analogously as described in Example D1 using 2-piperazin-1-yl-pyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1 ,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


TR [HPLC, Higgins Clupeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.60 and 3.84 min.

**Example D16**
1-fc/s-ri-(3-Chlorophenyl)-4-(4-pyrazin-2-ylpiperazin-1-yl)cyclohexylmethylamine dihydrochloride and 1-AtransAλ-(3-chlorophenyl)-4-(4-pyrazin-2-ylpiperazin-1-yl)cyclohexylmethylamine dihydrochloride.

The title compounds were prepared analogously as described in Example D1 using 3,4,5,6-tetrahydro-2H-[1,2']bipyrazine instead of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


Example D17

1-(cis-(1-(3-Chlorophenyl)-4-f2-fluoro-4-(methylsulfonyl)phenyl)piperazin-1-yl)cyclohexyl)methanamine dihydrochloride and 1-(trans-(1-(3-chlorophenyl)-4-f2-fluoro-4-(methylsulfonyl)phenyl)piperazin-1-yl)cyclohexyl)methanamine dihydrochloride.

The title compounds were prepared analogously as described in Example D1 using 1-(2-fluoro-4-methanesulphonyl-phenyl)-piperazine instead of S-trifluoromethyl-S,6,7,β-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES⁺): 480, 482 [M+H]⁺.

Example D18

1-(c/s-(1-r4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl)piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one dihydrochloride and 1-(fra/is-(1-f4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyl)piperidin4-yl)-1,3-dihydro-2H-benzimidazol-2-one dihydrochloride.

The title compounds were prepared analogously as described in Example D1 using 1-piperidin-4-yl-1,3-dihydro-benzimidazol-2-one instead of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

Example D19


The title compounds were prepared analogously as described in Example D1 using 2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone instead of 3-trifluoromethyl-8,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^{+}\)) : 418, 420 [M+H]\(^{+}\).

Example D20

1-(Cfs-M-(3-Chlorophenyl)-4-f 3.4-dihydroisoquinolin-2f-(1H)-yl)cyclohexyl)methanamine hydrochloride and [H]frans-M-(3-chlorophenyl)-4-(3.4-dihydroisoquinolin-2(1H)-yD)cyclohexyl)methanamine hydrochloride.

The title compounds were prepared analogously as described in Example D1 using 1,2,3,4-tetrahydroisoquinoline instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^{+}\)) : 355, 357 [M+H]\(^{+}\).

Example D21

1-fc/s-11-(3-ChlorophenylM-f 4-r4-(trifluoromethyl)pyrimidin-2-vnpiperazin-1-yl)cyclohexyl)methanamine hydrochloride and [H]frans-(1-(3-chlorophenyl)-4-(4-r4(trifluoromethyl)pyrimidin-2-vnpiperazin-1-yl)cyclohexyl)>methanamine hydrochloride.
The title compounds were prepared analogously as described in Example D1 using 2-piperazin-1-yl-4-trifluoromethyl-piperidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^+\)) \(454, 456\) [M+H\(^+\)].

\(T_R\) [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.46 min.

**Example D22**

Wc/s-r4-(Aminomethyl)-4-f3-chlorophenyl)cyclohexyn>-1.4-diazepan-5-one hydrochloride and 1-[c/s-r4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyn]-1.4-diazepan-5-one hydrochloride

The title compounds were prepared analogously as described in Example D1 using \([1,4]\)-diazepan-5-one instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^+\)) \(336, 338\) [M+H\(^+\)].

\(T_R\) [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.11 and 1.16 min.

**Example D23**

1-(c/s-(1-f3-Chlorophenyl)-4-f4-fluoro-2-(methylsulfonyl)phenyl)piperazin-1-ylicyclohexyl)methanamine hydrochloride and 1-[trans-(1-(3-chlorophenyl)-4-f4-fluoro-2-(methylsulfonyl)phenyripiperazin-1-yl)cyclohexyl]methanamine hydrochloride.

The title compounds were prepared analogously as described in Example D1 using 1-(4-fluoro-2-methanesulphonyl-phenyl)piperazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES\(^+\)) \(480, 482\) [M+H\(^+\)].

\(T_R\) [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.57 and 4.75 min.

**Example D24**
The title compounds were prepared analogously as described in Example D1 using 4-
[1,2,4]triazol-1-yl-piperidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-
a]pyrazine, and were isolated as a mixture of diastereoisomers.

MS (ES+): 374, 376 [M+H]+.

TR [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 2.81 min.

Example D25
4-(c/s-r4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl)piperazine-2-one

The title compound was prepared analogously as described in Example D1 using piperazine-
2-one instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES+): 322, 324 [M+H]+.

TR [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.13 min.
The title compound was prepared analogously as described in Example D1 using piperazine-2-one instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES^+): 322, 324 [M+H]^+.

Example D28

1-fl/-4-(4-Morpholin^-yl)-1-phenylcyclohexyDmethanamine dihydrochloride and 1-(frans^-morpholin^-yl)-1-phenylcyclohexy Ornethanamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 1-phenyl-4-oxo-cyclohexanecarbonitrile instead of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile and morpholine instead of S-trifluoromethyl-S,β,7,δ-tetrahydro-li^-triazolo^-S-aJpyrazine, and were isolated as a mixture of diastereoisomers.


Example D29

1-Fc/s-4-(4-Methylpiperazin-1-yl)-1-phenylcyclohexyOrmethanamine dihydrochloride and 1-rfrans-4-(4-methylpiperazin-1-yl)-1-phenylcyclohexynmethanamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 1-phenyl-4-oxo-cyclohexanecarbonitrile instead of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile and 1-methyl-piperazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1 ,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


Example D30
The title compound was prepared analogously as described in Example D1 using 1-phenyl-4-oxo-cyclohexanecarbonitrile instead of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile and cyclohexylamine instead of S-trifluoromethyl-δ,6,7,δ-tetrahydro-[1,2,4]triazolo[K,3-ajpyrazine, and were isolated as a mixture of diastereoisomers.


TR [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 2.99 and 4.39 min.

**Example D31**

H c/s^A-Azepan-1-yl-1-phenylcyclohexylmethanamine dihydrochloride and H trans-4-azepan-1-yl-1-phenylcyclohexylmethanamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 1-phenyl-4-oxo-cyclohexanecarbonitrile instead of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile and azepane instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


TR [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.36 min.

**Example D32**

Benzyl 4-rc/s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexylpiperazine-1-carboxylate hydrochloride and benzyl 4-frans-4-(aminomethyl)-4-(3-chlorophenylicyclohexylpiperazine-1-carboxylate hydrochloride

The title compound was prepared analogously as described in Example D1 using piperazine-1-carboxylic acid benzyl ester instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.


TR [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.40 min.
Example D33
c:s^-(Ami π omethylM-(3^hlorophenyl)-N-r(1,5-dimethyl-1H-pyrazol-3-
vDmethvncyclohexanamine dihydrochloride and fra/is-4-(aminomethyl)-4-(3-
chlorophenvD-N-rd.S-dimethyl-IH-pyrazol-S-vDmethvncvclohexanamine
dihydrochloride

The title compound was prepared analogously as described in Example D1 using C-(1,5-
dimethyl-1 H-pyrazol-3-yl)-methylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine, and were isolated as a mixture of diastereoisomers.
T_R [HPLC, Higgins Cilpeus 5 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.18 min.

Example D34
1-rc/s-4-f3-(Trifluoromethyl)-5,6-dihydron.2.4ltriazolor4.3-a1pyrazin-7(8H)-vn-1-(2.4.5-
trifluorophenvDcvclohexylimethanamine hydrochloride and 1-ffrans-4-f3-
(trifluoromethvn-5,6-dihvdrori,2.4ltriazolor4.3-a1pyrazin-7(8H)-vn-1-(2,4,5-
trifluorophenvDcvclohexynmethanamine hydrochloride

The title compound was prepared analogously as described in Example D1 using 4-oxo-1-
(2,4,5-trifluorophenyl)-cyclohexanecarbonitrile instead of 1-(3-chlorophenyl)-4-oxo-
cyclohexanecarbonitrile, and were isolated as a mixture of diastereoisomers.
T_R [HPLC, Higgins Cilpeus 5 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.40 and 5.93 min.

Example D35
1-(3-(rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cvclohexynamino)propyl)pyrrolidine-2.5-
dione hydrochloride

The title compound was prepared analogously as described in Example D1 using 1-(3-
amino-propyl)-pyrrolidine-2,5-dione instead of S-trifluoromethyl-S,β,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine.
Example D36
1-(3-(r<rans-4-(Aminomethyl)H-4-(3-chlorophenyl)cyclohexynamino)propyl)pyrrolidine-2,5-dione hydrochloride

The title compound was prepared analogously as described in Example D1 and D2 using 1-(3-amino-propyl)-pyrrolidine-2,5-dione instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-\([1,2,4]\)triazolo[4,3-a]pyrazine.

MS (ES\(^{+}\)): 378, 380 [M+H]\(^{+}\).

Example D37
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexytetrahydro-2H-pyran-4-amine hydrochloride and N-rfrans\(^{\ast}\)aminomethylIM-O-chlorophenvDcyclohexylltetrahydro-2H-pyran-4-amine hydrochloride

The title compounds were prepared analogously as described in Example D1 using tetrahydropyran-4-ylamine instead of S-trifluoromethyl-\(\delta\),\(\delta\)-tetrahydro-\([4,3-a]\)pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES\(^{+}\)): 378, 380 [M+H]\(^{+}\).

Example D38
c/s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-r(1-methyl-1H-imidazol-4-vDmethylicyclohexanamine hydrochloride

The title compound was prepared analogously as described in Example D1 using C-(1-methyl-1H-imidazol-4-yl)-methylamine instead of S-trifluoromethyl-S,\(\delta\),\(\delta\)-tetrahydro-\([1,2,4]\)triazolo[4,3-a]pyrazine.
Example D39

**fra/?s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-r(1-methvt-1H-imidazol-4-vDmethylicyclohexanamine hydrochloride**

The title compound was prepared analogously as described in Example D1 and D2 using C-(1-methyl-1H-imidazol-4-yl)-methylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(^{+}\)) : 333, 335 [M+H]\(^{+}\).

T\(_R\) [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\(_2\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.19 min.

Example D40

**c/s-4-(AminomethylM<-3-chlorophenyl>-N-(2-phenylethyl)cvclohexanamine hydrochloride and trans-4-(aminornethyl)-4-(3-chlorophenVM-N-(2- phenylethvDcyclohexanamine hydrochloride**

The title compounds were prepared analogously as described in Example D1 using 2-phenylethylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES\(^{+}\)) : 343, 345 [M+H]\(^{+}\).

T\(_R\) [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\(_2\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.22, 4.88 min.

Example D41

**3-rc/s-r4-(AminomethylM>-4-(3-chlorophenyl)cvclohexyn(methyl)amino1propanenitrile hydrochloride and 3-r<ra/is-f4-(aminomethylIM-(3- chlorophevOcyclohexylKmethvDaminolpropanenitrile hydrochloride**
The title compounds were prepared analogously as described in Example D1 using 3-ethylamino-propionitrile instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.13 min.

Example D42

c/s-4-(Aminomethyl)-N-benzyl-4-(3-chlorophenyl)cyclohexanamine hydrochloride and
trans-4-(aminomethyl-N-benzyl-4-f3-chlorophenyl)cyclohexanamine hydrochloride

The title compounds were prepared analogously as described in Example D1 using benzylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.54, 3.61 min.

Example D43

c/s-4-(AminomethylM-(3-chlorophenyl)-N-(cyclopropylmethyl)cyclohexanamine hydrochloride and
trans-4-(aminomethyl-N-(cyclopropylmethyl)-4-(3-chlorophenyl)-N-(cyclopropylmethyl)cyclohexanamine hydrochloride

The title compounds were prepared analogously as described in Example D1 using cyclopropyl-methylamine instead of S-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES⁺): 293, 295 [M+H]⁺.

Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.85 min.

Example D44

1-(cfs-li - (3-Chlorophenyl)-4-r4-(3-phenylpropyl)piperazin-1 - yl)cyclohexyrUmethanamine hydrochloride and 1-ffrans-M-(3-chlorophenyl)-4-r4-(3-phenylpropyl)piperazin-1-vncvclohexyn>methanamine hydrochloride
The title compounds were prepared analogously as described in Example D1 using 1-(3-phenyl-propyl)-piperazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.

**Example D45**

1-\textit{c/s}-f\textit{1}-(3-Chlorophenyl)-4-f\textit{4}-(2-methoxyethyl)piperazin-1-\textit{v}ncyclohexylDmethanamine \textit{hydrochloride and 1-ffrans-H(3-chlorophenvO-4-f\textit{4}-(2-methoxyethyl)piperazin-1-yl}cyclohexy \textit{π}methanamine \textit{hydrochloride}

The title compounds were prepared analogously as described in Example D1 using 1-(2-methoxyethyl)-piperazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES\textsuperscript{+}): 366, 368 [M+H]\textsuperscript{+}.

**Example D46**

1-\textit{rc/s-f4-r4-f1.3-Benzodioxol-5-ylmethyl)piperazin-1-yl}i-\textit{(3-chlorophenyl)cyclohexylVlmethanamine \textit{hydrochloride and 1-lffrans-(4-r4-(1.3-benzodioxol- δ-ylmethyl)piperazin-i-vn-i-O-chlorophenylcyclohexylDimethanamine \textit{hydrochloride}}

The title compounds were prepared analogously as described in Example D1 using C-cyclopropyl-methylamine instead of S-trifluoromethyl-S,β,7,δ-tetrahydro-\textit{t}i^{\\text{4.S-a}]pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES\textsuperscript{+}): 442, 444 [M+H]\textsuperscript{+}.

**Example D47**
c/s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-(2-thienylmethyl)cyclohexanamine hydrochloride and trans-4-(aminomethyl)-4-(3-chlorophenyl)-N-(2-thienylmethyl)cyclohexanamine hydrochloride

The title compounds were prepared analogously as described in Example D1 using C-thiophen-2-yl-methylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.40, 4.47 min.

Example D48

4-(c/s-r4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexynamino)butan-1-ol hydrochloride and 4-\{trans-r4-(aminomethyl)-4-(3-chlorophenyl)cyclohexynamino\>butan-1-ol hydrochloride

The title compounds were prepared analogously as described in Example D1 using 4-aminobutan-1-ol instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES⁺): 311, 313 [M+H]⁺.

Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.54 min.

Example D49

c/s-4-(Aminomethyl)M-(3-chlorophenyl)-N-r3-(1H-imidazol-1-y)propylcyclohexanamine hydrochloride and trans-4-(aminomethyl)-4-(3-chlorophenyl) π-N-rS-dH-imidazol-i-vDpropy πcyclohexanamine hydrochloride

The title compounds were prepared analogously as described in Example D1 using 3-imidazol-1-yl-propylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.09, 1.31 min.
Example D50

c/s-4-aminomethyl-(3-chlorophenyl)-N-(2-phenoxyethyl)cyclohexanamine hydrochloride and frans-4-(aminomethyl)-4-(3-chlorophenyl)-N-(2-phenoxyethyl)cyclohexanamine hydrochloride

The title compounds were prepared analogously as described in Example D1 using 2-phenoxy-ethylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and were isolated as a mixture of diastereoisomers.

MS (ES⁺): 359. 361 [M+H⁺].

Tᵣ [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.06, 4.71 min.

Example D51

1-[(c/s-1-(3-Chlorophenyl)-4-r2-cyclopropyl-4-(trifluoromethyl)-5.8-dihydropyridin-7(6H)-yl)-cvclohexyl)methanamine hydrochloride

The title compound was prepared analogously as described in Example D1 using 2-cyclopropylM-trifluoromethyl-S.ej. δ-tetrahydro-pyrido[3^-dpyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES⁺): 465 [M+H⁺].

Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.75 min.

Example D52

i-lfrans-i-O-ChlorophenylM-f 2-cyclopropyM-fr trifluoromethyD-S.8-dihydropyridors.\n\n\n\n\n\n\n\ncf|pyrimidin-7(6H)-v πcvclohexyl)methanamine hydrochloride

The title compound was prepared analogously as described in Examples D1 and D2 using 2-cyclopropyM-trifluoromethyl-S.ej. δ-tetrahydro-pyrido^dpyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES⁺): 465 [M+H⁺].

Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.64 min.
Example D53
2-(rc/s-4-(AminomethylV4-(3-chlorophenyl)cyclohexynamino)ethanol hydrochloride
and 2-fffra/7s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyriamino)ethanol
hydrochloride

The title compound was prepared according to Scheme D.

A) A mixture of fc/s/^n-fert-butyl-dimethyl-silanyloxyVethylaminoi-i-O-chloro-phenyl)-
cyclohexylmethylT-carbamic acid tert-butyl ester and ffrans-4-r2-(tert-butyl-dimethyl-
silanyloxy)-ethylaminol-1-(3-chloro-phenyl)-cyclohexylmethyπ-carbamic acid tert-butyl ester

The title compounds were prepared analogously as described in Example D1 using 2-(tert-
butyl-dimethyl-silanyloxy)-ethyamineinstead of 3-trifluoromethyl-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine and were obtained as a mixture of diastereoisomers.
T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_2CN+0.1%Formic acid/H_2O+0.1%
Formic acid for 5 min, flow 2.0 ml/min]: 2.99, 3.09 min.

B) A mixture of fc/s-1-(3-chloro-phenyl)-4-(2-hydroxy-ethylamino)-cyclohexylmethyri-
carbamic acid tert-butyl ester and [frans-1-(3-chloro-phenyl)-4-(2-hydroxy-ethylamino)-
cyclohexylmethyl]-carbamic acid tert-butyl ester

A mixture of [c/s-4-[2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-1-(3-chloro-phenyl)-
cyclohexylmethyl]-carbamic acid tert-butyl ester and [frans-4-[2-(tert-butyl-dimethyl-
silanyloxy)-ethylamino]-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester
(60mg, 0.121mmol) in tetrahydrofuran (3mL) was treated with a 1M solution of tetrabutyl
ammonium fluoride in tetrahydrofuran (240µL) and the mixture was stirred at room
temperature for 2 hours. The mixture was quenched with ammonium chloride (aq) and
extracted into dichloromethane (2x30ml). The combined extracts were washed with water
and brine, dried (MgSO_4) and concentrated. The residue was purified by automated flash
chromatography (Silica (4g), eluting 0%-20% methanol in dichloromethane) to give a mixture
of the title compounds as a colourless oil.
MS (ES^+): 327 [M+H-tBu]
T<sub>R</sub> [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH<sub>3</sub>CN+0.1%Formic acid/H<sub>2</sub>O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 2.31, 2.41 min.

C) 2-ffc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexylamino)ethanol hydrochloride and 2-(rfrans-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexynamino)ethanol hydrochloride

A mixture of [c/s-1-(3-chloro-phenyl)-4-(2-hydroxy-ethylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester and [frans-1-(3-chloro-phenyl)-4-(2-hydroxy-ethylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester (49mg, 0.128mmol) in trifluoroacetic acid (1mL) and dichloromethane (3mL) was stirred at room temperature for 2hours. The reaction mixture was applied to an SCX-2 ion exchange column and eluted sequentially with dichloromethane, methanol and a 2M solution of ammonia in methanol. Final purification was achieved using preparative reversed phase HPLC (acetonitrile/water containing 0.1% trifluoroacetic acid) and after treatment with excess hydrogen chloride in methanol the title compounds were obtained as a mixture of diastereoisomers.

MS (ES<sup>+</sup>): 283 [M+H]<sup>+</sup>.

T<sub>R</sub> [HPLC, Higgins Clupeus 5 micron C18; 5-95% CH<sub>3</sub>CN+0.1%Formic acid/H<sub>2</sub>O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.17 min.

**Example D54**

1-fc/s-1-(3-Chlorophenyl)-4-r4-cyclopropyl-2-(trifluoromethyl)-5,8-dihydropyrido3.4-dipyrimidin-7(6H)-π cyclohexyl)methanamine hydrochloride

The title compound was prepared analogously as described in Example D1 using 4-cyclopropyl-2-trifluoromethyl-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES<sup>+</sup>): 465 [M+H]<sup>+</sup>.

T<sub>R</sub> [HPLC, Higgins Clupeus 5 micron C18; 5-95% CH<sub>3</sub>CN+0.1%Formic acid/H<sub>2</sub>O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.80 min.

**Example D55**

1-{frans-1-(3-Chlorophenyl)-4-r4-cyclopropyl-2-(trifluoromethyl)-5.8-dihydropyrido3.4-dlpyrimidin-7(6H)-π cyclohexyl)methanamine hydrochloride
The title compound was prepared analogously as described in Example D1 using 4-cyclopropyl^-trifluoromethyl-S. β,7.δ-tetrahydro-pyrdo[1,5-d]pyrimidine instead of 3-trifluoromethyl-δ.e,7,β-tetrahydro-1^4triazolo^5,S-alpyrazine.


T_R [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.80 min.

Example D56

C-r8-(2,4-Difluoro-phenyl)-1,4-dioxa-spiror4.51dec-8-vn-methylamine

The title compound was prepared analogously as described in Example D1 step A to step E using 2,5-difluorophenylacetonitrile instead of 3-chlorophenylacetonitrile.


HPLC (Zorbax SB C18, 2min method (0-0.8min 10-95%ACN, 0.8-1.5min 95%ACN, 1.5-1.6min 95-10%ACN, 1.6-2min 10%ACN): 1.1 13 min.

Example D57

C-ri-(4-Methyl-pyridin-2-yl)-4-(3-trifluoromethyl-5.6-dihvdro-8H-n,2,41triazolof4.3-a1pyrazin-7-yl)-cvclohexyn-methylamine

The title compound was prepared analogously as described in Example D1 using (4-Methyl-pyridin-2-yl)-acetonitrile instead of 3-chlorophenylacetonitrile.


HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.55-6min 5%ACN): 3.39 min.

Example D58

C-(1-Phenyl-4-piperidin-1-y1-cvclohexyl)-methylamine

The title compounds were prepared analogously as described in Example D3 using piperidine instead of 4-benzylpiperidine and were isolated as a mixture of diastereoisomers.


T_R [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.27-3.24 min.
Example D59
C-f11-Phenyl-4-pyrrolidin-1-yl-cyclohexyl-methylamine

The title compounds were prepared analogously as described in Example D3 using pyrrolidine instead of 4-benzylpiperidine and were isolated as a mixture of diastereoisomers. MS (ES\(^+\)): 259 [M+H]\(^+\). TR [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.15 min.

Example D60
C-H-(3-Chloro-phenyl)-4-piperazin-1-yl-cyclohexyl-methylamine

To a solution of 4-[4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-piperazine-1-carboxylic acid benzyl ester (Example 32, 37 mg, 0.083 mmol) in acetic acid (1 mL) is added a 33% hydrogen bromide solution in acetic acid (0.1 mL) before stirring at rt for 1.5 hours. The solution is passed through an SCX-2 column and eluted with DCM, methanol and 2M ammonia in methanol before evaporation and purification by preparative reversed phase HPLC (acetonitrile/water containing 0.1% trifluoroacetic acid) to give a mixture of the two isomers. MS (ES\(^+\)): 308 [M+H]\(^+\). TR [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 1.17 min.

Example D61
r4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-phenethyl-amine

The title compounds were prepared analogously as described in Example D3 using phenylethylamine instead of 4-benzylpiperidine and were isolated as a mixture of diastereoisomers. MS (ES\(^+\)): 343-345 [M+H]\(^-\). TR [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.22-4.88 min.

Example D62
1Atrans-\(\Lambda\)-(3-Methylphenyl)-4-r3-(trifluoromethyl)-5.6-dihydrori ... 4.94 min.

Example D65

2-fc/s'-4-(AminomethylM-(3-chlorophenyl)cvclohexy π amino)ethanol dihydrochloride
The title compound was prepared analogously as described in Example D1 using 1-Amino-2-ethanol instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.57 min.

Example D66
4-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylamino-1-butyric acid methyl ester dihydrochloride

The title compound was prepared analogously as described in Example D1 using Methyl-4-amino butyrate hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.80 min.

Example D67
(3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylamino-1-propyl)-carbamic acid benzyl ester hydrochloride

The title compound was prepared analogously as described in Example D1 using N-CBZ-1,3-diamino propane instead of S-trifluoromethyl-S,β,7,δ-tetrahydro-triazolo-S,a]pyrazine.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.29 min.

Example D68
[2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylamino-1-ethyl]-carbamic acid benzyl ester hydrochloride
The title compound was prepared analogously as described in Example D1 using N-CBZ-1,3-diamino ethane instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 416 [M+H]\(^+\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.25 min.

**Example D69**

\(1-(\text{trans}-1-O\text{-Chloro-phenyl})-4-(2\text{-trifluoromethyl-5,6-dihydro-8H-M}_\text{2.41triazoloH.5-aipyzrazin-7-v }\pi\text{-cyclohexyry-methylamine dihydrochloride}\)

The title compound was prepared analogously as described in Example D1 and D2 using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 414 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.75 min.

**Example D70**

\(1-fcis-1-(3\text{-Chloro-phenyl}-4-f2\text{-trifluoromethyl-5,6-dihydro-8H-n}_\text{2.4UrJaZoloM.5-a1pyrazin-7-v }\pi\text{-cyclohexylyl}-methylamine dihydrochloride}\)

The title compound was prepared analogously as described in Example D1 using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 414 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

**Example D71**

\(1-Fcis-1-(3\text{-Chloro-phenyl})-4-(7\text{-methyl-3-trifluoromethyl-7,8-dihydro-ri}_\text{2.41triazolor4.3-cipvrimidin-6-vh-cyclohexvn-methylamine dihydrochloride}\)
The title compound was prepared analogously as described in Example D1 using 7-Methyl-S-trifluoromethyl-S.β.δ-tetrahydro-1H^-triazolo^-S^-clpyrimidine instead of 3-trifluoromethyl-S.e.T.δ-tetrahydro-1H^-triazolo^-S^-alpyrazine.

**MS (ES^+):** 428 [M+H]^+. 
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.88 min.

**Example D72**

1-rtrans-1-(3-Chloro-phenyl)-4-f7-methvt-3-trifluoromethyl-7.8-dihvdro-ri,2,41triazolor4.3-cipyrimidin-6-yl) cvclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 and D2 using 7-Methyl-3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-c]pyrimidine instead of 3-trifluoromethyl-δ.β.δ-tetrahydro-1H^-triazolo^-S^-alpyrazine.

**MS (ES^+):** 428 [M+H]^+. 
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.80 min.

**Example D73**

1-lcis-1-f3-Chloro-phenyl]-4-(7-ethyl-3-trifluoromethyl-7.8-dihvdro-ri .2.41triazolor4.3- c1pyrimidin-6-yl) cvclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 7-Ethyl-3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-c]pyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

**MS (ES^+):** 442 [M+H]^+. 
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.10 min.

**Example D74**
1-rtrans-1-(3-Chloro-phenyl-4-f7-ethyl-3-trifluoromethyl-7,8-dihydro-n,2,41triazolor4,3-clpyrimidin-6-yl)-cyclohexyll-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 and D2 using 7-Ethyl-3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-c]pyrimidine instead of 3-trifluoromethyl-5,6,7,δ-tetrahydro-ll^δtriazolo^,S-alpyrazine.

MS (ES^+): 442 [M+H]^+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.01 min.

Example D75
1-rcis-1-(3-Chloro-phenyl)-4-(4-cyclopropyl-2-methoxy-5,8-dihydro-6H-pyridor3.4-d1pyrimidin-7-yl)-cyclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 4-Cyclopropyl^-methoxy-S,ej. δ-tetrahydro-pyrido[3^δ-dlpyrimidine instead of 3-trifluoromethyl-δ,6,7,δ-tetrahydro-ll^δtriazolo^,S-alpyrazine.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.70 min.

Example D76
(-7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-4-cyclopropyl-5,6,7, 8-tetrahydro-pyridor3.4-d1pyrimidin-2-yl>-dimethylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using (4-Cyclopropyl-S,6,7,δ-tetrahydro-pyridoIS^δ-dlpyrimidin^-yO-dimethyl-amine instead of 3-trifluoromethyl-5,6,7, δ-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.


HPLC (Nucleosil C-16HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.93min.

Example D77
rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-2-(3-methanesulfonyl-phenyl)-ethyli-amine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 2-(3-Methanesulfonyl-phenyl)-ethylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.50 min.

Example D78
rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-(4-methanesulfonyl-benzyl)-amine dihydrochloride

The title compound was prepared analogously as described in Example D1 using A-Methanesulfonyl-benzylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.33 min.

Example D79
6-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-methyl-5,6,7,8-tetrahvdro-pyrido[4,3-d]pyrimidin-2-ylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 4-Methyl-s,6,7,8-tetrahydro-pyrido[4,5-d]pyrimidin^ylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 2.90 min.

Example D80
1-rcis-1-(3-Ethynyl-phenyl)-4-(3-trifluoromethyl-5,6-dihydro-8H-ri,2,4tri
azolor4,3-aipyrazin-7-yl)-cyclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 3-Ethynyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile.

MS (ES\(^+\)): 404 [M+H\(^+\)].

HPLC (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.44 min.

Example D81
i-rcis-i^-Methyl-pyridin-2-yl-M-O-trifluoromethyl- δ,δ-dihydro-SH-ri. 2,4itriazolor4,3- a1pyrazin-7-yl)-cyclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using (4-Methyl-pyridin-2-yl)-acetonitrile instead of 3-Chlorophenylacetonitrile.

MS (ES\(^+\)): 395 [M+H\(^+\)].

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 0.89 min.

Example D82
(6-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-methyl-5.6.7.8-tetrahydro- Pyridor4,3-d1pyrimidin-2-yl)-cyclopropylmethyl-amine dihydrochloride

The title compound was prepared analogously as described in Example D1 using Cyclopropylmethyl-(4-methyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl)-amine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 440 [M+H\(^+\)].

HPLC (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.36 min.

Example D83
1^-trans-1-(3-Methylphenyl)M-r3-(trifluoromethvn-5.6-dihydroF1,2,4itriazolor4,3- a1pyrazin-7(8H)-vncyclohexyl)methanamine dihydrochloride
The title compound was prepared analogously as described in Example D1 and D2 using 3-Methyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile and using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.72 min.

**Example D84**
1-(cis-1-(3-Methylphenyl)-3-(trifluoromethyl)-5,6-dihydrof1,2,41triazolor4,3-a1pyrazin-7(8H)-yllcvclohexyl)methanamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 3-Methyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile and using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.82 min.

**Example D85**
2-trtrans-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-2.3-dihvdro-isoindol-1-one dihydrochloride

The title compound was prepared analogously as described in Example D1 and D2 using 2-carbomethoxybenzylamine hydrochloride instead of S-trifluoromethyl-S,β,7,δ-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES⁺): 355 [M+H].
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.57 min.

**Example D86**
2-fcis^4-Arinomethyi=4-f3-eh!oro-phenvπ -cvclohexy π -2.3-dihvdro-isoindol-1-one dihydrochloride
The title compound was prepared analogously as described in Example D1 using 2-carbomethoxybenzylamine hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.44 min.

Example D87

1-rcis-1-(5-Chloro-2-fluoro-phenyl)-4-(2-trifluoromethyl-5,6-dihydro-8H-ri..triazolo.S-aipyrazin-Z-v π-cyclohexylπ-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 5-Chloro-2-fluorophenylacetonitrile instead of 3-Chlorophenylacetonitrile.
MS (ES+): 432 [M+H]+.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.79 min.

Example D88

1-rcis-i-O-Chloro-phenylM-IS. β-dirivdro-8H-ri. 2^triazolori.S-aipyrazin-y-vn- cyclohexyli-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1^triazolo^S-aPyrazine.
HPLC (Zorbax SB C18, 2min method (0-0.8min 10-95%ACN, 0.8-1.5min 95%ACN, 1.5-1.6min 95-10%ACN, 1.6-2min 10%ACN): 0.3 min.

Example D89

1-trans-1-(3-Chloro-phenyl)-4-(5. β-dirivdro-8H-ri. 2^triazoloπ .5-alpyrazin-7-yl)-cyclohexyli-methylamine dihydrochloride
The title compound was prepared analogously as described in Example D2 using 5,6,7,8-Tetrahydro-1,2,4-triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 346 [M+H]\(^+\).

HPLC (Zorbax SB C18, 2min method (0-0.8min 10-95%ACN, 0.8-1.5min 95%ACN, 1.5-1.6min 95-10%ACN, 1.6-2min 10%ACN): 0.25 min.

**Example D90**

1-rtrans-1-(3-Chloro-phenyl)-4-[5,6-dihydro-8H-F1,2,4]triazolo[4,3-a]pyrazin-7-yl)cyclohexyli-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D2 using 5,6,7,8-Tetrahydro-1,2,4-triazolo[4,3-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 346, 348 [M+H]\(^+\).

HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95%ACN, 5.55-6min 5%ACN): 3.09 min.

**Example D91**

1-fcis-1-l3-Chloro-phenyn-4-(5,6-dihydro-8H-Ri,2,4)triazolor4,3-alpyrazin-7-yl)cyclohexyli-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 5,6,7,8-Tetrahydro-1,2,4-triazolo[4,3-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine.

MS (ES\(^+\)): 346, 348 [M+H]\(^+\).

HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95%ACN, 5.55-6min 5%ACN): 3.57 min.

**Example D92**

3-J7-r4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5,6,7,8-tetrahvdro

-Pvridor3,4-d1pvrimidin-4-vl>-benzoic acid ethyl ester
The title compound was prepared analogously as described in Example D1 using 3-(5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-benzoic acid ethyl ester instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
MS (ES\(^+\)): 505 [M+H]\(^+\).
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.06 min.

Example D93
1-rtrans-1-(3-Chloro-phenyl)-4-(2-methyl-6,7-dihydro-4H-oxazolo5,4-c1pyridin-5-yl)-cyclohexyl-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D2 using 2-Methyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
MS (ES\(^+\)): 361 [M+H]\(^+\).
HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.55-6min 5%ACN): 3.51 min.

Example D94
1-fcis-1-(3-Chloro-phenyl)-4-(2-methyl-6,7-dihydro-4H-oxazolo5,4-c1pyridin-5-yl)-cyclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 2-Methyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
MS (ES\(^+\)): 362 [M+H]\(^+\).
HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.55-6min 5%ACN): 3.67 min.

Example D95
1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-phenyl-piperazine-2,3-dione dihydrochloride

The title compound was prepared analogously as described in Example D1 using N-(2-Amino-ethyl)-N-phenyl-oxalamic acid ethyl ester instead of 3-trifluoromethyl-5,6,7,8-
tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring after reductive amination step closed itself during workup.


HPLC (Agilent Eclipse XDB-C18, 1.8µm 4.6 x 50mm, 8min method (0-6min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.62 min.

**Example D96**

1-fcis-1-(2,5-Dichloro-phenyl-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo-7-yl)-cyclohexyn-methylamine dihydrochloride

The title compound was prepared analogously as described in Example D1 using 2,5-Dichlorophenylacetonitrile instead of 3-Chlorophenylacetonitrile.


**Example D97**

N-(cis-3-(2-r4-Aminomethy-4-(3-chloro-phenyl)-cyclohexylamino1-ethyl>-phenyl)-methanesulfonamide dihydrochloride

The title compound was prepared analogously as described in Example D1 using N-[3-(2-Amino-ethyl)-phenyl]-methanesulfonamide instead of S-trifluoromethyl-S,6,7,δ-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

**Example D98**

1-rcis-4-(3-Trifluoromethyl-5,6-dihydro-8H-π .2,41triazolor4,3-a1pyrazin-7-yl)-1 -(3-trifluoromethyl-phenyl)cyclohexy π-methylamine difluoroacetate

The title compound was prepared analogously as described in Example D1 using 3-(Trifluoromethyl)-phenylacetonitrile instead of 3-Chlorophenylacetonitrile.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.90 min.

**Example D99**
1-rtrans-4-f-Trifluoromethyl-5,6-dihydro-8H-nitrotriazolo[4,3-a]pyrazin-7-yl)-1-(3-trifluoromethyl-phenyl-cyclohexyll-methylamine

The title compound was prepared analogously as described in Example D2 using 3-(Trifluoromethyl)-phenylacetonitrile instead of 3-Chlorophenylacetonitrile.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.5-6min 5%ACN): 2.81 min.

Example D100
(S)-2-rcis-4-Aminomethyl-4-(3-chloro-phenyl-cyclohexyn-hexahydro-pyridin-2-apyrazin]-1,4-dione dihydrochloride

The title compound was prepared analogously as described in Example D1 using (S)-1-(2-Amino-acetyl)-piperidine-2-carboxylic acid methyl ester instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.55-6min 5%ACN): 2.21 min.

Example D101
2-rtrans-4-Aminomethyl~4-(3-chloro-phenyl)-cyclohexyn-1,4-dihydro-2H-isoquinolin-3-one hydrochloride

The title compound was prepared analogously as described in Example D2 using Methyl-2-aminoethylphenylacetate hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-20%ACN, 5.55-6min 20%ACN): 2.53 min.

Example D102
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-1,4-dihydro-2H-isoquinolin-3-one hydrochloride
The title compound was prepared analogously as described in Example D1 using Methyl-2-aminoethylphenylacetate hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step. MS (ES\(^{+}\)) : 369 [M+H]\. 
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 20-95\%ACN, 3.5-5.5min 95\%ACN, 5.5-5.55min 95-20\%ACN, 5.55-6min 20\%ACN): 2.44 min.

**Example D103**

3-(7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)cyclohexyln-5,6,7,8-tetrahydro-pyridin-3,4-dipyrimidin-4-yl)-benzoic acid trifluoroacetate

The title compound was prepared analogously as described in Example D1 step A to H using 3-(5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-benzoic acid ethyl ester instead of 3-trifluoromethyl-S,β,7,δ-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford 3-{7-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl}-benzoic acid ethyl ester and 3-{7-[4-(tert-Butoxycarbonylamino-methylO\(^{\alpha}\)-trans-S-chloro-phenylo-cyclohexylJ-δ,6,7,δ-tetrahydro-pyridotS\(^{\alpha}\)-dpyrimidin\(^{\alpha}\)-yl]-benzoic acid ethyl ester followed by step

I) 3-[7-f4-(tert-Butoxycarbonylamino-methy π-4-(cis-3-chloro-phenyl)-cyclohexy π-5,6,7,8-tetrahydro-pyrido3,4-d1pyrimidin-4-yl)-benzoic acid

To a solution of 3-{7-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl}-benzoic acid ethyl ester (45mg, 0.067mmol) in tetrahydrofurane (0.7ml) and water (0.3ml) was added Lithium hydroxide (9mg, 0.213mmol) . The mixture was stirred at room temperature for 16h. The reaction mixture was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5\(\mu\)m 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5\%ACN, 2.5-1 2.5min 5-100\%ACN, 12.5-15.0min 100\%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a pale yellow powder.

MS (ES\(^{+}\)) : 577 [M+H]\(^{+}\).

HPLC (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-5\%ACN): 4.77min.
J) 3-f7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-5.6.7.8-tetrahvdro-pyridor3.4-d1pyrimidin-4-yl)-benzoic acid trifluoroacetate

To 3-[7-[4-(tert-Butyloxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl]-benzoic acid (32mg, 0.045mmol) in dioxane (0.3ml) was added 4N hydrogen chloride solution in dioxane (223µl). The reaction mixture stirred at room temperature for 2h, then the dioxane solution was removed with a pipette. The residue was treated with diethyl ether in ultrasonic bath. The etheric phase was removed with a pipette. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-1 2.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.38min.

Example D104
1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-cyclobutyl-piperazine-2,5-dione

The title compound was prepared analogously as described in Example D1 using [(2-Amino-acetyl)-cyclobutyl-amino]-acetic acid ethyl ester hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

Example D105
4-[4-r4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2,5-dioxo-piperazin-1-yl]-piperidine-1-carboxylic acid ethyl ester

The title compound was prepared analogously as described in Example D1 using 4-[(2-Amino-acetyl)-ethoxycarbonylmethyl-amino]-piperidine-1-carboxylic acid ethyl ester
hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step.

MS (ES\(^+\)): 491 [M+H]

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.91 min.

**Example D106**

1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-4-benzyl-piperazine-2,5-dione

The title compound was prepared analogously as described in Example D1 using [(2-Aminoacetyl)-benzyl-amino]-acetic acid ethyl ester instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step.

MS (ES\(^+\)): 426 [M+H]

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.17 min.

**Example D107**

1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-4-(2-methoxy-ethyl)-piperazine-2,5-dione

The title compound was prepared analogously as described in Example D1 using [(2-Aminoacetyl)-(2-methoxy-ethyl)-amino]-acetic acid ethyl ester instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. The open ring closed itself during reductive amination step.

MS (ES\(^+\)): 394 [M+H]

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.84 min.

**Example DA1**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-trifluoromethyl-β,7-dihydro-5H-n.2.41triazolor4.3-aipyrizin-8-one dihydrochloride

The title compound was prepared analogously as described in Example D1 step A to H followed by step
1) 1-(cis-3-Chloro-phenyl)-4-oxo-3-trifluoromethyl-5,6-dihydro-8H-f1,2.4triazolo[4,3-a]pyrazin-7-yl)-cyclohexymethyl-carbamic acid tert-butyl ester

To a solution of [1-(cis-3-Chloro-phenyl)-4-(3-trifluoromethyl-5,6-dihydro-8H- [i^3triazolo^4^-yJ-cyclohexymethylJ-carbamic acid tert-butyl ester (60mg, 0.117mmol) in acetonitrile (1ml) and chloroform (1ml) was added a solution of sodium periodate (103mg, 0.48mmol) in water (1.5ml) and ruthenium dioxide hydrate (1mg, 0.008mmol). The mixture was stirred vigorously for 40mins at room temperature, then cautiously quenched with diethylether (10ml) and diluted with water (10ml). The product was extracted into ethyl acetate. The combined organic extracts were dried over sodium sulfate and filtered over Celite. The filtrate was concentrated in vacuo to give the title compound as a pale yellow solid.

MS (ES\(^+\)): 528 [M+H]\(^+\)

HPLC (Waters Symmetry C18 3.5 \(\mu\)m 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.65 min.

J) 7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-trifluoromethyl-6,7-dihydro-5H-f1,2.4triazolo[4,3-a]pyrazin-8-one dihydrochloride

Trifluoroacetic acid (1mL) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(8-oxo-3-trifluoromethyl-5,6-dihydro-8H-[1,2,4,triazolo[4,3-a]pyrazin-7-y]-cyclohexymethyl]-carbamic acid tert-butyl ester (55mg, 0.104mmol) in dichloromethane (1mL) and the reaction stirred at room temperature for 1h. The reaction mixture was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5 \(\mu\)m 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-18.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

MS (ES\(^+\)): 428 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5 \(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.81 min.
Example DA2

y-r-trans^-Aminomethyl-O-chloro-phenyl \( \pi \)-cyclohexyl-S-trifluoromethyl-6J-dihydro-5H-f1.2^\text{triazolo}M.S-alpyrazin-S-one dihydrochloride

The title compound was prepared analogously as described in Example DA1, step I from [1-(trans-3-Chloro-phenyl)-4-(8-oxo-3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester.

MS (ES\(^{+}\)): 428 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.84 min.

Example DA3

y-r-trans^-Aminomethyl-O-chloro-phenyl \( \pi \)-cyclohexyl-2-trifluoromethyl-\( \beta \)J-dihydro-5H-P1.2.41triazoloM.5-alpyrazin-\( \beta \)-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 and DA2 using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (step H).

MS (ES\(^{+}\)): 428 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.95 min.

Example DA4

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl \( \pi \)-cyclohexy \( \pi \)-2-trifluoromethyl-6.7-dihydro-
5H-F1.2.41triazoloM.5-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (step H).

MS (ES\(^{+}\)): 428 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.96 min.

Example DA5
**Example DA6**

7-(trans-4-Aminomethyl-4-m-tolyl-cyclohexyl)-2-trifluoromethyl-6,7-dihydro-5H-M,2,4,1triazol,5-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 and DA2 using 3-Methyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile and using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES⁺): 408 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.04 min.

**Example DA7**

7-[cis-4-Aminomethyl-4-m-tolyl-cyclohexyl]-2-trifluoromethyl-6,7-dihydro-5H-M,2,4UrJaZoloH,5-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 using 3-Methyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile and using 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES⁺): 408 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.06min.
**Example DA8**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3.4-dihydro-2H-isoquinolin-1-one

The title compound was prepared analogously as described in Example DA1 using 1,2,3,4-Tetrahydro-isoquinoline instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.


**Example DA9**

N-{6-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-methyl-5-oxo-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl)-acetamide

The title compound was prepared analogously as described in Example DA1 using N-(4-Methyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl)-acetamide instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.67min.

**Example DA10**

y^cis^-AminomethyM-m-tolyl-cyclohexyD-S-trifluoromethyl-β,Z-dihydro-SH,H,2,41triazolor4.3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 using 3-Methyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile.

MS (ES⁺): 408 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.82 min.

**Example DA11**

2-Amino-6-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-methyl-7,8-dihydro-SH-pyrido[4,3-d]pyrimidin-5-one
The title compound was prepared analogously as described in Example DA1 using 4-Methyl-δ,β,δ-tetrahydro-pyridoK.S-dpyrimidin^\-ylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(+\)): 400 [M+H]\(^{+}\).

HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.43min.

**Example DA12**

\(\text{y-trans}^{\pi}\-\text{AminomethylM-O-chloro-phenv \(\pi\)-cvclohexy}^{\pi}\-\beta\-\text{J-dihvdro-SH-n. 2.}^{\text{^\-\text{triazolo}}}_{\text{H.5-}\text{aipyrazin-8-one dihydrochloride}}\)

The title compound was prepared analogously as described in Example DA1 and DA2 using 5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (step H).

MS (ES\(+\)): 360 [M+H]\(^{+}\).

HPLC (Zorbax SB C18, 2min method (0-0.8min 10-95%ACN, 0.8-1.5min 95%ACN, 1.5-1.6min 95-10%ACN, 1.6-2min 10%ACN): 0.25 min.

**Example DA13**

\(7-(\text{trans-4-Aminomethyl-4-m-tolyl-cvclohexyl})\-\text{3-trifluoromethyl-6.7-dihvdro-5H-M,2,41triazolor4,3-a1pyrazin-8-one dihydrochloride}}\)

The title compound was prepared analogously as described in Example DA1 and DA2 using 3-Methyl-phenylacetonitrile instead of 3-Chlorophenylacetonitrile.

MS (ES\(+\)): 408 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.92min.

**Example DA14**

\(7-\text{rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6,7-dihvdro-5H-ri.2,41triazolo}_{\text{H.5-a1pyrazin-8-one dihydrochloride}}\)

The title compound was prepared analogously as described in Example DA1 using 5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (step H).
Example DA15
Z-rtrans-\(^-\)-Aminomethyl-\(\delta\)-chloro-2-fluoro-phenyl-cyclohexyn-S-trifluoromethyl-SJ-dihydro-5H-n.2,41triazolor4.3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 and DA2 using 5-Chloro\(^-\)-fluorophenylacetonitrile instead of 3-Chlorophenylacetonitrile.
MS (ES\(^+\)): 446 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

Example DA16
7-Fcis-4-Aminomethyl-4-(5-chloro-2-fluoro-phenyl)-cyclohexyn-3-trifluoromethyl-6.7-dihydro-5H-n.2,41triazolor4.3-alpyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 and DA2 using 5-Chloro\(^-\)-fluorophenylacetonitrile instead of 3-Chlorophenylacetonitrile.
MS (ES\(^+\)): 446 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.91 min.

Example DA17
7-ftrans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-\(\beta\).7-dihydro-5H-F1,2,41triazolo-r4.3-aipyzarin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DA1 and DA2 using 5,6,7,8-Tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine instead of S-trifluoromethyl-5.6,7,\(\delta\)-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
MS (ES\(^+\)): 360 [M+H]\(^+\).
HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.69 min.

Example DA18
7-\(f\)CsS-4-AmSnemethyl-4-(3-chloro-phenyl)cyclohexyn-6.7-dihydro-5H-ri.2,41triazolo-r4.3-a1pyrazin-8-one dihydrochloride
The title compound was prepared analogously as described in Example DA1 using 5,6,7,8-Tetrahydro-1H,4H-triazolo[4,3-a]pyrazine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.85 min.

**Example DA19**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-cyclopropyl-6,7-dihdro-5H-pyridor3.4-d1pyrimidin-8-one

The title compound was prepared analogously as described in Example DA1 using 4-Cyclopropyl-S,6,7,δ-tetrahydro-pyrido[3^[4-]dpyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.83min.

**Example DA20**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4(3-methanesulfonyl-phenyl)-6,7-dihydro-5H-pyridoF3.4-d1pyrimidin-8-one

The title compound was prepared analogously as described in Example DA1 using 4-(3-Methanesulfonyl-phenylO-5.e,7.δ-tetrahydro-pyridolS^dpyrimidine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.76min.

**Example DA21**

3-6-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-oxo-5,6,7,8-tetrahvdro-Pyridor4,3-d1pyrimidin-2-yl>benzoic acid dihydrochloride

The title compound was prepared analogously as described in Example DA1 using 3-(δ,6,7,δ-Tetrahydro-pyridoK.S^dpyrimidin^δO-benzoic acid ethyl ester instead of 3-
trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford 3-{6-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-5-oxo-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl}-benzoic acid ethyl ester followed by step:

K) 3-(6-flcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-oxo-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl>-benzoic acid dihydrochloride

Lithiumhydroxide (41.7mg, 0.98mmol) was added to a mixture of 3-{6-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-5-oxo-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl}-benzoic acid ethyl ester (56.3mg, 0.098mmol) in dioxane (0.8ml) and water (0.8ml) and the reaction was stirred at room temperature for 2h. The reaction mixture was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the trifluoroacetate of the title compound, which was dissolved in acetonitril and water and treated with an excess of 1M hydrogen chloride in water (15Oul, 0.15mmol). Removal of the volatiles by lyophilization gave the title compound as a white solid.

MS (ES^+): 491 [M+H]^+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.23min.

Example DA22
3-(7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidin-4-yl>-benzoic acid dihydrochloride

The title compound was prepared analogously as described in Example DA1 and DA2 using 3-(5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-benzoic acid ethyl ester instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. 

MS (ES^+): 491 [M+H]^+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.75min.

Example DA23
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6.7-dihydro-5H-pyrido[3,4-d]pyrimidin-8-one
The title compound was prepared analogously as described in Example DA1 using 5,6,7,8-
Tetrahydro-pyrido[3,4-d]pyrimidine instead of S-trifluoromethyl-S,β,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min
100%ACN, 7.5-8.0min 100-5%ACN): 3.42min.

**Example DA24**

6-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-(3-methanesulfonyl-phenyl)-
7.8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one hydrochloride

The title compound was prepared analogously as described in Example DA1 using 2-(3-
Methanesulfonyl-phenyl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine instead of 3-
trifluoromethyl-S,β,7,β-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min
100%ACN, 7.5-8.0min 100-5%ACN): 4.34min.

**Example DA25**

3-f6-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-oxo-5.6.7,8-tetrahydro-
Pyrido4.3-d1pyrimidin-2-yl>-N-methyl-benzenesulfonamide hydrochloride

The title compound was prepared analogously as described in Example DA1 using N-Methyl-
3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-yl)-benzenesulfonamide instead of 3-
trifluoromethyl-5A7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.
HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min
100%ACN, 7.5-8.0min 100-5%ACN): 4.37min.

**Example DA26**

N-(3-(6-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-oxo-5.6.7,8-tetrahydro-
Pyrido4.3-dipyrimidin-2-yl>-phenyl)-methanesulfonamide hydrochloride
The title compound was prepared analogously as described in Example DA1 using N-[3-(5,6,7,8-Tetrahydro-pyrido[4,3-d]pyrimidin-2-yl)-phenyl]-methanesulfonamide instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.

MS (ES\(^{+}\)): 540 [M+H]\(^{+}\).

HPLC (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.28min.

### Example DA27

**N-(3-(7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5,β,7,8-tetrahydro-pyridor3,4-d1pyrimidin-4-yl)-phenyl)-methanesulfonamide hydrochloride**

The title compound was prepared analogously as described in Example DA1 using N-[3-(5,6,7,8-Tetrahydro-pyrido[3,4-d]pyrimidin-4-yl)-phenyl]-methanesulfonamide instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1\(^\wedge\)\(^\wedge\)triazolo\(^\wedge\)\(^\wedge\)S-a]pyrazine.

MS (ES\(^{+}\)): 540 [M+H]\(^{+}\).

HPLC (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.82min.

### Example DA28

**7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-(5-methyl-x1,2,41oxadiazol-3-yl)-6,7-dihydro-5H-pyridoF3.4-d1pyrimidin-8-one**

The title compound was prepared analogously as described in Example DA1 using 4-(5-methyl-[1,2,4]oxadiazol-3-yl)-5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine instead of 3-trifluoromethyl-S,β,7,8-tetrahydro-li\(^\wedge\)\(^\wedge\)triazolo\(^\wedge\)\(^\wedge\)S-a]pyrazine.

MS (ES\(^{+}\)): 453 [M+H]\(^{+}\).

HPLC (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.74min.

### Example DA29

**7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3,5,β,7-tetrahvdro-pyridor3,4-dlpymridine-4,8-dione hydrochloride**
The title compound was prepared analogously as described in Example DA1 using 5,6,7,8-Tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.31 min.

**Example DA30**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-oxo-3.4-dihydro-pyrido3,4-diprymidin-7-ium chloride

The title compound was prepared analogously as described in Example DA1 using 5,6,7,8-Tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.03 min.

**Example DA31**

6-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-oxo-5.6.7,8-tetrahydro-pyridor4,3-d1pyrimidine-2-carboxylic acid amide trifluoroacetate

The title compound was prepared analogously as described in Example DA1 using 5,6,7,8-Tetrahydro-pyrido[4,3-d]pyrimidine-2-carboxylic acid amide instead of 3-trifluoromethyl-S,β,7.8-tetrahydro-li^\textsuperscript{\textdegree}triazolo^\textdegree-S-alpyrazine.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.40 min.

**Example DB1**

1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-Pyrrolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example D1 step A to H, using Methyl-4-aminobutyrate hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine to afford 4-[4-(tert-Butyloxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-butyric acid methyl ester and 4-[4-(tert-Butyloxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-butyric acid methyl ester followed by step

i) 1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl1-pyrrolidin-2-one hydrochloride

To a solution of 4-[4-(tert-Butyloxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-butyric acid methyl ester (80mg, 0.182mmol) in Dimethylformamide (3ml) was added Cesiumcarbonate (29mg, 0.912mmol). The mixture was stirred for 16 hours at 80°C, then treated with microwave at 150°C for 45min. The reaction mixture was treated with aqueous Sodium bicarbonate solution (cone.) The product was extracted into dichloromethane. The combined organic extracts were dried over magnesium sulfate. The filtrate was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.02 min.

Example DB2

trans^-Aminomethyl-O-chloro-phenyl-cyclohexyl-tetrahydro-pyrimidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DB1, using (3-Amino-propyl)-carbamic acid benzyl ester instead of Methyl-4-aminobutyrate hydrochloride, step I from {3-[4-(tert-Butyloxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-propyl}-carbamic acid benzyl ester.

Example DB3

1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-tetrahvdro-pyrimidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DB1, using (3-Amino-propyl)-carbamic acid benzyl ester instead of Methyl-4-aminobutyrate hydrochloride.

MS (ES\(^{+}\)): 322[M+H]\(^{+}\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.11 min.

Example DB4

i-rtrans^-Aminomethyl-M-Q-chloro-phenyD-cyclohexyn-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DB1, using (2-Amino-ethyl)-carbamic acid benzyl ester instead of Methyl-4-aminobutyrate hydrochloride.

MS (ES\(^{+}\)): 308[M+H]\(^{+}\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.21 min.

Example DB5

1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DB1, using (2-Amino-ethyl)-carbamic acid benzyl ester instead of Methyl-4-aminobutyrate hydrochloride.

MS (ES\(^{+}\)): 308[M+H]\(^{+}\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.17 min.
Example DC1
3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example D1 step A to H, using 1-Amino-2-ethanol instead of S-trifluoromethyl-S,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford [1-(cis-3-Chloro-phenyl)-4-(2-hydroxy-ethylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester and [1-(trans-3-Chloro-phenyl)-4-(2-hydroxy-ethylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester followed by step I) H-(cis-3-Chloro-phenylM-(2-oxo-oxazolidin-3-vO-cvclohexylmethyl)carbamic acid tert-butyl ester

To a solution of [1-(cis-3-Chloro-phenyl)-4-(2-hydroxy-ethylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester (103mg, 0.269mmol) in Dichloromethane (10ml) was added N,N'-Carbonyldiimidazole (69mg, 0.404mmol) and Triethylamine (39µL, 0.282mmol). The mixture was stirred for 16 hours at room temperature. The reaction mixture was treated with 1N Hydrochloric acid. The product was extracted into dichloromethane. The combined organic extracts were dried over magnesium sulfate. The filtrate was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

J) 3-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-oxazolidin-2-one hydrochloride

Trifluoroacetic acid (1mL) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(2-oxo-oxazolidin-3-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (78mg, 0.191mmol) in dichloromethane (2mL) and the reaction stirred at room temperature for 4h. The reaction mixture was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.
MS (ES+): 309 [M+H].
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5ml_/min, 12min method (0-1.5min
10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.98
min.

**Example DC2**

S-rtrans^-AminomethyM-O-chloro-phenv-cvclohexyn-ri.Sioxazinan- 2-one
hydrochloride

The title compound was prepared analogously as described in Example DC1 , using 1-
Amino-3-propanol instead of 1-Amino-2-ethanol, step I from [1-(trans-3-Chloro-phenyl)-4-(3-
hydroxy-propylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5ml_/min, 12min method (0-1.5min
10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.06
min.

**Example DC3**

3-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-ri.31oxazinan-2-one
hydrochloride

The title compound was prepared analogously as described in Example DC1 , using 1-
Amino-3-propanol instead of 1-Amino-2-ethanol.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL_/min, 12min method (0-1.5min
10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.97
min.

**Example DC4**

(S)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-4-methyl-oxazolidin-2-one
hydrochloride

The title compound was prepared analogously as described in Example DC1 , using (S)-2-
Amino-propan-1-ol instead of 1-Amino-2-ethanol.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 3.93 min.

Example DC5

(R)-3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy 4-methyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-2-Amino-propan-1-ol instead of 1-Amino-2-ethanol.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 3.96 min.

Example DC6

(S)-3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-methyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (S)-1-Amino-propan-2-ol instead of 1-Amino-2-ethanol.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 3.79 min.

Example DC7

(R)-3-trans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy 4-methyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-1-Amino-propan-2-ol instead of 1-Amino-2-ethanol.
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 3.81 min.
**Example DC8**

(S)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-phenyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (S)-2-Amino-2-phenylethanol instead of 1-Amino-2-ethanol.


HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.48 min.

**Example DC9**

(R)-3-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-phenyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-2-Amino-2-phenylethanol instead of 1-Amino-2-ethanol.


HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.47 min.

**Example DC10**

(S)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-phenyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (S)-2-Amino-1-phenylethanol instead of 1-Amino-2-ethanol.


HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.37 min.

**Example DC11**
(R)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-phenyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-2-Amino-1-phenylethanol instead of 1-Amino-2-ethanol.

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.36 min.

Example DC12

(S)-3-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-isopropyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (S)-2-Amino-3-methyl-butan-1-ol instead of 1-Amino-2-ethanol.

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.34 min.

Example DC13

(R)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-isopropyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-2-Amino-3-methyl-butan-1-ol instead of 1-Amino-2-ethanol.

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.33 min.

Example DC14

(S)-3-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-benzyl-oxazolidin-2-one hydrochloride
The title compound was prepared analogously as described in Example DC1, using (S)-2-Amino-3-phenyl-propan-1-ol instead of 1-Amino-2-ethanol.

**Example DC15**

(R)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-benzyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-2-Amino-3-phenyl-propan-1-ol instead of 1-Amino-2-ethanol.

**Example DC16**

1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn 3-phenvt-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-Phenylethlenediamine instead of 1-Amino-2-ethanol.

**Example DC17**

1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn 3-(4-cyclopentylmethoxy-phenv 3-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-(4-Cyclopentylmethoxyphenyl)-ethlenediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) \(399 \quad [M+H]^+\).

HPLC (Macherey-Nagel LiChrophor 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.62 min.

**Example DC15**

(R)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-benzyl-oxazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using (R)-2-Amino-3-phenyl-propan-1-ol instead of 1-Amino-2-ethanol.

**Example DC16**

1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn 3-phenvt-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-Phenylethlenediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) \(399 \quad [M+H]^+\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.65 min.

**Example DC16**

1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn 3-phenvt-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-Phenylethlenediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) \(384 \quad [M+H]^+\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.49 min.

**Example DC17**

1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn 3-(4-cyclopentylmethoxy-phenv 3-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-(4-Cyclopentylmethoxyphenyl)-ethlenediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) \(482 \quad [M+H]^+\).
Example DC18
1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-3-methyl-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-Methylethlynediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) : 322[M+H]\(^{+}\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 3.71 min.

Example DC19
1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-butyl-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-Butylethlynediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) : 364[M+H]\(^{+}\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.32 min.

Example DC20
1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-benzyl-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DC1, using N-Benzylethlynediamine instead of 1-Amino-2-ethanol.

MS (ES\(^{+}\)) : 398[M+H]\(^{+}\).

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 4.42 min.
Example DD1

N-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-cyclopropylmethyl-5-phenyl-
nicotinamide hydrochloride

The title compound was prepared analogously as described in Example D1 step A to H, using Cyclopropanemethylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine to afford [1-(cis-3-Chloro-phenyl)-4-(cyclopropylmethyl-amino)-
cyclohexylmethyl]-carbamic acid tert-butyl ester and [1-(trans-3-Chloro-phenyl)-4-
(cyclopropylmethyl-amino)-cyclohexylmethyl]-carbamic acid tert-butyl ester followed by step

I) (1-(cis-3-Chloro-phenyl)-4-fcyclopropylmethyl-(5-phenyl-pyridine-3-carbonyl)-amino1-
cyclohexylmethyl]carbamic acid tert-butyl ester

To a solution of [1-(cis-3-Chloro-phenyl)-4-(cyclopropylmethyl-amino)-cyclohexylmethyl]-
carbamic acid tert-butyl ester (40mg, 0.102mmol) and 5-PhenylNicotinic acid (28mg, 0.132mmol) in Dimethylformamide (1ml) was added 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-
tetramethyluronium hexafluorophosphate (59mg, 0.153mmol) and diisopropylethylamine (71 µL, 0.407mmol). The mixture stirred at room temperature for one hour. The reaction mixture was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-
15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

MS (ES⁺): 574 [M+H]⁺.

J) N-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cydohexylT-N-cvclopropylmethyl-5-phenyl-
nicotinamide hydrochloride

To {1-(cis-3-Chloro-phenyl)-4-[cy clopropylmethyl-(5-phenyl-pyridine-3-carbonyl)-amino]-
cyclohexylmethyl]-carbamic acid tert-butyl ester (56mg, 0.098mmol) was added 4N hydrogen chloride solution in dioxane (10ml). The reaction mixture stirred at room temperature for one hour, then it was concentrated in vacuo. The residue was treated with diethyl ether in ultrasonic bath. The etheric phase was removed with a pipette. The residue was lyophilized in vacuo to give the title compound as white crystals.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.50min.

**Example DD2**  
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-N-cyclopropyl-5-phenyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Cyclopropylamine instead of Cyclopropanemethylamine.  
MS (ES⁺): 460 [M+H]⁺.  
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.33min.

**Example DD3**  
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-(2-methoxy-ethyl)-5-phenyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 2-Methoxyethylamine instead of Cyclopropanemethylamine.  
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.24min.

**Example DD4**  
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-methylcarbamoylmethyl-5-phenyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 2-Amino-N-methylacetamide hydrochloride instead of Cyclopropanemethylamine.  
MS (ES⁺): 491 [M+H]⁺.  
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.97min.
Example DD5
6-Acetylamino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-cyclopropylmethyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 6-Acetylaminonicotinic acid instead of 5-Phenylnicotinic acid.
MS (ES⁺): 455 [M+H]⁺.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.96min.

Example DD6
6-Acetylamino-N-fcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-cyclopropyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Cyclopropylamine instead of Cyclopropanemethylamine and 6-Acetylaminonicotinic acid instead of 5-Phenylnicotinic acid.
MS (ES⁺): 441 [M+H]⁺.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.81 min.

Example DD7
6-Acetylamino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-(2-methoxy-ethvD-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 2-Methoxyethylamine instead of Cyclopropanemethylamine and 6-Acetylaminonicotinic acid instead of 5-Phenylnicotinic acid.

Example DD8
6-Acetylamino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-methylcarbamoylmethyl-nicotinamide hydrochloride
The title compound was prepared analogously as described in Example DD1 using 2-Amino-N-methylacetamide hydrochloride instead of Cyclopropanemethylamine and 6-Acetylaminonicotinic acid instead of 5-Phenylnicotinic acid.

**MS (ES\(^{+}\))**: 472 [M+H\(^{+}\)].

**HPLC** (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-5\%ACN): 3.34min.

**Example DD9**

**Pyridazine-3-carboxylic acid rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-cyclopropyl-amide hydrochloride**

The title compound was prepared analogously as described in Example DD1 using Cyclopropylamine instead of Cyclopropanemethylamine and Pyridazine-3-carboxylic acid instead of 5-Phenylnicotinic acid.

**MS (ES\(^{+}\))**: 385 [M+H\(^{+}\)].

**HPLC** (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-5\%ACN): 3.76min.

**Example DD10**

**Pyridazine-3-carboxylic acid rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-(2-methoxy-ethyl)-amide hydrochloride**

The title compound was prepared analogously as described in Example DD1 using 2-Methoxyethylamine instead of Cyclopropanemethylamine and Pyridazine-3-carboxylic acid instead of 5-Phenylnicotinic acid.

**MS (ES\(^{+}\))**: 403 [M+H\(^{+}\)].

**HPLC** (Nucleosil C-18HD 4x70mm 3\(\mu\)m, 8min method (0-6min 5-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-5\%ACN): 3.60min.

**Example DD11**

**Pyridazine-3-carboxylic acid rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-methylcarbamovimethyl-amide hydrochloride**
The title compound was prepared analogously as described in Example DD1 using 2-Amino-N-methylacetamide hydrochloride instead of Cyclopropanemethylamine and Pyridazine-3-carboxylic acid instead of 5-Phenylnicotinic acid.

**Example DD12**

1-Isopropyl-1H-benzotriazole-5-carboxylic acid rcis-4-aminomethyl-4-(3-chlorophenyl)-cyclohexyl-cyclopropylmethylamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 1-Isopropyl-1H-1,2,3-benzotriazole-5-carboxylic acid instead of 5-Phenylnicotinic acid.

**Example DD13**

1-Isopropyl-1H-benzotriazole-5-carboxylic acid fcis-4-aminomethyl-4-(3-chlorophenyl)-cyclohexyl-cyclopropylamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Cyclopropylamine instead of Cyclopropanemethylamine and 1-Isopropyl-1H-1,2,3-benzotriazole-5-carboxylic acid instead of 5-Phenylnicotinic acid.

**Example DD14**

1-Isopropyl-1H-benzotriazole-5-carboxylic acid rcis-4-aminomethyl-4-(3-chlorophenyl)-cyclohexyl1-(2-methoxy-ethyl)-amide hydrochloride
The title compound was prepared analogously as described in Example DD1 using 2-Methoxyethylamine instead of Cyclopropanemethylamine and 1-Isopropyl-1H-1,2,3-benzotriazole-5-carboxylic acid instead of 5-Phenylnicotinic acid.

**Example DD15**

1-Isopropyl-1H-pyrazole^-bipyridine-S-carboxylic acid fcis-4-aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-cvclopropylmethyl-amide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 1-isopropyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid instead of 5-Phenylnicotinic acid.

**Example DD16**

6-Amino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-N-cvclopropylmethyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 6-Aminonicotinic acid instead of 5-Phenylnicotinic acid.

**Example DD17**

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-N-cvclopropylmethyl-isonicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Isonicotinic acid instead of 5-Phenylnicotinic acid.

MS (ES⁺): 484 [M+H]^+.  

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.25min.

Example DD15

1-Isopropyl-1H-pyrazole^-bipyridine-S-carboxylic acid fcis-4-aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-cvclopropylmethyl-amide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 1-isopropyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.65min.

Example DD16

6-Amino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-N-cvclopropylmethyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 6-Aminonicotinic acid instead of 5-Phenylnicotinic acid.

MS (ES⁺): 413 [M+H]^+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.57min.

Example DD17

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-N-cvclopropylmethyl-isonicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Isonicotinic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.57min.

Example DD17

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-N-cvclopropylmethyl-isonicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Isonicotinic acid instead of 5-Phenylnicotinic acid.

**Example DD18**

N-rcis-4-Aminomethyl-4-(3-chloro-phenyO-cvclohexyll-N-cvclopropylmethyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using Nicotinic acid instead of 5-Phenylnicotinic acid.

MS (ES⁺): 398 [M+H]

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.56min.

**Example DD19**

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-N-(2-methanesulfonyl-ethyl)-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 2-Methanesulfonyl-ethylamine instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-Phenylnicotinic acid.

MS (ES⁺): 450 [M+H⁺].

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.17min.

**Example DD20**

ffcis-4-Aminomethyl-4-(3-chloro-phenyO-cvclohexyll-(pyridine-3-carbonyl)-amino1-acetic acid hydrochloride

The title compound was prepared analogously as described in Example DD1 using Amino-acetic acid tert-butyl ester hydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.11min.
Example DD21
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-(3H-imidazol-4-ylmethyl)-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using C-(3H-imidazol-4-yl)-methylamine hydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.09min.

Example DD22
3-Fccis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-(pyridine-3-carbonyl)-amino1-propionic acid ethyl ester hydrochloride

The title compound was prepared analogously as described in Example DD1 using Amino-propionic acid ethyl ester hydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.56min.

Example DD23
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-N-[2-hydroxy-ethyl]-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DD1 using 2-Aminoethanol hydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.09min.
Example DD24

3-rrcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-π-fpyridine-3-carbonyl)-amino1-propionic acid hydrochloride

The title compound was prepared analogously as described in Example DD1 step A to I using Aminopropionic acid ethyl ester hydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-Phenynicotinic acid followed by step J) 3-fr4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chlorophenyl)-cyclohexyl-(pyridine-3-carbonyl)-amino1-propionic acid

To a solution of 3-[[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chlorophenyl)-cyclohexyl]--(pyridine-3-carbonyl)-amino]-propionic acid ethyl ester (55mg, 0.101mmol) in dioxane (0.5ml) and water (0.15ml) was added Lithium hydroxide (8.6mg, 0.202mmol). The mixture was stirred at 45°C for one hour. The reaction mixture was treated with 2N Hydrochloric acid and was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN)). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.


K) 3-ftfcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-(pyridine-3-carbonyl)-amino1-propionic acid hydrochloride

To {3-[[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chlorophenyl)-cyclohexyl]--(pyridine-3-carbonyl)-amino]-propionic acid (39mg, 0.076mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for one hour, then it was concentrated in vacuo. The residue was treated with diethyl ether in ultrasonic bath. The etheric phase was removed with a pipette. The residue was lyophilized in vacuo to give the title compound as white crystals.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.16min.
Example DD25
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-N-(2H-pyrazol-3-ylmethyO-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-H-pyrazol-3-ylmethyamine dihydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-PhenylNicotinic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.28min.

Example DD26
N-f^AminomethyM-O-chloro-phenv π-cyclohexyli-N-fiH-imidazol- 2-ylmethyl)-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 1-H-imidazol-2-ylmethyamine dihydrochloride instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-PhenylNicotinic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.93min.

Example DD27
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-r2-(3-methanesulfonyl-phenvD-ethvn-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-(3-Methanesulfonyl-phenyl)-ethylamine instead of Cyclopropanemethylamine and Nicotinic acid instead of 5-PhenylNicotinic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 2.50min.

Example DD28
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2,2,2-trifluoro-N-r2-(3-
methanesulfonyl-phenyl)-ethv π-acetamide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-(3-
Methanesulfonyl-phenyl)-ethylamine instead of Cyclopropanemethylamine and
Trifluoroacetic acid instead of 5-Phenylnicotinic acid.
MS (ES+): 517 [M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min
100%ACN, 7.5-8.0min 100-5%ACN): 2.39min.

Example DD29
Tetrahydropyran-4-carboxylic acid rcis-4-aminomethyl-4-(3-chloro-phenyl)-
cyclohexyn-r2-(3-methanesulfonyl-phenyl)-ethvn-amide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-(3-
Methanesulfonyl-phenyl)-ethylamine instead of Cyclopropanemethylamine and
Tetrahydropyran-4-carboxylic acid instead of 5-Phenylnicotinic acid.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min
100%ACN, 7.5-8.0min 100-5%ACN): 3.42min.

Example DD30
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-r2-(3-methanesulfonyl-
phenyl)-ethvn-3-methoxy-propionamide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-(3-
Methanesulfonyl-phenyl)-ethylamine instead of Cyclopropanemethylamine and 3-
Methoxypropionic acid instead of 5-Phenylnicotinic acid.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min
100%ACN, 7.5-8.0min 100-5%ACN): 3.43min.

Example DD31
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-2-(3-methanesulfonyl-phenyl)-ethyl 2-methoxy-acetamide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-(3-Methanesulfonyl-phenyl)-ethylamine instead of Cyclopropanemethylamine and Methoxyacetic acid instead of 5-Phenylnicotinic acid.


HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.30min.

Example DD32
Piperidine-4-carboxylic acid rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-F2-(3-methanesulfonyl-phenyl)-ethvn-amide hydrochloride

The title compound was prepared analogously as described in Example DC1 using 2-(3-Methanesulfonyl-phenyl)-ethylamine instead of Cyclopropanemethylamine and Piperidine-1,4-dicarboxylic acid mono-tert-butyl ester instead of 5-Phenylnicotinic acid.

MS (ES+): 532 [M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.57min.

Example DE1
1-rcis-4-Aminomethyl-4-(3-chloro-pheny  π-cyclohexyn-piperazine-2,5-dione

The title compound was prepared analogously as described in Example D1 step A to H using (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride instead of 3-trifluoromethyl-5,β,7,8-tetrahydro-li**triazolo**.S-alpyrazine to afford (2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-acetylamin)-acetic acid ethyl ester and (2-[4-(tert-Butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-acetylamin)-acetic acid ethyl ester followed by step

1) f1-(cis-3-Chloro-phenyl)-4-(2,5-dioxo-piperazin-1-yl)-cyclohexylmethvn-carbamic acid tert-butyl ester
{2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-acetylaminoj-acetic acid ethyl ester (128mg, 0.252mmol) was dissolved in a mixture of toluene (5ml), n-Butanol (5ml) and acetic acid (1ml). The solution was heated in microwave at 150°C for one hour, then the mixture was concentrated in vacuo to give the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.19 min.

J) 1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-piperazine-2,5-dione

Trifluoroacetic acid (0.4mL) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(2,5-dioxo-piperazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (87mg, 0.180mmol) in dichloromethane (4mL) and the reaction was stirred at room temperature for 5 hours, then it was stirred at 40°C for 6 hours. The reaction mixture was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo, then partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated in vacuo to give the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.58 min.

Example DE2
1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-4-phenyl-piperazin-2-one hydrochloride

The title compound was prepared analogously as described in Example DE1 using [(2-Amino-ethyl)-phenyl-amino]-acetic acid ethyl ester hydrochloride instead of (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride.

The reaction mixture of step J was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method...
(0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

**MS (ES⁺):** 398 [M+H]⁺.

**HPLC** (Agilent Eclipse XDB-C18 4.6×50mm, 1.8μm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.26 min.

**Example DE3**

**(7R,8aS)-2-trans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-7-hydroxy-hexahydro-pyrrolon,2-1pyrazine-1,4-dione formate**

The title compound was prepared analogously as described in Example DE1 using (2S,4R)-1-{(2-Amino-acetyl)-4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester hydrochloride instead of (2-Amino-acetylaminoc)acetic acid ethyl ester hydrochloride, step I from (2S,4R)-1-{[2-4-(tert-Butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-acetyl}-4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester.

The reaction mixture of step J was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 OBD 5μm 19×50mm, flow 20mL/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

**MS (ES⁺):** 392 [M+H]⁺.

**HPLC** (Waters Symmetry C18 3.5μm 2.1×50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.38 min.

**Example DE4**

**1-tcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-phenyl-piperazine-2,5-dione**

The title compound was prepared analogously as described in Example DE1 using [(2-Amino-acetyl)-phenyl-amino]-acetic acid ethyl ester hydrochloride instead of (2-Amino-acetylaminoc)acetic acid ethyl ester hydrochloride.

**MS (ES⁺):** 412 [M+H]⁺.

**HPLC** (Waters Symmetry C18 3.5μm 2.1×50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 20%ACN): 2.41 min.
Example DE5

(7R,8aS)-2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-7-hydroxy-hexahydropyrrolo[2,1-a]pyrazine-1,4-dione formate

The title compound was prepared analogously as described in Example DE1 using (2S,4R)-1-(2-Amino-acetyl)-4-hydroxy-pyrrolidine-2-carboxylic acid methyl ester hydrochloride instead of (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride.

The reaction mixture of step J was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5 µm 19 x 50 mm, flow 20 ml/min, 15 min method (0-2.5 min 5% ACN, 2.5-12.5 min 5-100% ACN, 12.5-15.0 min 100% ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

MS (ES+): 392 [M+H]+

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50 mm, 6 min method (0-3 min 5-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 2.56 min.

Example DE6

3-f4-r4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexyn-2.5-dioxo-piperazin-1-yl)-benzoic acid formate

The title compound was prepared analogously as described in Example DE1 using 3-{4-(tert-Butoxycarbonylamino-methyl)-4-(3-chloro-phenyl)-cyclohexyn-2,5-dioxo-piperazin-1-yl}benzoic acid and 3-f((f4-(tert-Butoxycarbonylamino-methyl)-4-(3-chloro-phenyl)-cyclohexyn-carboxymethyl-carbamoyl)-methyl)-amino1-benzoic acid followed by step J)

To a solution of 3-{4-(tert-Butoxycarbonylamino-methyl)-4-(3-chloro-phenyl)-cyclohexyl}-2,5-dioxo-piperazin-1-yl]-benzoic acid ethyl ester (43 mg, 0.074 mmol) in tetrahydrofurane (1 ml) and water (1 ml) was added Lithium hydroxide (16 mg, 0.368 mmol). The mixture was stirred at 60°C for 4 h. The reaction mixture was treated with 1 N Hydrochloric acid and extracted into dichloromethane. The organic layer was dried over sodium sulfate and evaporated in vacuo to give a mixture of the title compounds as a white solid.
HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-20%ACN, 5.55-6min 20%ACN): 3.60 min.

H) 3-(4-f4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-2.5-dioxo-piperazin-1-yl>-benzoic acid formate

To the solution of the mixture of 3-[4-(tert-Butoxycarbonylamino-methyl)-4-(3-chlorophenyl-cyclohexyl]-5-dioxo-piperazin-1-yl]benzoic acid and 3-[[4-(tert-Butoxycarbonylamino-methyl)-4-(3-chloro-phenyl)-cyclohexyl]-carboxymethyl-carbamoyl]-methyl]-amino]-benzoic acid (38mg, 0.068mmol) in dichloromethane (2.5ml) was added trifluoroacetic acid (0.4mL). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the title compound were lyophilized in vacuo to give the title compound as a white solid.

MS (ES^+): 456 [M+H]^+

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-20%ACN, 5.55-6min 20%ACN): 2.11 min.

Example DE7

(S)-1-ltrans-4-Aminomethvl-4-f3-chloro-phenyl)-cyclohexyn-3-benzyl-piperazine-2.5-dione trifluoroacetate

The title compound was prepared analogously as described in Example DE1 using (S)-2-(2-Amino-acetylamino)-3-phenyl-propionic acid methyl ester instead of (2-Amino-acetylamino)acetic acid ethyl ester hydrochloride, step I from [4-((S)-3-Benzyl-2,5-dioxo-piperazin-1-yl)-1-(trans-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester.

The reaction mixture of step J was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

MS (ES^+): 426 [M+H]^+.

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.55-6min 5%ACN): 2.76 min.
Example DE8
fS)-1-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-benzyl-piperazine-2,5-dione formate

The title compound was prepared analogously as described in Example DE1 using (S)-2-(2-Amino-acetylamino)-3-phenyl-propionic acid methyl ester instead of (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride.

The reaction mixture of step J was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-14.25min 5-100%ACN, 15.75-16.25min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

MS (ES+): 426 [M+H]+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

Example DE9
(R)-2-f cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-hexahydro-pyrrolori.2-apyrazine-1,4-dione

The title compound was prepared analogously as described in Example DE1 using (R)-1-(2-Amino-acetyl)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride instead of (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.73 min.

Example DE10
3-r((fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-carboxymethyl-carbamoyl> methvD-aminol-benzoic acid formate

The title compound was prepared analogously as described in Example DE6, isolating the title compound as a white solid during the prep. HPLC purification in step H.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.34 min.

**Example DE11**

(S)-2-r4-Aminomethvi-4-(3-chloro-phenyl)-cyclohexyn-hexahvdro-pyridori,2-alpyrazine-1,4-dione

The title compound was prepared analogously as described in Example DE1 using (S)-1-(2-Amino-acetyl)-piperidine-2-carboxylic acid methyl ester trifluoroacetate instead of (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.93 min.

**Example DF1**

7-cris-4-Aminomethyl-4-(3-chloro-phenv π-cyclohexyn-3-methyl-7,8-dihvdro-rri,2.41triazolor4,3-a1pyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example D1 step A to H using (2-Amino-acetylamino)-acetic acid ethyl ester hydrochloride instead of 3-trifluoromethyl-5,e,7,8-tetrahydro-li^^triazolo^.S-alpyrazine to afford a mixture of {2-[4-(tert-Butoxycarbonylarnino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylarnino]-acetamino]-acetic acid ethyl ester and {2-[4-(tert-Butoxycarbonylarnino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylarnino]-acetamino]-acetic acid ethyl ester followed by step

1) f1-(cis-3-Chloro-phenyl)-4-(2.5-dioxo-piperazin-1-yl)-cyclohexylmethvn-carbamic acid tert-butyl ester and fi-ftrans-S-Chloro-phenylM^+. 5-dioxo-piperazin-i-yD-cyclohexylmethvn-carbamic acid tert-butyl ester

A mixture of {2-[4-(tert-Butoxycarbonylarnino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylarnino]-acetamino]-acetic acid ethyl ester and {2-[4-(tert-Butoxycarbonylarnino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylarnino]-acetamino]-acetic acid ethyl ester (437mg, 0.907mmol) was dissolved in a mixture of toluene (6ml), n-Butanol (6ml) and acetic acid (1.2ml). The solution was stirred in a sealed tube at 170°C for 2h. The mixture was
quenched with water and the product was extracted 3x into ethyl acetate. The combined organic fractions were dried over sodium sulfate and concentrated in vacuo to give the title compound as a yellow oil.

\[ \text{MS (ES\(^+\)) : 458 [M+Na]^+} \]

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.01 min (trans) and 3.19 min (cis).

\[ \text{J) f1-(cis-3-Chloro-phenyl)-4-(5-ethoxy-2-oxo-3,6-dihydro-2H-pyrazin-1-yl)-cyclohexylmethylcarbamic acid tert-butyl ester and 1-(trans-3-Chloro-phenyl)-4-(5-ethoxy-2-oxo-3,6-dihydro-2H-pyrazin-1-yl)-cyclohexylmethyl1-carbamic acid tert-butyl ester} \]

To a suspension of a mixture of [1-(cis-3-Chloro-phenyl)-4-(2,5-dioxo-piperazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester and [1-(trans-3-Chloro-phenyl)-4-(2,5-dioxo-piperazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (100mg, 0.229mmol) in dichloromethane (2ml) were added Triethyloxonium tetrafluoroborate (1N in dichloromethane, 1.15ml, 1.15mmol) and anhydrous sodium carbonate (485mg, 4.58mmol) The reaction mixture was stirred at room temperature for 16h. The mixture was quenched with water and the product was extracted 2x into dichloromethane. The combined organic fractions were dried over sodium sulfate and concentrated in vacuo to give the title compound as a yellow oil.

\[ \text{MS (ES\(^+\)) : 464 [M+H]^+} \]

\[ \text{K) f1-(cis-3-Chloro-phenyl)-4-(3-methyl-6-oxo-5,6-dihydro-8H-1,2,4-triazol-3,1-pyrazin-7-yl)-cyclohexylmethylT-carbamic acid tert-butyl ester} \]

To a solution of a mixture of [1-(cis-3-Chloro-phenyl)-4-(5-ethoxy-2-oxo-3,6-dihydro-2H-pyrazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester and 1-(trans-3-Chloro-phenyl)-4-(5-ethoxy-2-oxo-3,6-dihydro-2H-pyrazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (55mg, 0.15mmol) in n-Butanol (1ml) was added a solution of Acetic acid hydrazide (19mg, 0.23mmol) in n-Butanol (1ml). The reaction mixture was refluxed for 5h. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by prep.

HPLC (Waters Sphire Prep CL 8 ODB 5µm 19 x 50mm, flow 20mi/min, 15min method (0-
2.5 min 5% ACN, 2.5-22.5 min 5-100% ACN, 22.5-25.0 min 100% ACN). Fractions containing the product were concentrated in vacuo to give the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5μm 2.1 x 50 mm, 6 min method (0-3 min 20-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-20% ACN, 5.55-6 min 20% ACN): 3.09 min.

L) 7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-3-methyl-7,8-dihydro-1,2,4-triazolo[4,3-a]pyrazin-6-one dihydrochloride

Trifluoroacetic acid (0.5 mL) was added to a solution of 1-(cis-3-Chloro-phenyl)-4-(3-methyl-6-oxo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclohexylmethyl-carbamic acid tert-butyl ester (5 mg, 0.011 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at room temperature for 10 minutes. The mixture was concentrated in vacuo to give the trifluoroacetate of the title compound, which was dissolved in methanol and treated with an excess of 2 M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5μm 2.1 x 50 mm, 6 min method (0-3 min 5-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 2.64 min.

Example DF2
7-rtrans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-methyl-7,8-dihydro-1,2,4-triazolo[4,3-a]pyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example DF1, step L from 1-(trans-3-Chloro-phenyl)-4-(3-methyl-6-oxo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclohexylmethyl-carbamic acid tert-butyl ester.


HPLC (Waters Symmetry C18 3.5μm 2.1 x 50 mm, 6 min method (0-3 min 5-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 2.24 min.

Example DF3
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-pyridin-4-yl-7,8-dihydro-1,2,4-triazolo[4,3-a]pyrazin-6-one dihydrochloride
The title compound was prepared analogously as described in Example DF1, using isonicotinic acid hydrazide instead of acetic acid hydrazide.

**Example DF4**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using oxamic acid hydrazide instead of acetic acid hydrazide.

**Example DF5**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-f1H-indol-3-ylmethyl)-7,8-dihydro-1,2,4-triazolo-4,3-alpyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example DF1, using indole-3-acetic acid hydrazide instead of acetic acid hydrazide.

**Example DF6**

7-rtrans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-3-(3-methoxy-phenyl)-7,8-dihydro-1,2,4-triazolo-4,3-alpyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example DF2, using 3-methoxybenzoic acid hydrazide instead of acetic acid hydrazide.

**Example DF7**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using lsonicotinic acid hydrazide instead of acetic acid hydrazide.

**Example DF8**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using oxamic acid hydrazide instead of acetic acid hydrazide.

**Example DF9**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using indole-3-acetic acid hydrazide instead of acetic acid hydrazide.

**Example DF10**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using lsonicotinic acid hydrazide instead of acetic acid hydrazide.

**Example DF11**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using oxamic acid hydrazide instead of acetic acid hydrazide.

**Example DF12**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-5,7,8-tetrahydro-1,2,4-triazolo-4,3-alpyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DF1, using indole-3-acetic acid hydrazide instead of acetic acid hydrazide.
HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 4.05 min.

**Example DF7**

*γ*-trans*-Aminomethyl-O-chloro-phenyl-cyclohexyn-S-pyridin-Z-yl-y,S-dihydro-π.2.41triazolo[4,3-b]pyrazin-β-one dihydrochloride

The title compound was prepared analogously as described in Example DF2, using Pyridine-2-carboxylic acid hydrazide instead of Acetic acid hydrazide.


HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.98 min.

**Example DF8**

*γ*-trans*-Aminomethyl-O-chloro-phenyl-cyclohexyn-S-O.4-dimethoxy-phenyl)-?-^-dihydro-f1.2.41triazolo[4,3-b]pyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example DF2, using 3,4-Dimethoxybenzoic acid hydrazide instead of Acetic acid hydrazide.

MS (ES⁺): 496 [M+H]⁺.

HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.98 min.

**Example DF9**

*T*-trans*-Aminomethyl-O-chloro-phenyl-cyclohexyn-S-dH-indol-S-ylmethyD-y. 8-dihydro-H.2.41triazolof4.3-a1pyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example DF2, using Indole-3-acetic acid hydrazide instead of Acetic acid hydrazide.

MS (ES⁺): 489 [M+H]⁺.

HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 4.06 min.

**Example DF10**
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(3-methoxy-phenyl)-7,8-dihydro-li,2,41triazolor4,3-a1pyrazin-6-one dihydrochloride

The title compound was prepared analogously as described in Example DF1, using 3-Methoxybenzoic acid hydrazide instead of Acetic acid hydrazide.

MS (ES⁺): 466 [M+H]⁺.

HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 4.24 min.

Example DG1

3-f7-rtrans-4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexyn-8-oxo-5.6 - 7,8-tetrahydro-n,2,41triazolor4,3-a1pyrazin-3-yl>-benzoic acid methyl ester dihydrochloride

The title compound was prepared analogously as described in Example D1 step A to H using (2-Amino-ethyl)-carbamic acid benzyl ester hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford {2-[4-((tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-ethyl}-carbamic acid benzyl ester and {2-[4-(tert-Butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-ethyl}-carbamic acid benzyl ester followed by step

1) N-(2-Benzoxycarbonylamino-ethyl)-N-f4-(tert-butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenvO-cyclohexyl)-oxalamic acid ethyl ester

To a solution of {2-[4-(tert-Butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-ethyl}-carbamic acid benzyl ester (451 mg, 0.874mmol) were added at 0°C 4-(Dimethylamino) pyridine (11mg, 0.087mmol), Triethylamine (608µl, 4.37mmol) and Ethyl oxalyl chloride (146µl, 1.31mmol). The reaction mixture was stirred at room temperature for 3 days. The mixture was quenched with 1N Hydrochloric acid and the product was extracted 2x into dichloromethane. The combined organic fractions were dried over sodium sulfate and the residue was purified by prep. HPLC (InterChrom C18 ODB 10µm 28 x 250mm, flow 40ml/min, 45min method (0-2.5min 20%ACN, 2.5-42.5min 20-100%ACN, 42.5-45.0min 100%ACN). Fractions containing the product were concentrated in vacuo to give the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.24 min.

J) f1-(trans-3-Chloro-phenyl)-4-(2,3-dioxo-piperazin-1-yl)-cyclohexylmethyn-carbamic acid tert-butyl ester

To a solution of N-(2-Benzylxocarbamlamo-ethyl)-N-[4-(tert-butoxycarbamlamo-methyl)-4-(trans-3-chloro-phenyl)-cyclohexyl]-oxalamic acid ethyl ester (206mg, 0.334mmol) in Ethanol abs. (5ml) was added Palladium (10% on charcoal) (4mg, 0.033mmol) and after purge with nitrogen the reaction mixture was stirred at room temperature under hydrogen atmosphere for 16h. A further 4mg of Palladium (10% on charcoal) (0.033mmol) was added to the reaction mixture under flushed nitrogen atmosphere. Then the reaction mixture was stirred at room temperature under hydrogen atmosphere for 3h. The black suspension was filtered over Celite and washed with ethanol. The combined filtrates were concentrated in vacuo. The residue was purified by flash chromatography (Silica cartridge) using gradient elution from 100% dichloromethane to dichloromethane: methanol 4:1. Fractions containing the product were concentrated in vacuo to give the title compound as a pale yellow oil.

MS (ES⁺): 438 [M+H]+

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.16 min.

K) f1-(trans-3-Chloro-phenyl)-4-(5-ethoxy-6-oxo-3.6-dihvdro-2H-pyrazin-1-VL)-cyclohexylmethy-carbamic acid tert-butyl ester

To a solution of [1-(trans-3-Chloro-phenyl)-4-(2,3-dioxo-piperazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (99mg, 0.226mmol) in dichloromethane (8ml) were added Triethylxoxonium tetrafluoroborate (215mg, 1.13mmol) and anhydrous sodium carbonate (479mg, 4.52mmol). The reaction mixture was stirred at room temperature for 3h. The mixture was quenched with water and the product was extracted 2x into dichloromethane. The combined organic fractions were dried over sodium sulfate and concentrated in vacuo to give the title compound as a yellow oil.

MS (ES⁺): 464 [M+H]+

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.61 min.
L) 3-(7-f4-(tert-Butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexyn-8-oxo-5.6.7.8-tetrahvdro-f1.2,41triazolor4,3-a1pyrazin-3-yl)-benzoic acid methyl ester

To a solution of [1-(trans-3-Chloro-phenyl)-4-(5-ethoxy-6-oxo-3,6-dihydro-2H-pyrazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (52mg, 0.13mmol) in n-Butanol (2ml) was added 3-Hydrazinocarbonyl-benzoic acid methyl ester (44mg, 0.23mmol). The reaction mixture was refluxed for 3 days. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 20%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo to give the title compound as a pale yellow oil.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.61 min.

M) S-IZ-ftrans^-AminomethvM-O-chloro-phenv π-cvclohexyll-δ-oxo-S.e.y. δ-tetrahvdro-f1.2,41triazolo4,3-a1pyrazin-3-yl]-benzoic acid methyl ester dihvdrochloride

Trifluoroacetic acid (0.2mL) was added to a solution of 3-{7-f4-(tert-Butoxycarbonylamino-methyl}^-trans-S-chloro-phenyO-cyclohexyl- δ-oxo-S.e.y. δ-tetrahvdro-Π^-triazolo^-S-a]pyrazin-3-yl]-benzoic acid methyl ester (7mg, 0.0Hmmol) in dichloromethane (1mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Nucleosil C18 HD 5µm 21 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 4.22 min.
Example DG2

**y-rtrans^-AminomethyM-O-chloro-phenyD-cyclohexyn-S-pyridin-S-yl-ej-dihydro-SH-li .2,41triazolof4,3-alpyrazin-8-one dihydrochloride**

The title compound was prepared analogously as described in Example DG1, using Nicotinic acid hydrazide instead of 3-Hydrazinocarbonyl-benzoic acid methyl ester.


HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.79 min.

Example DG3

**y-ftrans^-AminomethyM-O-chloro-phenyD-cyclohexyn-S-dH-indol-__2-ylmethyD-βJ - dihydro-5H-n .2,41triazolor4,3-a1pyrazin-8-one dihydrochloride**

The title compound was prepared analogously as described in Example DG1, using Indole-3-acetic acid hydrazide instead of 3-Hydrazinocarbonyl-benzoic acid methyl ester.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min.

Example DG4

**7-rtrans-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-3-r3-(4-methoxy-phenyl)-isoxazol-5-vn-6,7-dihvdro-5H-M,2,41triazolor4,3-a1pyrazin-8-one dihydrochloride**

The title compound was prepared analogously as described in Example DG1, using 3-(4-Methoxy-phenyl)-isoxazole-5-carboxylic acid hydrazide instead of 3-Hydrazinocarbonyl-benzoic acid methyl ester.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.29 min.

Example DG5

**7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-3-(1H-Sndol-2-ylmethyl)-6,7-dihvdro-5H-n,2.41triazolor4,3-a1pyrazin-8-one dihydrochloride**
The title compound was prepared analogously as described in Example DG1, using Indole-3-acetic acid hydrazide instead of 3-Hydrazinocarbonyl-benzoic acid methyl ester, step I from \{2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-ethyl\}-carbamic acid benzyl ester.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.00 min.

Example DG6

7-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-cyclopropyl-6,7-dihydro-5H-pyrazolo[2,4,3-a]pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using Cyclopropane carboxylic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES^+): 400 [M+H]^+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.73 min.

Example DG7

7-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(3,4-dimethoxy-phenyl)-6,7-dihydro-5H-n.2,4,3-triazolo[2,4,3-a]pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3,4-Dimethoxybenzoic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES^+): 496 [M+H]^+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.91 min.

Example DG8

7-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(4-methoxy-phenyl)-6,7-dihydro-5H-n.2,4,3-triazolo[2,4,3-a]pyrazin-8-one dihydrochloride
The title compound was prepared analogously as described in Example DG5, using 4-Methoxybenzoic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES\(^{+}\)) : 466 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.96 min.

**Example DG9**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(3-methanesulfonyl-phenyl)-6,7-dihydro-5H-1,2,4-triazolo[4,3-a]pyrazin-8-one \textit{dihydrochloride}

The title compound was prepared analogously as described in Example DG5, using 3-Methanesulfonyl-benzoic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES\(^{+}\)) : 514 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

**Example DG10**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(4-fluoro-phenyl)-6.7-dihydro-

5H-M,2,4triazolo[4,3-a]pyrazin-8-one \textit{dihydrochloride}

The title compound was prepared analogously as described in Example DG5, using 4-Fluorobenzoic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES\(^{+}\)) : 454 [M+H]\(^{+}\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.10 min.

**Example DG11**

7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(3-fluoro-phenyl)-6.7-dihydro-

5H-M,2,4triazolo[4,3-a]pyrazin-8-one \textit{dihydrochloride}

The title compound was prepared analogously as described in Example DG5, using 3-Fluorobenzoic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES\(^{+}\)) : 454 [M+H]\(^{+}\).
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.05 min.

Example DG12

7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-8-oxo-5,β.7.8-tetrahydro-1,2,41triazolo4,3-apyrazine-3-carboxylic acid amide dihydrochloride

The title compound was prepared analogously as described in Example DG5, using Oxamic acid hydrazide instead of Indole-3-acetic acid hydrazide.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.86 min.

Example DG13

7-cis^-Aminomethyl-4-(3-chloro-phenyltevclohexy π^<-3-(4H-ri,2 ,41triazol-3-yl)-6J-dihydro-5H-ri,2,41triazol4,3-a1pyrazin-8-one trihydrochloride

The title compound was prepared analogously as described in Example DG5, using 1H-[1,2,4]triazole-3-carboxylic acid hydrazide instead of Indole-3-acetic acid hydrazide.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

Example DG14

7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-3-pyridin-4-yl-6,7-dihydro-5H-H \_2,41triazol4,3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using Isonicotinic acid hydrazide instead of Indole-3-acetic acid hydrazide.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.79 min.

Example DG15
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-methyl-6.7-dihydro-5H-
H,2,41triazolor4,3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using Acetic acid hydrazide instead of Indole-3-acetic acid hydrazide.
MS (ES\textsuperscript{+}): 374 [M+H]\textsuperscript{+}.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.79 min.

Example DG16
S-fy-rcis^-AminomethylM-O-chloro-phenvD-cyclohexyn-S-oxo-S. βJ.S-tetrahvdro-
H,2,4UriazoloF4,3-a1pyrazin-3-yl>-benzoic acid dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-Hydrazinocarbonyl benzoic acid instead of Indole-3-acetic acid hydrazide.
MS (ES\textsuperscript{+}): 480 [M+H]\textsuperscript{+}.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.11 min.

Example DG17
7-fcis-4-Aminomethyl-4-f3-chloro-phenv π-cyclohexyn-3-r3-(4-fluoro-phenyl)-isoxazol-
5-vπ-6.7-dihydro-5H- π ,2,41triazolor4,3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-(4-Fluoro-phenyl)-isoxazole-5-carboxylic acid hydrazide dihydrochloride instead of Indole-3-acetic acid hydrazide.
MS (ES\textsuperscript{+}): 521 [M+H]\textsuperscript{+}.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.32 min.

Example DG18
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-f2-hydroxy-propy π-6.7-
dihydro-5H-ri,2,41triazolor4.3-a1pyrazin-8-one dihydrochloride
The title compound was prepared analogously as described in Example DG5, using 3-Hydroxybutanohydrazide instead of Indole-3-acetic acid hydrazide.

**Example DG19**

7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(2-methoxy-ethyl)-6,7-dihydro-5H-2,4-triazolor4,3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-Methoxypropionic acid hydrazide instead of Indole-3-acetic acid hydrazide.

**Example DG20**

4-(7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5,6,7,8-tetrahydro-2,4-triazolor4,3-a1pyrazin-3-yl)-2-methyl-2H-phthalazin-1-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-Methyl-4-oxo-3,4-dihydro-phtalazine-1-carboxylic acid hydrazide instead of Indole-3-acetic acid hydrazide.

**Example DG21**

4-(7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5,6,7,8-tetrahydro-M,2,4-triazolor4,3-a1pyrazin-3-yl)-benzamide dihydrochloride

The title compound was prepared analogously as described in Example DG5, using A-(Hydrazinocarbonylb)enzamide instead of Indole-3-acetic acid hydrazide. The product of step L [4-[3-(4-Carbamoyl-phenyl)-8-oxo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-1-
(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester was partly esterified during boc deprotection step M when it was treated with 2N HCl in methanol. The resulting two compounds 4-{7-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-8-oxo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl}-benzamide and 4-{7-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-8-oxo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl}-benzoic acid methyl ester were separated by prep. HPLC. See also example DG26.

**Example DG22**

7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy \( \pi \)-8-oxo-5,6,7,8-tetrahydro-[1,2,4]triazolof4,3-aipyrazine-3-carboxylic acid isopropylamide dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 2-Hydrazino-N-isopropyl-2-oxoacetamide instead of Indole-3-acetic acid hydrazide.

MS (ES\(^+\)) : 518 [M+H\(^+\)]

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min.

**Example DG23**

3-(2-[7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy \( \pi \)-8-oxo-5,6,7,8-tetrahydro-[1,2,4]triazolof4,3-aipyrazin-3-yl]-ethyl)-5,5-dimethyl-imidazolidine-2,4-dione trihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-(4,4-Dimethyl-2,5-dioxo-imidazolidin-1-yl) propionic acid hydrazide instead of Indole-3-acetic acid hydrazide.

MS (ES\(^+\)) : 518 [M+H\(^+\)]

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min.

**Example DG24**

...
The title compound was prepared analogously as described in Example DG5, using 3-Hydrazino-N-methyl-3-oxopropanamide instead of Indole-3-acetic acid hydrazide.

$\text{MS (ES}^+\text{): 518 [M+H]}^+.$

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min.

**Example DG25**

7-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5.6.7.8-tetrahydro-ri,2,4,1triazolo4,3-a1pyrazine-3-carboxylic acid cyclopropylamide dihydrochloride

The title compound was prepared analogously as described in Example DG5, using N-Cyclopropyl-2-hydrazino-2-oxoacetamide instead of Indole-3-acetic acid hydrazide.

$\text{MS (ES}^+\text{): 518 [M+H]}^+.$

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min.

**Example DG26**

4-{7-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5, ,7,8-tetrahydro-n,2,4,1triazolor4,3-a1pyrazin-3-yl>-benzoic acid methyl ester dihydrochloride

The title compound was prepared analogously as described in Example DG21. The product of step L [4-{3-(4-Carbamoyl-phenyl)-8-oxo-5,6-dihydro-8H-[1 ,2,4]triazolo[4,3-a]pyrazin-7-yl]-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester was partly esterified during boc deprotection step M when it was treated with 2N HCl in methanol. The resulting two compounds 4-{7-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-8-oxo-5,6 $\text{7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl}-benzamide and 4-{7-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-8-oxo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl}-benzoic acid methyl ester were separated by prep. HPLC. See also example DG21.

$\text{MS (ES}^+\text{): 518 [M+H]}^+.$

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min
Example DG27
2-7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5,6,7,8-tetrahydro-1i,2.41triazolor4.3-aiyprazin-3-yl>-acetamide trihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-Hydrazino-3-oxo propanamide instead of Indole-3-acetic acid hydrazide.
MS (ES\(^+\)): 417 [M+H].
HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.69 min.

Example DG28
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-cyclobutyl-6,7-dihydro-5H-M,2,41triazolor4,3-aiyprazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using Cyclobutanecarboxylic acid hydrazide dihydrochloride instead of Indole-3-acetic acid hydrazide.
MS (ES\(^+\)): 414 [M+H].
HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.83 min.

Example DG29
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(2-methoxy-pyrimidin'5-yl)-6,7-dihydro-5H-l,2.41triazolor4,3-aiyprazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 2-Methoxy-pyrimidine-5-carboxylic acid hydrazide dihydrochloride instead of Indole-3-acetic acid hydrazide.
MS (ES\(^+\)): 468 [M+H].
HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.79 min.

Example DG30
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl-cyclohexyn-3-(3-fluoro-pyridin-4-yl)-6.7-dihydro-5H-π.2.41triazolo4.3-a1pyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG5, using 3-Fluoro-isonicotinic acid hydrazide dihydrochloride instead of Indole-3-acetic acid hydrazide. MS (ES⁺): 455 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.79 min.

Example DG31
3-{7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-8-oxo-5,6,7,8-tetrahydro-1.2.41triazolo4.3-a1pyrazin-3-yl}-N-methyl-benzamide dihydrochloride

The title compound was prepared analogously as described in Example DG5, step A to L using 3-Hydrizinocarbonyl-benzoic acid dihydrochloride instead of Indole-3-acetic acid hydrazide to afford 3-{7-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyn]-8-oxo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl}-benzoic acid followed by step:

IVD d-rcis-S-Chloro-phenylM-fS-O-methylcarbamoyl-phenylβ-oxo-δ,β-dihydro-SH-f1.2.41triazolof4.3-a1pyrazin-7-yll-cyclohexylmethylIV-carbamic acid tert-butyl ester

To a solution of 3-{7-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-S-oxo-5,β,7,δ-tetrahydro-II,2,4]triazolo[4,3-a]pyrazin-3-yl}-benzoic acid (33mg, 0.057mmol) in dichloromethane (2ml) was added O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (43mg, 0.1 14mmol), Diisopropylethylamine (20µl, 0.114mmol) and Methylamine hydrochloride (6mg, 0.086mmol). The reaction mixture was stirred at room temperature for 16h. The mixture was diluted with dichloromethane and washed with water, 1N Hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified over silica gel cartridge by MPLC (ISCO Companion) eluting with dichloromethane to dichloromethane / methanol 9:1. Fractions containing the product were concentrated in vacuo to give the title compound as a yellow solid. MS (ES⁺): 593 [M+H]⁺.
HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.47 min.

N) 3-f7-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-8-oxo-5.6.7.8-tetrahvdro-[1,2.41triazolor4.3-alpyrazin-3-yl]-N-methyl-benzamide dihydrochloride

Trifluoroacetic acid (0.2mL) was added to a solution of {1-(cis-3-Chloro-phenyl)-4-[3-(3-methylcarbamoyl-phenyl)-8-oxo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-cyclohexylmethylj-carbamic acid tert-butyl ester (15mg, 0.025mmol) in dichloromethane (0.5ml). The reaction mixture was stirred at room temperature for 2h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Nucleosil C18 HD 5μm 21 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo to give the formate salt of the title compound, which was dissolved in 2M hydrogen chloride in methanol. Methanol was removed by evaporation. The residue was dissolved in dioxane, frozen and lyophilized to give the title compound as a white solid.

MS (ES): 493 [M+H]

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.81 min.

Example DG32
7-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(3-fluoro-pyridin-4-yl)-β,7-dihydro-5H-11,2,41triazolor4.3-aipyrazin-8-one dihydrochloride

The title compound was prepared analogously as described in Example DG31, using Morpholine instead of Methylamine hydrochloride.

MS (ES): 549 [M+H].

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.87 min.

Example DH1
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-r2-f3-methanesulfonyl-phenVO-ethyn-acetamide hydrochloride
The title compound was prepared analogously as described in Example D1 step A to H, using 2-(3-Methanesulfonyl-phenyl)-ethylamine instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford \{1-(cis-3-Chloro-phenyl)-4-[2-(3-methanesulfonyl-phenyl)-ethylamino]-cyclohexylmethyl\}-carbamic acid tert-butyl ester and \{1-(cis-3-Chloro-phenyl)-4-[2-(3-methanesulfonyl-phenyl)-ethylamino]-cyclohexylmethyl\}-carbamic acid tert-butyl ester followed by step D4.

D\(_4\)-(Acetyl-f2-(3-methanesulfonyl-phenyl)-ethyl-amo>-1-(cis-3-chloro-phenyl)-cyclohexylmethyl-T-carbamic acid tert-butyl ester

To a mixture of \{1-(cis-3-Chloro-phenyl)-4-[2-(3-methanesulfonyl-phenyl)-ethylamino]-cyclohexylmethyl\}-carbamic acid tert-butyl ester (30mg, 0.058mmol) and Diisopropylethylamine (22µL, 0.127mmol) in dichloromethane (1ml) was added a solution of Acetylchloride (5µl, 0.069mmol) in dichloromethane (1ml) dropwise at room temperature. The resulting mixture was stirred at room temperature for 5 minutes. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

MS (ES\(^+\)): 508 [M-tBu+H]\(^+\).

\(J\) N-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-r2-(3-methanesulfonyl-phenyl)-ethyl-acetamide hydrochloride

To \[4-{Acetyl-[2-(3-methanesulfonyl-phenyl)-ethyl]-amino}-1-(cis-3-chloro-phenyl)-cyclohexylmethyl\]-carbamic acid tert-butyl ester (23mg, 0.041mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 1h, then it was concentrated in vacuo. The residue was treated with diethyl ether in ultrasonic bath. The etheric phase was removed with a pipette. The residue was lyophilized in vacuo to give the title compound as a white solid.

MS (ES\(^+\)): 463 [M+H]\(^+\).

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.08min.
Example DH2

N-rcis-4-Aminomethyl-4-f3-chloro-phenyt)-cvclohexyn-N-(4-methanesulfonyl-benzyl)-acetamide hydrochloride

The title compound was prepared analogously as described in Example DH1, using 4-Methanesulfonyl benzylamide hydrochloride instead of 2-(3-Methanesulfonyl-phenyl)-ethylamine.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.80 min.

Example DH3

N-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-r2-(3-methanesulfonylamino-phenvD-ethvn-acetamide

The title compound was prepared analogously as described in Example DH1, using N-[3-(2-Amino-ethyl)-phenyl]-methanesulfonamide instead of 2-(3-Methanesulfonyl-phenyl)-ethylamine.


Example DH4

Cyclopropanecarboxylic acid rcsi-4-aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-F2-O-methanesulfonyl-phenvD-ethyl-amiide hydrochloride

The title compound was prepared analogously as described in Example DH1, using Cyclopropanecarbonyl chloride instead of Acetyl chloride.

MS (ES+): 489 [M+H]^+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 1.61 min.

Example DH5

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-f2-(3-methanesulfonyl-phenvD-ethvn-propionamide hydrochloride
The title compound was prepared analogously as described in Example DH1, using Propionyl chloride instead of Acetyl chloride.

**Example DH6**

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-N-r2-(3-methanesulfonyl-phenyl)-ethyi-methanesulfonamide hydrochloride

The title compound was prepared analogously as described in Example DH1, using Methanesulfonyl chloride instead of Acetyl chloride.

**Example DH7**

rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-r2-(3-methanesulfonyl-phenyl)-ethyi-carbamic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH1, using Methyl chloroformate instead of Acetyl chloride.

**Example DH8**

rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-r2-(3-methanesulfonyl-phenyl) π-ethyi-carbamic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH1, using 4-Morpholinecarbonylchloride instead of Acetyl chloride.
**Example DH9**

1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-1-r2-(3-methanesulfonyl-phenyl)-ethyn-3-methyl-urea hydrochloride

The title compound was prepared according to Scheme D.

The title compound was prepared analogously as described in Example DH1, using Methyl isocyanate instead of Acetyl chloride and Triethylamine instead of Diisopropylethylamine.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.30 min.

**Example DM**

3-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl>--
benzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example D1 step A to H using (2-Amino-ethyl)-carbamic acid benzyl ester hydrochloride instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford (2-[4-(tert-Butoxycarbonylamino-methyl)-3-chloro-phenyl]-cyclohexylamino]-ethyl)-carbamic acid benzyl ester and (2-[4-(tert-Butoxycarbonylamino-methyl)-4-(trans-3-chloro-phenyl)-cyclohexylamino]-ethyl)-carbamic acid benzyl ester followed by step

I) [1-(cis-3-Chloro-phenyl)-4-(2-oxo-imidazolidin-1-yl)-cyclohexylmethyl1-carbamic acid tert-butyl ester

To a solution of (2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-ethyl)-carbamic acid benzyl ester (720mg, 1.40mmol) in Dimethylformamide (15ml) was added Cesiumcarbonate (2.28g, 7.00mmol). The mixture was stirred for 3h at 90°C. The reaction mixture was treated with aqueous Sodium bicarbonate solution (cone.) The product was extracted 2x into dichloromethane. The combined organic extracts were dried over magnesium sulfate. The filtrate was concentrated in vacuo to afford a mixture of the title compound and 1-[cis-4-Aminomethyl-4-(3-chloro-benzyl)-cyclohexyl]-imidazolidin-2-one, which was purified by prep. HPLC (Waters SunFire
Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-
12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were
lyophilized in vacuo to give the title compound as a white solid.

MS (ES⁺): 408 [M+H]⁺.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml_/min, 8min method (0-6.0min
20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 4.56 min.

J) 3-[3-f4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cvclohexyl1-2-oxo-
imidazolidin-1-yl]-benzoic acid methyl ester

To a solution of [1-(cis-3-Chloro-phenyl)-4-(2-oxo-imidazolidin-1-yl)-cyclohexylmethyl]-
carbamic acid tert-butyl ester (50mg, 0.123mmol) in toluene (1ml) was added 3-Bromo-
benzoic acid methyl ester (26mg, 0.123mmol), Cesiumcarbonate (56mg, 0.172mmol), (±)-
2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (6mg, 0.01 mmol) and
Tris(dibenzylideneacetone)dipalladium(0) (5mg, 0.005mmol). The mixture was stirred for
2.5h at 100°C. The reaction mixture was filtered, then the filtrate was concentrated in vacuo
to give the title compound as a white solid.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml_/min, 8min method (0-6.0min
20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 6.31 min.

K) 3-[3-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-imidazolidin-1-ylV-benzoic acid methyl ester hydrochloride

To 3-[3-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-2-oxo-
imidazolidin-1-yl]-benzoic acid methyl ester (66mg, 0.122mmol) was added 4N hydrogen
chloride solution in dioxane (3ml). The reaction mixture stirred at room temperature for 2h,
then it was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire
Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-
12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were
lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in
methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the
volatiles gave the title compound as a white solid.

MS (ES⁺): 442 [M+H]⁺.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8μm, flow 1.5ml_/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.44 min.

Example DI2
4-l3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyl1-2-oxo-imidazolidin-1-yl]-
benzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DM, using 4- 
Bromo-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
MS (ES+): 442 [M+H]+.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8μm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.53 min.

Example DI3
1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-3-(4-methanesulfonyl-phenyl)-
imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DH, using 1-
Bromo-4-methanesulfonyl-benzene instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8μm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.05 min.

Example DI4
1-rcis-4-Aminomethyl-4-f3-chloro-phenyl)-cvclohexyn-3-(3-methanesulfonyl-phenyl)-
imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DH, using 1-
Bromo-3-methanesulfonyl-benzene instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8μm, flow 1.5mL_/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.10 min.

Example DI5
3-f3-r4-Aminomethyt-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-imidazolidin-1-yl>-benzoic
acid hydrochloride
The title compound was prepared analogously as described in Example D1 step A to K to afford 3-[3-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-2-oxo-imidazolidin-1-yl]-benzoic acid methyl ester hydrochloride followed by step L 3-(3-f4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-y1V-benzoic acid hydrochloride

To a solution of 3-[3-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-2-oxo-imidazolidin-1-yl]-benzoic acid methyl ester hydrochloride (15mg, 0.034mmol) in dioxane (1ml) was added 1N aqueous Potassium hydroxide solution (0.5ml). The reaction mixture was treated with microwave at 120°C for 5min, then it was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.03 min.

**Example D16**

4^3-f4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl]-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example D15 , using 4-Bromo-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES^+): 442 [M+H]^+.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.93 min.

**Example D17**

3-(3-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl]-benzenesulfonamide hydrochloride
The title compound was prepared analogously as described in Example DM, using N-(tert-butoxycarbonyl)-(3-bromophenyl)-sulfonamide instead of 3-Bromo-benzoic acid methyl ester. MS (ES\(^+\)): 463 [M+H].

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.82 min.

**Example DI8**

4-(3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl)-benzenesulfonamide hydrochloride

The title compound was prepared analogously as described in Example DM, using N-(tert-butoxycarbonyl)-(4-bromophenyl)-sulfonamide instead of 3-Bromo-benzoic acid methyl ester. MS (ES\(^+\)): 463 [M+H].

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.77 min.

**Example DI9**

1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-(3-amino-phenyl)-imidazoHdin-2-one hydrochloride

The title compound was prepared analogously as described in Example DM, using (3-Bromo-phenyl)-carbamic acid tert-butyl ester instead of 3-Bromo-benzoic acid methyl ester. MS (ES\(^+\)): 399 [M+H].

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.05 min.

**Example DMO**

5-(3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-ylV-nicotinic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DM, using 5-Bromo-nicotinic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester. MS (ES\(^+\)): 443 [M+H].

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.68 min.
Example DH1
5-f3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy2-oxo-imidazolidin-1-yl)-nicotinic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using 5-Bromo-nicotinic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 1.95 min.

Example DH2
5-{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy2-oxo-imidazolidin-1-yl)-thiophene-2-carboxylic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DM, using 5-Bromo-thiophene-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.38 min.

Example DM3
1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy3-pyrimidin-5-yl-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DH, using 5-Bromo-pyrimidine instead of 3-Bromo-benzoic acid methyl ester.
MS (ES+): 386 [M+H]+.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.40 min.

Example DH4
5-l3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy2-oxo-imidazolidin-1-yl)-thiophene-2-carboxylic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using 5-Bromo-thiophene-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
MS (ES\textsuperscript{+}) : 434 [M+H]\textsuperscript{+}.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\textmu m, flow 1.5mL/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 2.87 min.

Example DM5
4\texttext{-}[3\texttext{-}cis\texttext{-}4\texttext{-}Aminomethyl\texttext{-}4\texttext{-}(3\texttext{-}chloro\texttext{-}phenyl)\texttext{-}cyclohexyn\texttext{-}2\texttext{-}oxo\texttext{-}imidazolidin\texttext{-}1\texttext{-}yl)\texttext{-} pyridine\texttext{-}2\texttext{-}carboxylic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example 011, using 4-Bromo-pyridine-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
MS (ES\textsuperscript{+}): 443 [M+H]\textsuperscript{+}.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\textmu m, flow 1.5mL/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 2.33 min.

Example DM6
2\text{-}[3\text{-}rcis\text{-}4\text{-}Aminomethyl\text{-}4\text{-}(3\text{-}chloro\text{-}phenyl)\text{-}cyclohexyn\text{-}2\text{-}oxo\text{-}imidazolidin\text{-}1\text{-}yl)\text{-} isonicotinic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH, using 2-Bromo-isonicotinic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
MS (ES\textsuperscript{+}): 443 [M+H]\textsuperscript{+}.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\textmu m, flow 1.5mL/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 3.28 min.

Example DH7
4\text{-}[3\text{-}rcis\text{-}4\text{-}Aminomethyl\text{-}4\text{-}(3\text{-}chloro\text{-}phenyl)\text{-}cyclohexyn\text{-}2\text{-}oxo\text{-}imidazolidin\text{-}1\text{-}yl)\text{-} pyridine\text{-}2\text{-}carboxylic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using 4-Bromo-pyridine-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
MS (ES\textsuperscript{+}): 429 [M+H]\textsuperscript{+}.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\textmu m, flow 1.5mL/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 1.68 min.

Example DH8
2-|3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-imidazolidin-1-yl>-isonicotinic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using 2-Bromoisonicotinic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.43 min.

Example DH9

3-|3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-tetrahvdro-pyrimidin-1-vD-benzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH using (3-Amino-propyl)-carbamic acid benzyl ester instead of (2-Amino-ethyl)-carbamic acid benzyl ester hydrochloride.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.29 min.

Example DI20

4-|3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexy π-2-oxo-imidazolidin-1-ylIV-benzamide hydrochloride

The title compound was prepared analogously as described in Example DH using 4-bromobenzamide instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.54 min.

Example DI21

2-|3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-imidazolidin-1-yl>-benzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH, using 2-Bromo-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES^+): 442 [M+H]^+.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml_/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.10 min.

**Example DI22**
6-{3-rcis-4-Aminomethvl-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-imidazolidin-1-yl>-pyridine-2-carboxylic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH, using 6-Bromo-pyridine-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
MS (ES⁺): 442 [M+H]⁺.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml_/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.33 min.

**Example DI23**
1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-3-phenyl-tetrahvdro-pyrimidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DM9, using Bromobenzene instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.08 min.

**Example DI24**
4-{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-2-oxo-tetrahvdro-pyrimidin-1-ylVbenzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DM9, using 4-Bromo-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.30 min.

**Example DI25**
4\{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl\}-2-methyl-benzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example 011, using 4-Bromo-2-methyl-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 456 \[M+H\]^+

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\(\mu\)m, flow 1.5ml/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 1.82 min.

Example DI26
6\{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl\}\nicotinic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH, using 6-Bromo-nicotinic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 443 \[M+H\]^+

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\(\mu\)m, flow 1.5ml/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 3.33 min.

Example DI27
3\{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl\}-N.N-dimethyl-benzamide hydrochloride

The title compound was prepared analogously as described in Example DM, using 3-Bromo-N,N-dimethyl-benzamide instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 455 \[M+H\]^+

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8\(\mu\)m, flow 1.5mL/min, 8min method (0-6.0min 20-100\%ACN, 6.0-7.5min 100\%ACN, 7.5-8.0min 100-20\%ACN): 2.94 min.

Example DI28
4\{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl\}-benzonitrile hydrochloride

The title compound was prepared analogously as described in Example DH, using 4-Bromo-benzonitrile instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 409 \[M+H\]^+
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.51 min.

**Example DI29**

3-[3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl]-benzonitrile hydrochloride

The title compound was prepared analogously as described in Example DM, using 3-Bromo-benzonitrile instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.56 min.

**Example DI30**

2-(3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl)-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using 2-Bromo-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.67 min.

**Example DI31**

6-(3-cis-4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl)-pyridine-2-carboxylic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using 6-Bromo-pyridine-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.35 min.

**Example DI32**

3-[3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-tetrahydro-pyrimidin-1-yl]-benzoic acid hydrochloride
The title compound was prepared analogously as described in Example DI5 using (3-Amino-propyl)-carbamic acid benzyl ester instead of (2-Amino-ethyl)-carbamic acid benzyl ester hydrochloride.

MS (ES\(^+\)): 442 [M+H]\(^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.82 min.

**Example DI33**

4-\{(3-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-tetrahydro-pyrimidin-1-yl)benzoic acid hydrochloride\}

The title compound was prepared analogously as described in Example DI32, using 4-Bromo-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 442 [M+H]\(^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.80 min.

**Example DI34**

4-\{(3-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-2-oxo-imidazolidin-1-yl)-2-methyl-benzoic acid hydrochloride\}

The title compound was prepared analogously as described in Example DI5, using 4-Bromo-2-methyl-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 442 [M+H]\(^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.09 min.

**Example DI35**

6-\{(3-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl)-nicotinic acid hydrochloride\}

The title compound was prepared analogously as described in Example DI5, using 6-Bromo-nicotinic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 429 [M+H]\(^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.64 min.
Example DI36

1-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-4-(1H-tetrazol-5-yl)-phenylnimidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DM, step A to J using 4-Bromo-benzonitrile instead of 3-Bromo-benzoic acid methyl ester to afford {1-(cis-3-Chloro-benzyl)-4-[3-(4-cyano-phenyl)-2-oxo-imidazolidin-1-yl]-cyclohexylmethyl}-carbamic acid tert-butyl ester followed by step.

K) (1-(cis-3-Chloro-benzyl)-4-[2-oxo-3-f4-(1H-tetrazol-5-yl)-phenylnimidazolidin-1-yl]-cyclohexylmethylO-carbamic acid tert-butyl ester

To a solution of {1-(cis-3-Chloro-benzyl)-4-[3-(4-cyano-phenyl)-2-oxo-imidazolidin-1-yl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (75mg, 0.147mmol) in toluene (5ml) and dimethylformamide (0.5ml) were added Trimethylsilyl azide (300µl, 2.21mmol) and Tetrabutylammonium fluoride trihydrate (240mg, 0.738mmol). The mixture was treated with microwave for 2h at 120°C. The reaction mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN)). Fractions containing the product were lyophilized in vacuo to give the title compound as a white solid.

MS (ES+): 569 [M+H2O]

HPLC (Agilent Eclipse XDB-C18 4.6’50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 5.21 min.

L) 1-fcis-4-Aminomethyl-4-(3-chloro-benzyl)-cyclohexyl1-3-r4-(1 H-tetrazol-5-yl)-phenylnimidazolidin-2-one hydrochloride

To (1-(cis-3-Chloro-benzyl)-4-[2-oxo-3-[4-(1 H-tetrazol-5-yl)-phenyl]-imidazolidin-1-yl]-cyclohexylmethyl)-carbamic acid tert-butyl ester (20mg, 0.036mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN)). Fractions containing
the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

**Example DI37**

1-rcis-4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexyn-3-f3-(1H-tetrazol-5-v π-pheny-imidazolidin-2-one hydrochloride

The title compound was prepared analogously as described in Example DI36, using 3-Bromo-benzonitrile instead of 4-Bromo-benzonitrile.

MS (ES\(^+\)): 452 \([M+H]^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.86 min.

**Example DI38**

3-{3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl)-N-methyl-benzamide hydrochloride

The title compound was prepared analogously as described in Example DM, using 3-Bromo-N-methyl-benzamide instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 441 \([M+H]^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.79 min.

**Example DI39**

4-{3-fcis-4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexy π-2-oxo-imidazolidin-1 -yl)-N-methyl-benzamide hydrochloride

The title compound was prepared analogously as described in Example DM, using 4-Bromo-N-methyl-benzamide instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^+\)): 441 \([M+H]^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.65 min.
Example DI40

4-{3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-2-oxo-imidazolidin-1-yl}-N,N-dimethyl-benzamide hydrochloride

The title compound was prepared analogously as described in Example DH, using 4-Bromo-N,N-dimethyl-benzamide instead of 3-Bromo-benzoic acid methyl ester.

MS (ES+): 455 [M+H]+.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.85 min.

Example DI41

5-(3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-2-oxo-imidazolidin-1-yl)-pyridine-2-carboxylic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DH, using 5-Bromo-pyridine-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.81 min.

Example DI42

4-{3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-2-oxo-imidazolidin-1-yl)-3-methyl-benzoic acid methyl ester hydrochloride

The title compound was prepared analogously as described in Example DM, using 4-Bromo-3-methyl-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.32 min.

Example DI43

3-{3-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy-2-oxo-imidazolidin-1-yl)-benzamide hydrochloride

The title compound was prepared analogously as described in Example DM, using 3-Bromo-benzamide instead of 3-Bromo-benzoic acid methyl ester.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.53 min.

**Example DI44**

5-|3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2-oxo-imidazolidin-1-yl)-pyridine-2-carboxylic acid hydrochloride

The title compound was prepared analogously as described in Example DH₁ using 5-Bromo-pyridine-2-carboxylic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester. MS (ES⁺): 429 [M+H]⁺.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.04 min.

**Example DI45**

4-f3-rcis-4-Aminomethylvt-4-(3-chloro-phenyl)-cyclohexy π-2-oxo-imidazolidin-1-yl)-3-methyl-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example DH₁ using 4-Bromo-3-methyl-benzoic acid methyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES⁺): 442 [M+H]⁺.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.80 min.

**Example DI46**

4-|[(R)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-5-methyl-2-oxo-imidazolidin-1-yl]-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using ((R)-2-Amino-1-methyl-ethyl)-carbamic acid benzyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES⁺): 442 [M+H]⁺.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.05 min.
Example DI47

4-f(S)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyH-5-methyl-2-oxo-
imidazolidin-1-yl)-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using ((S)-2-Amino-1-methyl-ethyl)-carbamic acid benzyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^{+}\)): 442 [M+H]\(^{+}\).

HPLC (Agilent Eclipse XDB-C18 4.6’50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.06 min.

Example DI48

4-((S)-3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-methyl-2-oxo-
imidazolidin-1-yl>-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using ((S)-2-Amino-propyl)-carbamic acid benzyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^{+}\)): 442 [M+H]\(^{+}\).

HPLC (Agilent Eclipse XDB-C18 4.6’50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.37 min.

Example DI49

4-{(R)-3-rcis-4-Aminomethyl-4-f3-chloro-phenv x-cyclohexyn-4-methyl-2-oxo-
imidazolidin-1-yl>-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example DI5, using ((R)-2-Amino-propyl)-carbamic acid benzyl ester instead of 3-Bromo-benzoic acid methyl ester.

MS (ES\(^{+}\)): 442 [M+H]\(^{+}\).

HPLC (Agilent Eclipse XDB-C18 4.6’50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.37 min.

Example DJ1

(S)-2-rtrans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-hexahydro-pyrrolon,2-
aipyrazine-1,4-dione
The title compound was prepared analogously as described in Example D1 step A to H using (S)-1-\((2\text{-Amino-acyl})\text{-pyrrolidine-2-carboxylic acid}\) instead of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to afford a mixture of (S)-1-\([2\text{-}\{(\text{-Butoxy carbonylamino-methyl})\text{-4-(cis-3-chloro-phenyl)cyclohexylamino\}-acyl}\text{-pyrrolidine-2-carboxylic acid}\) and (S)-1-\([2\text{-}\{(\text{-Butoxy carbonylamino-methyl})\text{-4-(trans-3-chloro-phenyl)cyclohexylamino\}-acyl}\text{-pyrrolidine-2-carboxylic acid}\) followed by step J)

\(\text{H}\{\text{cis-3-Chloro-phenyl}\}-4-((\text{S})\text{-1.4-dioxo-hexahydropyrrolo 1,2-a1pyrazin-2-y1)}\text{-cyclohexylmethyl1-carbamic acid tert-butyl ester}\)

To a mixture of (S)-1-\([2\text{-}\{(\text{-Butoxy carbonylamino-methyl})\text{-4-(cis-3-chloro-phenyl)cyclohexylamino\}-acyl}\text{-pyrrolidine-2-carboxylic acid}\) and (S)-1-\([2\text{-}\{(\text{-Butoxy carbonylamino-methyl})\text{-4-(trans-3-chloro-phenyl)cyclohexylamino\}-acyl}\text{-pyrrolidine-2-carboxylic acid}\) (413mg, 0.836mmol) in dichloromethane (400ml) was added 1-Hydroxybenzotriazole hydrate (452mg, 3.34mmol) and N-(3-Dimethy lamino propyl)-N'-ethylcarbodiimide hydrochloride (658mg, 3.34mmol). The solution was stirred at 0°C for 30 minutes, then Triethylamine (1.16ml, 8.36mmol) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 16h. To the reaction mixture was added some ice and 1M Hydrochloric acid until pH=2, then water was added and the product was extracted into dichloromethane. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, then dried over sodium sulfate and concentrated in vacuo. The residue containing both diastereoisomers was purified and separated by prep. HPLC (InterChrom C18 ODB 10µm 28 x 250mm, flow 40mL/min, 45min method (0-2.5min 20%ACN, 2.5-42.5min 20-100%ACN, 42.5-45.0min 100%ACN). Fractions containing the products were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution seperately. The organic layers were dried over sodium sulfate and concentrated in vacuo to give the title compounds as white solids.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.24 min (trans) and 3.42 min (cis).
Trifluoroacetic acid (640 µL) was added to a solution of [1-(trans-3-Chloro-phenyl)-4-((S)-1,4-dioxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (64 mg, 0.121 mmol) in dichloromethane (4 mL) and the reaction was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo and the residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5 µm 19 x 50 mm, flow 20 mL/min, 15 min method (0-2.5 min 5% ACN, 2.5-12.5 min 5-100% ACN, 12.5-15 min 100% ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated in vacuo to give the title compound as a white solid. MS (ES⁺): 376 [M+H⁺].

**Example DJ2**

(S)-2-[trans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyln-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione

The title compound was prepared analogously as described in Example DJ1 step J from [1-(cis-3-Chloro-phenyl)-4-((S)-1,4-dioxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-cyclohexylmethylj-carbamic acid tert-butyl ester. MS (ES⁺): 376 [M+H⁺].

**Example DJ3**

(R)-1-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-3-benzyl-piperazine-2,5-dione

The title compound was prepared analogously as described in Example DJ2, using (R)-2-(2-Amino-acetylamino)-3-phenyl-propionic acid instead of (S)-1-(2-Amino-acetyl)-pyrrolidine-2-carboxylic acid.
MS (ES\textsuperscript{+}): 426 [M+H]\textsuperscript{+}.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.02 min.

**Example DJ4**

(Rt-i-ftrans\textsuperscript{^-}-AminomethyM-O-chloro-phenv π-cvclohexyn-S-benzyl-piperazine-2.S-dione)

The title compound was prepared analogously as described in Example DJ1, using (R)-2-(2-Amino-acetylamino)-3-phenyl-propionic acid instead of (S)-1-(2-Amino-acetyl)-pyrrolidine-2-carboxylic acid.

MS (ES\textsuperscript{+}): 426 [M+H]\textsuperscript{+}.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.82 min.

**Example E1**

N-rc/s-4-(aminomethyl)-4-(3-chlorophenyl)cvclohexynpyrida2ine-3-carboxamide hydrochloride

The title compound was prepared according to Scheme E.

A) c/s-4-Aminomethyl-4-(3-chlorophenvO-cvclohexanol

Borane tetrahydrofuran adduct (74.6mL, 74.6mmol of a 1M solution in THF) was carefully added to a solution of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile (4.36g, 18.6mmol) in tetrahydrofuran (120mL) at 40°C. The reaction was then heated at reflux for 3 hours. After cooling, the reaction mixture was carefully quenched by the addition of 6M aqueous hydrochloric acid (200 ml), and was stirred at room temperature for 3 hours. The mixture was basified to pH10 with 1M aqueous sodium hydroxide and extracted with ethyl acetate (3 x 200ml). The combined organsics were washed with brine, dried (MgSO\textsubscript{4}) and concentrated in vacuo to give the title compound as a white solid.

MS (ES\textsuperscript{+}): 240, 242 [M+H]\textsuperscript{+}.

T\textsubscript{R} [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\textsubscript{3}CN+0.1%Formic acid/H\textsubscript{2}O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 1.96 min.
B) \( \text{fc/s-1-(3-Chlorophenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester} \)

tert-Butyloxycarbonyl anhydride (4.46g, 20.0mmol) was added to a solution of \( \text{cis-4-aminomethyl-4-(3-chlorophenyl)-cyclohexanol} \) (4.46g, 18.6mmol) and triethylamine (3.86mL, 27.9mmol) in tetrahydrofuran (50mL) and the mixture stirred at room temperature for 3 hours. The reaction mixture was neutralized by the addition of 1M aqueous hydrochloric acid and the mixture extracted with ethyl acetate. The extracts were washed with water and brine, dried \( \text{(MgSO}_4\text{)} \) and concentrated \textit{in vacuo} to give a yellow oil. The oil was purified by flash chromatography (NH\textsubscript{2} anion exchange cartridge (5Og) using 20\% ethyl acetate in cyclohexane as eluent) to give the title compound as a colourless oil.

\text{MS (ES\textsuperscript{+}): 340, 342 \ [M+H]}. \\
\text{T\textsubscript{R} [HPLC, Phenomenex Luna 3 micron C18; 5-95\% CH\textsubscript{3}CN+0.1\%Formic acid/H\textsubscript{2}O+0.1\% Formic acid for 5 min, flow 2.0 ml/min]: 3.49 min.}

C) \( \text{2-Fluorobenzoic acid rfrans-4-(tert-butoxycarbonylamino-methyl)-4-(3-chlorophenyl)-cyclohexyll ester} \)

Di-isopropyl-azodicarboxylate (2.55mL, 12.94mmol) was added to a solution of \( \text{[c/s-1-(3-chlorophenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester} \) (2.0g, 5.88mmol), triphenylphosphine (3.4g, 12.94mmol) and 2-fluorobenzoic acid (1.98g, 14.11mmol) in tetrahydrofuran (30mL) and the mixture was stirred at room temperature overnight. The mixture was concentrated \textit{in vacuo} and the residue was purified by column chromatography (silica, using gradient elution with 0-20\% ethyl acetate in cyclohexane) to give the title compound as a colourless oil that solidified on standing.

\text{MS (ES\textsuperscript{+}): 484 \ [M+Na].} \\
\text{T\textsubscript{R} [HPLC, Phenomenex Luna 3 micron C18; 5-95\% CH\textsubscript{3}CN+0.1\%Formic acid/H\textsubscript{2}O+0.1\% Formic acid for 5 min, flow 2.0 ml/min]: 4.57 min.}

D) \( \text{lfrans-1-(3-Chlorophenyl)-4-hydroxy-cyclohexylmethyl1-carbamic acid tert-butyl ester} \)

Sodium methoxide (528mg, 9.77mmol) was added to a solution of 2-fluorobenzoic acid \( \text{[frans-4-(tert-butoxycarbonylamino-methyl)-4-(3-chlorophenyl)-cyclohexyl] ester} \) (1.88g, 4.07mmol) in methanol (50mL) and tetrahydrofuran (50mL) and the mixture was stirred at
room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane and water. 1M aqueous hydrochloric acid was added until the pH was 7 and the mixture was extracted with dichloromethane. The combined organic phases were washed with brine, dried (MgSO₄) and concentrated. The residue was purified by column chromatography (silica, using 1:1 cyclohexane:ethyl acetate as eluent) to afford the title compound as an oil. 

**T₂** [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.32 min.

**1Hnmr** [400 MHz, CDCl₃, tetramethylsilane as internal standard], δ 1.30 (2H, m), 1.39 (9H, s), 1.56 (2H, m), 1.88 (2H, br d), 2.27 (2H, br d), 3.17 (2H, d), 3.72 (1H, br t), 4.23 (1H, br t), 7.19-7.35 (4H, m).

**E)** Methanesulphonic acid ftrans-4-((tert-butoxycarbonylamino-methyl)-4-(3-chlorophenyl)-cyclohexyll ester

Triethylamine (2.86mL, 20.55mmol) and methanesulphonyl chloride (0.8mL, 10.3mmol) were added to a solution of [trans-1-(3-chlorophenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester (1.4g, 4.11mmol) in dichloromethane (60mL) with cooling to 0°C. The mixture was then stirred at room temperature for 2 hours. The mixture was washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate and brine. After drying (MgSO₄), the volatiles were evaporated and the residue was purified by chromatography (silica, using 40% ethyl acetate in cyclohexane as eluent) to give the title compound as a colourless oil.

**T₂** [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.80 min.

**1Hnmr** [400 MHz, CDCl₃, tetramethylsilane as internal standard], δ 1.39 (9H, s), 1.68 (4H, m), 2.05 (2H, m), 2.25 (2H, m), 2.97 (3H, s), 3.21 (2H, d), 4.24 (1H, br t), 4.77 (1H, m), 7.19-7.35 (4H, m).

**F) fc/s-4-Azido-1-(3-chlorophenyl)-cyclohexylmethyl-carbamic acid tert butyl ester.**

A mixture of sodium azide (125mg, 1.91mmol) and methanesulphonic acid [trans-4-((tert-butoxycarbonylamino-methyl)-4-(3-chlorophenyl)-cyclohexyl] ester (200mg, 0.478mmol) in dimethylformamide (10mL) was stirred at 100°C for 5 hours. After cooling, the mixture was
diluted with ethyl acetate and washed with water and brine. The organic layer was dried
\((\text{MgSO}_4)\) and concentrated \textit{in vacuo} to give the title compound as a colourless oil that was
used directly in the next step.

\[ T_R \text{[HPLC, Phenomenex Luna 3 micron C18; 5-95\% CH}_3\text{CN+0.1\%Formic acid/H}_2\text{O+0.1\%Formic acid for 5 min, flow 2.0 ml/min]} : 4.48 \text{ min.} \]

\( \text{G) fc/s-4-Amino-1-(3-chlorophenyl)-cyclohexylmethyl-1-carbamic acid tert butyl ester.} \)

Triphenylphosphine \((2.2g, 8.4\text{mmol})\) and water \((0.8\text{mL})\) were added to a solution of [c/s-4-
azido-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester \((1.54g, 4.2\text{mmol})\) in
toluene \((20\text{mL})\) and the mixture was heated at \(50^\circ\text{C}\) for 20 hours. The crude reaction mixture
was applied to an SCX cartridge and eluted sequentially with dichloromethane, methanol and
\(2\text{M ammonia in methanol. After combining and concentrating the fractions containing}
the desired product the residue was purified by column chromatography (silica, using
gradient elution with \(0-10\% \text{ 2M ammonia in methanol/dichloromethane}\) to give the title
compound as a colourless oil, which solidified on standing.

MS \((\text{ES}^+)) : 339 \text{[M+H]}^+. \]

\[ T_R \text{[HPLC, Phenomenex Luna 3 micron C18; 5-95\% CH}_3\text{CN+0.1\%Formic acid/H}_2\text{O+0.1\%Formic acid for 5 min, flow 2.0 ml/min]} : 2.35 \text{ min.} \]

\( \text{H) fcis-1-(3-Chlorophenyl)-4-f(pyridazine-3-carbonyl)-aminol-cyclohexylmethyl)-carbamic}
acid tert-butyl ester} \)

[c/s-4-Amino-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester \((50\text{mg,}
0.148\text{mmol})\) was added to a solution of pyridazine-2-carboxylic acid \((27\text{mg, 0.221 mmol}), \text{O-}
(7-azabenzotriazoM -yl)-N,N,N',N''-tetramethyluronium hexafluorophosphate \((84\text{mg,}
0.221 \text{mmol})\) and diisopropylethylamine \((78\mu\text{L})\) in dimethylformamide \((1\text{mL})\) and the mixture
stirred at room temperature for 2 days. The reaction was then diluted with ethyl acetate and
washed repeatedly with water and brine. The organic layer was dried \((\text{MgSO}_4)\) and
concentrated \textit{in vacuo} to give a yellow oil. The oil was purified by flash chromatography
(silica, eluting sequentially with \(1:1 \text{ cyclohexane : ethyl acetate and ethyl acetate}\) to give the
title compound as a white solid.

MS \((\text{ES}^+)) : 467 \text{[M+Na]}^+. \]
TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.65 min.

i) N-fc/s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexylpyridazine-3-carboxamide hydrochloride

Trifluoroacetic acid (0.6mL) was added to a solution of (cis-1-(3-chlorophenyl)-4-[(pyridazine-3-carbonyl)-amino]-cyclohexylmethyl)-carbamic acid tert-butyl ester (60mg, 0.135mmol) in dichloromethane (6mL) and the mixture was stirred at room temperature for 90 mins. After concentrating the mixture in vacuo the residue was purified by chromatography (SCX cartridge, eluting sequentially with dichloromethane, methanol and 0.5M ammonia in methanol) to give the free base of the title compound. The free base was dissolved in dichloromethane and treated with excess 1M hydrogen chloride in methanol. Evaporation and drying afforded the title compound as a white solid.


TR [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.18 min.

Example E2

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-1-benzofuran-2-carboxamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using benzofuran-2-carboxylic acid instead of pyridazine-2-carboxylic acid.


TR [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.88 min.

Example E3

N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-2-morpholin-4-ylacetamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using morpholin-4-yl-acetic acid instead of pyridazine-2-carboxylic acid.
Example E4

1-Acetyl-N-fc/s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexy piperidine-4-carboxamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using 1-acetyl-piperidine-4-carboxylic acid instead of pyridazine-2-carboxylic acid.


Example E5

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy n-pyridin-3-ylacetamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using pyridine-3-yl-acetic acid instead of pyridazine-2-carboxylic acid.


Example E6

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy n-pyridin-3-ylpropanamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using 3-pyridine-3-yl-propionic acid instead of pyridazine-2-carboxylic acid.

Example E7

_N-fc/s-_4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl_3.5-dimethylisoxazole-4-carboxamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using 3,5-dimethyl-isoxazole-4-carboxylic acid instead of pyridazine-2-carboxylic acid.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.38 min.

Example E8

_N-rc/s-_4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-1H-benzimidazole-5-carboxamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using 1H-benzimidazole-5-carboxylic acid instead of pyridazine-2-carboxylic acid.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.16 min.

Example E9

_N-rc/s-_4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-2-furamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using 2-furoic acid instead of pyridazine-2-carboxylic acid.

MS (ES⁺): 333, 335 [M+H]⁺.

Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.21 min.

Example E10

_N-fc/s-_4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexynbenzamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using benzoic acid instead of pyridazine-2-carboxylic acid.

T R [HPLC, Higgins Clipeus δ micron C18; 5-95% CH₃CN+0.1% Formic acid/H₂O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 5.70 min.

Example E11
N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexynpyrazine-2-carboxamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using pyrazine-2-carboxylic acid instead of pyridazine-2-carboxylic acid.
T R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1% Formic acid/H₂O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 5.03 min.

Example E12
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-1,2,3-thiadiazole-4-carboxamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using [1,2,3]thiadiazole-4-carboxylic acid instead of pyridazine-2-carboxylic acid.
MS (ES⁺): 351, 353 [M+H]+.
T R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1% Formic acid/H₂O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 5.10 min.

Example E13
N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-2-(4-methylphenoxy)acetamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using para-tolylloxy-acetic acid instead of pyridazine-2-carboxylic acid.
T R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1% Formic acid/H₂O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 6.36 min.
Example E14
N-rc/s-4-(AminomethylM-(3-chlorophenyl)cyclohexyn-3-(phenylsulfonv π propanamide hydrochloride

The title compounds were prepared analogously as described in Example E1 using 3-benzenesulfonyl-propionic acid instead of pyridazine-2-carboxylic acid.


Tₚ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.17 min.

Example E15
N-(2-{rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cvclohexynaminoV2-oxoethvDbenzamide hydrochloride

The title compound was prepared analogously as described in Example E1 using N-benzoylglycine instead of pyridazine-3-carboxylic acid.

MS (ES⁺): 400, 402 [M+H]⁺.

Tₚ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.00 min.

Example E16
N-(2-{fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cvclohexynaminoV2-oxoethvDcyclopropanecarboxamide hydrochloride

The title compound was prepared analogously as described in Example E1 using (cyclopropanecarbonyl-amino)-acetic acid instead of pyridazine-3-carboxylic acid.


Tₚ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.20 min.

Example E17
N-(2-JTc/s-4-(AminomethylM-(3-chlorophenvπcvclohexynamino>-2-oxoethyl)-2-
furamide hydrochloride
The title compound was prepared analogously as described in Example E1 using [(furan-2-carbonyl)-amino]-acetic acid instead of pyridazine-3-carboxylic acid.

**MS (ES^+):** 390, 392 [M+H]^+.

**TR [HPLC]:** Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min: 5.55 min.

**Example E18**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-4-morpholin-4-yl-4-oxobutanamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 4-morpholin-4-yl-4-oxo-butyric acid instead of pyridazine-3-carboxylic acid.

**MS (ES^+):** 408, 410 [M+H]^+.

**TR [HPLC]:** Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min: 5.17 min.

**Example E19**

N-fc/s-4-(Aminomethyl)>-4-(3-chlorophenyl)cyclohexyn-4-pyridazine-4-carboxamide hydrochloride

The title compound was prepared analogously as described in Example E1 using pyridazine-4-carboxylic acid instead of pyridazine-3-carboxylic acid.

**MS (ES¹):** 343, 345 [M-H]^-

**TR [HPLC]:** Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min: 5.16 min.

**Example E20**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-2-(1-oxo-1,3-dihydro-2H-isooindol-2-yl)acetamide hydrochloride

The title compound was prepared analogously as described in Example E1 using (1-oxo-1,3-dihydro-isooindol-2-yl)-acetic acid instead of pyridazine-3-carboxylic acid.

**MS (ES¹):** 412, 414 [M+H]^+.
Example E21

**N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-2-(1-oxo-1,3-dihydro-2H-isooindol-2-yl)acetamide hydrochloride**

The title compound was prepared analogously as described in Example E1 using acetyl chloride instead of pyridazine-3-carboxylic acid.


T<sub>R</sub> [HPLC, Higgins Clipeus 5micron C18; 5-95% CH<sub>3</sub>CN+0.1%Formic acid/H<sub>2</sub>O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.13 min.

Example E22

**N-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-phenyl-nicotinamide dihydrochloride**

The title compound was prepared analogously as described in Example E1 using 5-Phenylnicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.14min.

Example E23

**N-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-5-methyl-nicotinamide dihydrochloride**

The title compound was prepared analogously as described in Example E1 using 5-Methylnicotinic acid instead of pyridazine-3-carboxylic acid.

MS (ES+): 358[M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.38min.

Example E24

**6-Acetviamino-N-fcis-4-aminomethyl-4-(3-chioro-phenvi)-cvciohexy π-nicotinamide hydrochloride**
The title compound was prepared analogously as described in Example E1 using 6-Acetylamino-nicotinic acid instead of pyridazine-3-carboxylic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.57min.

**Example E25**
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-methoxy-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 6-Methoxy-nicotinic acid instead of pyridazine-3-carboxylic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.87min.

**Example E26**
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-β-morpholin-4-yl-nicotinamide dihydrochloride

The title compound was prepared analogously as described in Example E1 using 6-Morpholin-4-yl-nicotinic acid instead of pyridazine-3-carboxylic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.48min.

**Example E27**
N-rcis-4-Aminomethyl-(3-chloro-phenyO-cvclohexyn-3-formylamino-4-hydroxy-benzamide trifluoroacetate

The title compound was prepared analogously as described in Example E1 using Benzooxazole-5-carboxylic acid instead of pyridazine-3-carboxylic acid. The oxazole ring opened during purification.
Example E28

1-isopropyl-2-trifluoromethyl-1H-benzoimidazole-5-carboxylic acid f cis-4-aminomethyl-O-chlorophenyl-cyclohexylamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 1-isopropyl-2-(trifluoromethyl)-1H-benzoimidazole-5-carboxylic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.58min.

Example E29

1-isopropyl-1H-benzotriazole-5-carboxylic acid f cis-4-aminomethyl-4-(3-chlorophenyl-cyclohexylamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 1-isopropyl-1H-benzotriazole-5-carboxylic acid instead of pyridazine-3-carboxylic acid.

MS (ES+): 426[M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.15min.

Example E30

1-isopropyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid f cis-4-aminomethyl-4-(3-chlorophenyl-cyclohexylamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 1-isopropyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid instead of pyridazine-3-carboxylic acid.

MS (ES+): 426[M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.18min.

Example E31
1-Methyl-1 H-indole-5-carboxylic acid rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-amide

The title compound was prepared analogously as described in Example E1 using 1-Methyl-1H-indole-5-carboxylic acid instead of pyridazine-3-carboxylic acid.

MS (ES+): 396[M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.20min.

Example E32

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using Nicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 1.98min.

Example E33

N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-isonicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using Isonicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.30min.

Example E34

2-Acetylamino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-isonicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 2-Acetylaminoisonicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.55min.
Example E35
6-Amino-N-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 6-Aminonicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.30min.

Example E36
N-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-trifluoromethyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 6-(Trifluoromethyl)-nicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.23min.

Example E37
3.4.5.6-Tetrahydro-2H-ri.2'1bipyridinyl-4'-carboxylic acid cis-4-aminomethyl-4-(3-chloro-phenyl)cyclohexyl-amide dihydrochloride

The title compound was prepared analogously as described in Example E1 using 3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4'-carboxylic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 2.03min.

Example E38
N-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-methyl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 6-Methylnicotinic acid instead of pyridazine-3-carboxylic acid.
MS (ES+): 358[M+H]+.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 1.87min.

**Example E39**

**N-F4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexyn-2-methoxy-isonicotinamide hydrochloride**

The title compound was prepared analogously as described in Example E1 using 2-Methoxyisonicotinic acid instead of pyridazine-3-carboxylic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 2.23min.

**Example E40**

**N^-AminomethyM-O-chloro-phenvD-cyclohexyn-β^-methyl-piperazin-i-yl)- nicotinamide dihydrochloride**

The title compound was prepared analogously as described in Example E1 using 6-(4-methyl-piperazin-1-yl)-nicotinic acid instead of pyridazine-3-carboxylic acid.
MS (ES+): 442[M+H]+.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 1.84min.

**Example E41**

**1-Cyclopropyl-1H-benzoimidazole-5-carboxylic acid r4-aminomethyl-4-(3-chloro-phenvD-cyclohexyll-amide hydrochloride**

The title compound was prepared analogously as described in Example E1 using 1-Cyclopropyl-1H-benzoimidazole-5-carboxylic acid instead of pyridazine-3-carboxylic acid.
HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.09min.

**Example E42**
S-Isopropyl-isoxazolo[S^-bipyridine-S-carboxylic acid r4-aminomethyl-4-(3-chloro-phenvO-cvclohexyll-amide hydrochloride

The title compound was prepared analogously as described in Example E 1 using 3-Isopropyl-isoxazolo[5,4-b]pyridine-5-carboxylic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.35min.

Example E43

6-(Acetylamino-methyl)-N-r4-aminomethyl-4-(3-chloro-phenvπ-cvclohexyn_nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E 1 using 6-(Acetylamino-methyl)-nicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.37min.

Example E44

N-r4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-ri,2,41triazol-1-yl-nicotinamide hydrochloride

The title compound was prepared analogously as described in Example E 1 using 6-[1,2,4]triazol-1-yl-nicotinic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.83min.

Example E45

N-r4-Aminomethyl-4-(3-chloro-phenvπ-cyclohexyn-3-methanesulfonyl-benzamide hydrochloride

The title compound was prepared analogously as described in Example E 1 using 3-Methanesulfonyl-benzoic acid instead of pyridazine-3-carboxylic acid.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.74min.

**Example E46**

N^\-Aminomethyl-O-chloro-phenylM-cyclohexylM-methanesulfonyl-benzamide hydrochloride

The title compound was prepared analogously as described in Example E1 using 4-Methanesulfonyl-benzoic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.76min.

**Example E47**

S-H/lethanesulfonyl-thiophene-2-carboxylic acid r4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-amide hydrochloride

The title compound was prepared analogously as described in Example E1 using 5-Methanesulfonyl-thiophene-2-carboxylic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.92min.

**Example E48**

2-(3-Methanesulfonyl-phenylH-pyrimidine-4-carboxylic acid r4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-amide hydrochloride

The title compound was prepared analogously as described in Example E1 using 2-(3-Methanesulfonyl-phenyl)-pyrimidine-4-carboxylic acid instead of pyridazine-3-carboxylic acid.


HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.32min.

**Example E49**

N^\-AminomethylM-O-cthtoro-phenyD-cyclohexyn- 2-O-methanesulfonylamino-phenyp-acetamide hydrochloride
The title compound was prepared analogously as described in Example E1 using 2-(3-methanesulfonylamino-phenyl)-acetic acid instead of pyridazine-3-carboxylic acid.

MS (ES+): 450[M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.69min.

**Example E50**

4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylamine hydrochloride

The title compound was prepared analogously as described in Example E1, step A to G followed by step H.

H) 4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylamine hydrochloride

Trifluoroacetic acid (271µl) was added to a solution of [4-Amino-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (120mg, 0.354mmol) in dichloromethane (3ml). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was dissolved in dioxane and treated with an excess of 4M hydrogen chloride in dioxane. Lyophilization of the mixture gave the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.28 min.

**Example EA1**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-isoindole-1.3-dione

The title compound was prepared according to Scheme E.

The title compound was prepared analogously as described in Example E1, step A to G followed by step H.

H) N-f4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cvclohexyn-phthalamic acid
To a solution of [4-Amino-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (100mg, 0.274mmol) in chloroform (2mL) was added phthalic anhydride (55mg, 0.37mmol). The reaction mixture was stirred at 70°C for 16h. The mixture was concentrated in vacuo. The residue was purified by flash chromatography (Silica cartridge) using gradient elution from 100% cyclohexane to 100% ethylacetate, then dichloromethane/methanol 8:2. Fractions containing the product were concentrated in vacuo to give the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.50 min.

I) 1-(cis-3-Chloro-phenyl)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclohexylmethyn-carbamic acid tert-butyl ester

To a solution of N-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-phthalamic acid (100mg, 0.191mmol) in acetonitrile (2mL) were added (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (119mg, 0.229mmol) and triethylamine (32µl, 0.229mmol). The reaction mixture was stirred at room temperature for 4h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-18.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.39 min.

J) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl1-isoindole-1,3-dione

Trifluoroacetic acid (500µl) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(1,3-dioxo-1,3-dihydro-isooindol-2-yl)-cyclohexylimethyl]-c=ri3amic acid tert-butyl ester (50rr,g,
0.099 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5 µm 19 x 50 mm, flow 20 mL/min, 15 min method (0-2.5 min 5% ACN, 2.5-12.5 min 5-100% ACN, 12.5-15.0 min 100% ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

**MS (ES+)**: 369 [M+H]+.

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50 mm, 6 min method (0-3 min 5-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 2.81 min.

**Example EB1**

4-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-3-oxo-piperazine-1-carboxylic acid benzyl ester

The title compound was prepared analogously as described in Example E1, step A to G followed by step H) (Benzyloxy carbonyl-l2-f4-(tert-butoxy carbonyl amino)-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino1-ethyl(V-amino)-acetic acid ethyl ester

To a solution of [4-Amino-1-(cis-3-chloro-phenyl)-cyclohexyl methyl]-carbamic acid tert-butyl ester (406 mg, 1.20 mmol) in 1,2-Dichloroethane (3 mL) were added [Benzyloxy carbonyl-(2-oxo-ethyl)-amino]-acetic acid ethyl ester (300 mg, L00 mmol) and acetic acid (57 µL, 1.4 mmol). The mixture was stirred at room temperature for 1 h, then Sodium triacetoxyborohydride was added. The reaction mixture was stirred at room temperature for 16 h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5 µm 30 x 100 mm, flow 40 mL/min, 45 min method (0-2.5 min 20% ACN, 2.5-42.5 min 20-100% ACN, 42.5-45.0 min 100% ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.
MS (ES\(^+\)): 602 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.49 min.

J) 4-f4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

A solution of (Benzyloxycarbonyl-{2-[4-(tert-butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexylamino]-ethyl}-amino)-acetic acid ethyl ester (50mg, 0.083mmol) in a mixture of toluene (1ml), n-Butanol (1ml) and acetic acid (215µl) was treated with microwave at 150°C for 40 minutes. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

MS (ES\(^+\)): 580 [M+Na]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.49 min.

J) 4-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

Trifluoroacetic acid (177µl) was added to a solution of 4-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (21 mg, 0.035mmol) in dichloromethane (1mL). The reaction mixture was stirred at room temperature for 2h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was treated with diethylether. After removal of the etheric phase with a pipette, the residue was dissolved in Methanol and treated with an excess of 2M Hydrochloric acid in methanol.
The volatiles were evaporated, then the residue was dissolved in dioxane and lyophilized to give the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.70 min.

**Example F1**

N-rc/s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyn-3,5-dimethylisoxazole-4-sulfonamide and N-ffra πs^-faminomethylM-O-chlorophenvDcvclohexyn-S. δ-dimethylisoxazole-4-sulfonamide

The title compounds were prepared according to Scheme F.

A) A mixture of ffrans-1-(3-chlorophenyl)-4-hydroxy-cyclohexylmethyl-carbamic acid tert-butyl ester and fc/s-1-(3-chlorophenyl)-4-hydroxy-cyclohexylmethyl-carbamic acid tert-butyl ester

Sodium borohydride (361 mg, 9.6mmol) was added to a solution of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile (1.61g, 4.78mmol) in tetrahydrofuran (20mL) and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate (2x150ml). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (silica cartridge (50g), using a gradient elution from 5% ethyl acetate in cyclohexane to 40% ethyl acetate in cyclohexane) to give a mixture of the title compounds as a colourless oil.


Tᵢ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.30 and 3.44 min.

B) A mixture of methanesulphonic acid ffrans-4-(tert-butoxycarbamino-methyl)-4-(3-chlorophenvD-cvclohexyni ester and methanesulphonic acid rc/s-4-(tert-butoxycarbamino-methyl)-4-(3-chlorophenyl)-cyclohexyn ester

Triethylamine (1.15mL, 8.3mmol) and methane sulphonyl chloride (0.32mL, 4.16mmol) were added to a solution of a mixture of *trans-1-(S-chlorophenylH-hydroxy-cyclohexylmethyl)-
carbamic acid tert-butyl ester and [c/s-1-(3-chlorophenyl)-4-hydroxy-cyclohexylmethyl]-
carbamic acid tert-butyl ester (564mg, 1.66mmol) in dichloromethane (10mL) and the
mixture was stirred at room temperature for 2 hours. The mixture was partitioned between
aqueous ammonium chloride and dichloromethane (2x150ml). The combined organics were
washed with aqueous sodium hydrogen carbonate and brine, dried (MgSO₄) and
concentrated. The residue was purified by flash chromatography (Silica cartridge (50g),
using a gradient elution from 10% ethyl acetate in cyclohexane to 30% ethyl acetate in
cyclohexane) to give a mixture of the title compounds as a colourless gum.

Tᵣ[HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%
Formic acid for 5 min, flow 2.0 ml/min]: 3.96 min.

C) A mixture of Trans-4-azido-1-(3-chlorophenyl)-cyclohexylmethyl-carbamic acid tert-butyl
ester and fc/s-4-azido-1-(3-chlorophenyl)-cyclohexylmethyl-carbamic acid tert-butyl ester.

Sodium azide (1.72g, 26.51 mmol) was added to a solution of a mixture of methanesulphonic acid [Trans-4-(tert-butoxycarbonylamino-methyl)-4-(3-chlorophenyl)-cyclohexyl] ester and
methanesulphonic acid [c/s-4-(tert-butoxycarbonylamino-methyl)-4-(3-chlorophenyl)-
cyclohexyl] ester (2.77g, 66.3mmol) in dimethylformamide (140mL) and the reaction mixture
was heated at 100°C for 5 hours. After cooling, the mixture was diluted with water and
extracted with ethyl acetate (4x150ml), the combined extracts were washed with water and
brine, and dried (MgSO₄). Concentration in vacuo afforded a mixture of the title compounds
as a yellow oil, which was used directly in the next step.

Tᵣ[HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%
Formic acid for 5 min, flow 2.0 ml/min]: 4.40 and 4.46 min.

D) A mixture of Trans-4-amino-1-(3-chlorophenyl)-cyclohexylmethy lπ carbamic acid tert-butyl
ester and fc/s-4-amino-1-(3-chlorophenyl)-cyclohexylmethy ncarbamic acid tert-butyl ester.

Triphenylphosphine (3.44g, 13.1mmol) and water (1.18mL) were added to a mixture of
[Trans-4-azido-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester and [c/s-4-
azido-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester (2.41 g, 6.57mmol)
in toluene (40mL) and the reaction mixture was heated at 50°C overnight. After cooling, the
reaction mixture was concentrated in vacuo to remove most of the solvent. The residual
solution was initially purified by ion exchange chromatography (SCX-2 column (25g), eiuting
sequentially with dichloromethane, 1:1 dichloromethane:methanol, methanol and 2M ammonia in methanol). Fractions containing the desired products were further purified by flash chromatography (silica (70g), eluting with 200:2:0.5 dichloromethane:ethanol:(aq)ammonia to 200:8:1 dichloromethane:ethanol:(aq)ammonia) the mixture of title compounds as a yellow oil.

MS (ES⁺): 285 [M+H-tBu]

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 2.28 and 2.38 min.

E) A mixture of [trans-1-(3-chlorophenyl)-4-(3,5-dimethylisoxazole-4-sulfonylamino)-
cyclohexylmethyl carbamic acid tert-butyl ester and [c/s-1-(3-chlorophenyl)-4-(3,5-
dimethylisoxazole-4-sulfonylamino)-cyclohexylmethyl carbamic acid tert-butyl ester

N-Methyl morpholine (80µL, 0.7mmol) and 3,5-dimethyl-isoxazole-4-sulphonyl chloride (102mg, 0.52mmol) were added to a stirred mixture of [fra/7S-4-amino-1-(3-chlorophenyl)-
cyclohexylmethylj-carbamic acid tert-butyl ester and [c/s-4-amino-1-(3-chlorophenyl)-
cyclohexylmethyl] carbamic acid tert-butyl ester (118mg, 0.35mmol) in dichloromethane (3mL) and stirring was continued for 3 hours. The mixture was washed with 1M hydrochloric acid (2mL) and evaporated. The residue was purified by flash chromatography (silica (5g), eluting with pentane then pentane:diethyl ether 1:1) to give the title compounds as a colourless oil.


T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.93 and 4.11 min.

F) A mixture of N-fc/s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyll-3.5-dimethylisoxazole-4-sulfonamide and N-frans^-aminomethylM-P-chlorophenvDcyclohexylT-S.S-
dimethylisoxazole-4-sulfonamide

A mixture of [frans-1-(3-chlorophenyl)-4-(3,5-dimethylisoxazole-4-sulfonylamino)-
cyclohexylmethyl]-carbamic acid tert-butyl ester and [c/s-1-(3-chlorophenyl)-4-(3,5-
dimethylisoxazole-4-sulfonylamino)-cyclohexylmethyl] carbamic acid tert-butyl ester (137mg, 0.28mmol) trifluoroacetic acid (0.5mL) and dichloromethane (2mL) was stirred for 2h, then blown down to dryness. The residue was chromatographed (SCX cartridge (5g) eluting
sequentially with dichloromethane, dichloromethane:methanol 1:1, and dichloromethane:methanol 1:1 with 5% aq. ammonia) to give a colourless oil. The oil was further purified by chromatography (silica, (5g) eluting sequentially with dichloromethane:ethanol:ammonia, 400:8:1, 200:8:1 then 100:8:1) to give a mixture of the title compounds in the form of a white solid.

MS (ES\(^{+}\)): 398, 400 [M+H\(^{+}\)].

T\(_{R}\) [HPLC, Higgins Clipeus \(5\) micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.20 and 6.89 min.

**Example F2**


The title compounds were prepared analogously as described in Example F1 using thiophene-2-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.

MS (ES\(^{+}\)): 385, 387 [M+H\(^{+}\)].

T\(_{R}\) [HPLC, Higgins Clipeus \(5\) micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.82 min.

**Example F3**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy pyridine-3-sulfonamide hydrochloride and N-rfra/is^-faminomethylIM-O-chlorophenvDcyclohexyntiophene-pyridine-S-sulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using pyridine-3-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.

MS (ES\(^{+}\)): 380, 382 [M+H\(^{+}\)].

T\(_{R}\) [HPLC, Higgins Clipeus \(5\) micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.63 min.
Example F4


The title compounds were prepared analogously as described in Example F 1 using methane-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.

MS (ES\(^+\)) : 317, 319 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clupeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.30 and 5.00 min.

Example F5

N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-4-(trifluoromethyl)benzenesulfonamide hydrochloride and N-rfrans^-fcminornethylM-te-chlorophenv \(\pi\)cyclohexyrM-(trifluoromethyl)benzenesulfonamide hydrochloride.

The title compounds were prepared analogously as described in Example F 1 using 4-(trifluoromethyl)-benzene-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The diastereomers were separated by mass directed preparative HPLC. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying.

\(Cis\) diastereisomer

MS (ES\(^+\)) : 447, 449 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clupeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 7.52 min.

\(Trans\) diastereoisomer

MS (ES\(^+\)) : 447, 449 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clupeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.94 min.
Example F6
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-1-methyl-1H-imidazole-4-
sulfonamide hydrochloride and N-\textit{trans}-4-(aminomethyl)-4-(3-
chlorophenyl)cyclohexyn-1-methyl-1H-imidazole-4-sulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using 1-methyl-
1H-imidazole-4-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The
hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol
followed by drying. The title compounds were obtained as a mixture.
MS (ES\textsuperscript{+}): 383, 385 [M+H]\textsuperscript{+}.
T\textsubscript{R} [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\textsubscript{3}CN+0.1%Formic acid/H\textsubscript{2}O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.34 and 6.16 min.

Example F7
N-\textit{fc}/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-6-chloroimidazor2,1-
biri.31thiazole-5-sulfonamide hydrochloride and N-\textit{trans}-4-(aminomethyl)-4-(3-
chlorophenyl)cyclohexyn-6-chloroimidazor2,1-bif1.31thiazole-5-sulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using 6-chloro-
imidazo[2,1-b]thiazole-5-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl
chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid
in methanol followed by drying. The title compounds were obtained as a mixture.
MS (ES\textsuperscript{+}): 459, 461,463 [M+H]\textsuperscript{+}.
T\textsubscript{R} [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\textsubscript{3}CN+0.1%Formic acid/H\textsubscript{2}O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.75 and 7.25 min.

Example F8
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-\textit{\pi}-4-(trifluoromethoxy)benzenesulfonamide hydrochloride and N-\textit{trans}-4-(aminomethyl)-4-O-chloropheny\textit{\pi} cyclohexylM-trifluoromethoxybenzenesulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using 4-
trifluoromethoxy-benzenesulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl
chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.


**Example F9**

N-rc/s-4-(Aminomethyl)H-(3-chlorophenyl)cyclohexy
π-2-
(trifluoromethyl)benzenesulfonamide hydrochloride and N-rtrans-4-(aminomethyl)-4-
O-chloropheny
π-cyclohexy
π-2-ftrifluoromethylDbenzenesulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using 2-trifluoromethyl-benzenesulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.


**Example F10**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy
π-5-(phenylsulfonyl)thiophene-2-
sulfonamide hydrochloride and N-rtrans-4-faminomethyl)-4-(3-
chlorophenyl)cyclohexyn-5-(phenylsulfonyl)thiophene-2-sulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using 5-(phenylsulfonyl)-thiophene-2-sulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.

MS (ES^+): 525, 527 [M+H]^+. 

**Example F11**
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-1-phenylmethanesulfonamide hydrochloride and N-rfraws^-fcminomethylIM-O-chlorophenyOcyclohexylI-i - phenylmethanesulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using benzylsulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.

MS (ES\(^+\)): 393, 395[M+H].

T\(_R\) [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.54 and 7.09 min.

Example F12

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenv \(\pi\)cyclohexyn-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethanesulfonamide hydrochloride and N-rftrans-4-(aminomethyl)-4-(3-chlorophen\(\pi\)cyclohexyn-2-d.S-dioxo-L.S-dihydro- 2H-isoindol-2-vDethanesulfonamide hydrochloride

The title compounds were prepared analogously as described in Example F1 using 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonyl chloride instead of 3,5-dimethyl-isoxazole-4-sulphonyl chloride. The hydrochloride salts were prepared by treatment with excess hydrochloric acid in methanol followed by drying. The title compounds were obtained as a mixture.

MS (ES\(^+\)): 476, 478 [M+H].

T\(_R\) [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.63 and 7.01 min.

Example G1

N-Fc/s-4-(aminomethylM-(3-chlorophenyl)cyclohexy \(\pi\)benzenesulfonamide hydrochloride and N-r*a/is-4-(aminomethyl)-4-(3-chlorophenyhvcyclohexy \(\pi\)benzenesulfonamide hydrochloride.

The title compounds were prepared according to Scheme G.
A) A mixture of N-fc/s-4-(3-chlorophenyl)-4-cvano-cvclohexyl1-benzenesulfonamide and N-f/rans-4-(3-chlorophenyl)-4-cvano-cvclohexyl1-benzenesulfonamide.

Sodium cyanoborohydride (128mg, 2.03mmol) was added to a stirred mixture of ammonium chloride (453mg, 8.47mmol), 3A molecular sieves and 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile (396mg, 1.69mmol) in methanol (5mL) at 0°C and stirring in an ice bath was continued over night. Triethylamine (0.47mL, 3.39mmol) and benzenesulfonyl chloride (0.65mL, 5.1mmol) were added and the mixture was stirred for a further 2 hours. The reaction mixture was neutralized with 1M hydrochloric acid and extracted with ethyl acetate. The aqueous phase was basified with aqueous sodium bicarbonate and extracted with ethyl acetate. The organics were combined, washed with water and brine, dried (MgSO4), and concentrated. The residue was purified by flash chromatography (Silica (10g), eluting with 10% ethyl acetate in cyclohexane) to give a mixture of the title compounds as a pale yellow oil.

MS (ES⁺): 373 [M-H]-.
T_R (HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min): 3.93 min.


Borane-tetrahydrofuran complex (600µL, 0.15mmol of a 1M solution in tetrahydrofuran) was added to a solution of a mixture of N-[c/s-4-(3-chlorophenyl)-4-cyano-cyclohexyl]-benzenesulfonamide and N-[ftra/7s-4-(3-chlorophenyl)-4-cyano-cyclohexyl]-benzenesulfonamide (50mg, 0.134mmol) in tetrahydrofuran (3mL) under a nitrogen atmosphere. The reaction mixture was refluxed for 4hours. Carefully, concentrated sulphuric acid (1.5ml) was added and the mixture was refluxed for a further 2 hours. After cooling to room temperature the mixture was basified with aqueous sodium hydroxide. The mixture was extracted with dichloromethane (3x20ml), the combined extracts were washed with water and brine, dried (MgSO4) and concentrated. The residue was purified by chromatography (SCX-2 column (5g), eluting sequentially with dichloromethane, ethyl acetate, methanol and 2M ammonia in methanol), and then by flash chromatography (Silica (2g), eluting with 100:4:4:0.5 dichloromethane:ethanol:methanol:aq. ammonia). Finally,
purification by reversed phase HPLC ( ) afforded the separated title compounds which were converted to hydrochloride salts (Example F2).

* cis diastereoisomer

**MS (ES+)**: 379, 381 [M+H]+.

**T_R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]**: 6.38 min.

* trans diastereoisomer

**MS (ES+)**: 379, 381 [M+H]+.

**T_R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]**: 5.60 min.

**Example H1**

(c/s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-f2-(trifluoromethyldbenznyucosehexanecarboxamide hydrochloride)

The title compound was prepared according to Scheme H.

A) 1-(3-Chlorophenyl)-4-methoxymethylene-cyclohexanecarbonitrile.

Lithium bis(trimethylsilylamide) (12.8mL, 12.8mmol of a 1M solution in tetrahydrofuran) was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (4.53g, 12.8mmol) in tetrahydrofuran (13 mL) under an argon atmosphere at 0°C. After 30 min, the suspension was added to a solution of 1-(3-chlorophenyl)-4-oxo-cyclohexanecarbonitrile (2.0g, 8.55mmol) in tetrahydrofuran (19 mL) with cooling to 0°C. After 5h of stirring at 0°C, water was carefully added and the mixture was extracted with diethyl ether. The combined extracts were washed with water, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash chromatography (silica, gradient elution with cyclohexane to ethyl acetate 92:8) to give the title compound as a white solid.

**1Hnmr [400 MHz, CDCl₃, tetramethylsilane as internal standard]**: δ 1.76 (2H, m), 2.18 (4H, m), 2.47 (2H, m), 2.95 (2H, m), 3.58 (3H, s), 5.87 (1H, br. s), 7.25-7.35 (2H, m), 7.38 (1H, m), 7.45 (1H, br. s).

B) c/s-1-(3-Chlorophenyl)-4-formyl-cyclohexanecarbonitrile.
Hydrochloric acid (1M, 2mL) was added to a solution of 1-(3-chlorophenyl)-4-methoxymethylene-cyclohexanecarbonitrile (549mg, 2.09mmol) in acetonitrile (4.8mL) and the mixture was stirred at room temperature for 16 hours. The mixture was neutralised by the addition of saturated aqueous sodium bicarbonate and extracted with diethyl ether. The extracts were washed with water (twice), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica, gradient elution with cyclohexane/ethyl acetate 99:1 to 82:18) to give trans-1-(3-chlorophenyl)-4-formyl-cyclohexanecarbonitrile as the minor isomer and the title compound, c/s-1-(3-chlorophenyl)-4-formyl-cyclohexanecarbonitrile, as the major isomer.

**Trans** diastereoisomer:

$^1$Hnmr [400 MHz, CDCl$_3$, tetramethylsilane as internal standard], δ 1.72-1.92 (2H, m), 2.00-2.25 (4H, m), 2.2-2.93 (2H, m), 2.69 (1H, t), 7.25-7.36 (3H, m), 7.42 (1H, br. s), 9.76 (1H, s).

**Cis** diastereoisomer:

$^1$Hnmr [400 MHz, CDCl$_3$, tetramethylsilane as internal standard], δ 1.75-1.98 (4H, m), 2.03-2.41 (5H, m), 7.27-7.44 (3H, m), 7.48 (1H, br. s), 9.68 (1H, s).

C) c/s-4-(3-Chlorophenyl)-4-cyano-cyclohexanecarboxylic acid

A mixture of sodium chlorite (245mg, 2.16mmol) and sodium dihydrogenphosphate monohydrate (381 mg, 2.70mmol) in water (8ml) was added to a suspension of c/s-1-(3-chlorophenyl)-4-formyl-cyclohexanecarbonitrile (268mg, 1.08mmol) in a solution of 2-methyl-2-butene (458µL, 4.32mmol) in tert-butanol (6mL). After stirring for 1 hour, the mixture was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give the title compound as a white solid.

MS (ES$^-$): 262 [M-H]-.

$T_R$ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.27 min.

D) cis-4-(3-Chlorophenyl)-cyano-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide

Diisopropylethylamine (146µL, 0.85mmol) and then O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (119mg, 0.31 mmol) were added to a solution of C7S-4-(3-chlorophenyl)-4-cyano-cyclohexanecarboxylic acid (75mg, 0.28mmol) and 2-
(trifluoromethyl)benzylamine (54.8mg, 0.31 mmol) in dimethylformamide (2.5mL). After stirring for 20h, saturated aqueous sodium bicarbonate was added and the mixture was extracted with dichloromethane. The extracts were washed with water, filtered through a hydrophobic membrane and concentrated in vacuo. The residue was purified by flash chromatography (silica, gradient elution with cyclohexane/ethyl acetate 9:1 to 75:25) to give the title compound as a white solid.


T_r [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 3.97 min.

E) c/s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-f2-(trifluoromethyl)benzylamide hydrochloride.

cis-4-(3-Chlorophenyl)-cyano-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide (92mg, 0.21 mmol) and cobalt II chloride hexahydrate (104mg, 2.18mmol) were dissolved in methanol (7mL) under a nitrogen atmosphere. The mixture was stirred and sodium borohydride (83mg, 2.18mmol) was added portionwise, allowing the effervescence to subside between additions; then the mixture was stirred for 16hours. The reaction was adjusted to pH=2 by the addition of 1M hydrochloric acid at 0°C. After stirring for 10 min the mixture was basified with saturated aqueous sodium bicarbonate and extracted thoroughly with ethyl acetate. The combined extracts were washed with water, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash chromatography (silica, gradient elution with dichloromethane/2M ammonia in methanol 98.5:1.5 to 96:4) to give the free base of the title compound. The hydrochloride salt was prepared by dissolution of the free base in methanol, treatment with a small excess of hydrochloric acid and evaporation of volatiles. After drying, the title compound was obtained as an off-white solid.


T_r [HPLC, Higgins Cliqueus Smicron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 7.29 min.

Example H2

1-{fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexycarbonylV1.4-diazepan-5-one hydrochloride
The title compound was prepared analogously as described in Example H1 using [1,4]diazepan-5-one instead of 2-(trifluoromethyl)benzylamine.

**Example H3**

\[ \text{1-(c/s-1-}(3\text{-Chlorophenyl})\text{-4-}(r3-}(3\text{-trifluoromethyl})\text{-5,6-dihydropyrazolo}\text{-2,4-}\text{triazolo[4,3-}\text{a}]\text{pyrazine} \text{hydrochloride} \]

The title compound was prepared analogously as described in Example H1 using 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine instead of 2-(trifluoromethyl)benzylamine.

**Example H4**

\[ \text{1-(1-{rc/s-4-}(Aminomethyl)-4-(3-chlorophenyl)cyclohexanecarboxyl} \text{piperidinyl-4-yl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride} \]

The title compound was prepared analogously as described in Example H1 using 1-piperidin-4-yl-1,3-dihydro-benzimidazol-2-one instead of 2-(trifluoromethyl)benzylamine.
MS (ES⁺): 467, 469 [M+H]⁺.

**Example H5**

\[ \text{c/s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-(pyridin-3-ylmethyl)cyclohexanecarboxamide hydrochloride} \]

The title compound was prepared analogously as described in Example H1 using C-pyridin-3-yl-methylamine instead of 2-(trifluoromethyl)benzylamine.
Example H6

c/s-4-(Aminomethyl)-4-(3-chlorophenyl)-N-(1-ethyl-1H-pyrazol-5-yl)cyclohexanecarboxamide hydrochloride

The title compound was prepared analogously as described in Example H1 using 2-ethyl-2H-pyrazol-3-ylamine instead of 2-(trifluoromethyl)benzylamine.


Example H7

1-fc/s-1-(3-chlorophenyl)-4-(3,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-ylcarbonyl)cyclohexylmethanamine dihydrochloride and 1-Trans-(3-chlorophenyl)-4-(3,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-ylcarbonyl)cyclohexylmethanamine dihydrochloride

The title compounds were prepared analogously as described in Example H1 using 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine instead of 2-(trifluoromethyl)benzylamine, and a mixture of cis- and trans-4-(3-chlorophenyl)-4-cyano-cyclohexanecarboxylic acid.

Cis diastereoisomer:

MS (ES⁺): 373, 375 [M+H]+.

Example H

1-(cis-1-f3-chlorophenyl)-4-ir3-(trifluoromethvn-5.6-dihvdrori .2.41triazolor4,3-aipyrazin-7(8H)-vnmethy1)cvdohexyl)methanamine dihydrochloride
Borane-dimethylsulphide complex (236 µl, 2.49 mmol) was added dropwise during 20 min to a solution of 1-(3-chlorophenyl)-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-cyclohexanecarbonitrile (156 mg, 0.35 mmol) in tetrahydrofuran (9 mL) under an argon atmosphere. The mixture was warmed to 60°C under reflux. After stirring for 18 hours, the reaction was allowed to cool to room temperature and was then cooled to 0°C. Water (7 mL) was added and then the reaction was heated at 60°C for 3 hours. After cooling, the mixture was extracted with ethyl acetate, the extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by flash chromatography (silica cartridge eluting with dichloromethane then dichloromethane/2M ammonia in methanol), and then by reversed phase preparative HPLC (15% to 95% CH$_3$CN in H$_2$O at 1 mL/min, flow 5 mL/min). Appropriate fractions were concentrated in vacuo and treated with hydrogen chloride in methanol. Evaporation of the volatiles in vacuo and final drying under high vacuum afforded the title compound as an amorphous solid.

**Example J1**

6-(Aminomethyl)-6-(3-chlorophenyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4(1H)-one

The title compound was prepared according to Scheme J.

A) 6-(3-Chlorophenyl)-2-methyl-4-oxo-3.4.5.6.7.8-hexahydroquinazoline-6-carbonitrile

A mixture of 5-(3-chlorophenyl)-5-cyano-2-oxo-cyclohexanecarboxylic acid methyl ester (100 mg, 0.34 mmol) acetamide hydrochloride (58 mg, 0.60 mmol) and potassium carbonate (96 mg, 0.69 mmol) in methanol (2 mL) was heated at 75°C for 18 hours. After cooling to room temperature, the mixture was acidified to pH=7 with concentrated hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to give the title compound as an off-white solid.

MS (ES$^+$): 300, 302 [M+H]$^+$.  

$T_R$ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 2.67 min.
6-(Aminomethyl)-6-(3-chlorophenyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4(1H)-one

6-(3-Chlorophenyl)-2-methyl-4-oxo-3,4,5,6,7,8-hexahydro-quinazoline-6-carbonitrile (55mg, 0.18mmol) and cobalt II chloride hexahydrate (88mg, 0.36mmol) were dissolved in methanol (2.75ml) under a nitrogen atmosphere. The mixture was stirred and sodium borohydride (49mg, 1.27mmol) was added portionwise, allowing the effervescence to subside between additions; then the mixture was stirred for 20 hours. The reaction mixture was filtered through diatomaceous earth, the pad rinsed with methanol and the washings and filtrate were concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with water and the organic phase dried (Na$_2$SO$_4$). After concentration, the residue was purified on an ion exchange cartridge (SCX-2 cartridge, eluting with dichloromethane/methanol 1:1 then 2M ammonia in methanol). The residue was further purified by flash chromatography (silica, gradient elution with dichloromethane/2M ammonia in methanol 98.5:1.5 to 93:7) to give the title compound as a colourless oil.


$T_R$ [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.72 min.

**Example J2**

6-(Aminomethyl)-6-(3-chlorophenyl)-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(1H)-one

The title compound was prepared analogously as described in Example J1 using benzamidine hydrochloride instead of acetamidine hydrochloride.


$T_R$ [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH$_3$CN+0.1%Formic acid/H$_2$O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.11 min.

**Example K1**

N-rfra/7s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexynpyridazine-3-carboxamide Hydrochloride

The title compound was prepared according to Scheme K.
A) Methanesulfonic acid 4-(tert-butoxycarbonylamino-methyl)-4-(3-chloro-phenyl)-cyclohexyl ester

Triethylamine (2.3mL, 16.5mmol) and methanesulphonyl chloride (0.64mL, 8.24mmol) were added to a solution of [c/s-1-(3-chlorophenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester [Example E1] (1.4g, 4.12mmol) in dichloromethane (65mL) at 0°C. The mixture was stirred at room temperature for 2 hours. The solution was washed with aqueous ammonium chloride, aqueous sodium bicarbonate and brine, then dried and concentrated in vacuo to give a yellow oil. The oil was purified by flash chromatography (silica, eluting with 40% ethyl acetate in cyclohexane) to give the title compound as a colourless oil.

MS (ES+): 440 [M+Na]

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.45 min.

B) rtrans-4-Azido-1-(3-chloro-phenyl)-cyclohexylmethyl-carbamic acid tert-butyl ester

Sodium azide (809mg, 12.44mmol) was added to a solution of methanesulfonic acid 4-(tert-butoxycarbonylamino-methyl)-4-(3-chloro-phenyl)-cyclohexyl ester (1.3g, 3.1 mmol) in dimethylformamide (80mL) and the mixture was stirred at 100°C for 5 hours. After cooling, the mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried and concentrated in vacuo to give the title compound as a colourless oil.

MS (ES+): 406 [M+H acetonitrile adduct].

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 4.38 min.

C) ftrans-4-Amino-1-(3-chlorophenyl)-cyclohexylmethylcarbamic acid tert butyl ester.

Triphenylphosphine (1.41g, 5.37mmol) and water (0.5mL) were added to a solution of [trans-4-azido-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester (980mg, 2.68mmol) in toluene (20mL) and the mixture was heated at 50°C for 20 hours. The crude reaction mixture was purified twice on an ion exchange column (SCX, eluting sequentially with dichloromethane, methanol and 2M ammonia in methanol) to give the title compound as a colourless oil, which solidified on standing.

MS (ES+): 339 [M+H]
D) (trans-1-(3-Chlorophenyl)-4-(pyridazine-3-carbonyl)-aminocyclohexylmethyl)carbamoyl
acid tert-butyl ester

[trans-4-Amino-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamoyl acid tert butyl ester (100mg,
0.295mmol) was added to a solution of pyridazine-3-carboxylic acid (55mg, 0.442mmol), O-
(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (168mg,
0.442mmol) and diisopropylethylamine (0.16mL, 0.885mmol) in dimethylformamide (2mL)
and the mixture stirred at room temperature for 20 hours. The reaction was concentrated in
vacuo and partitioned between ethyl acetate and aqueous sodium bicarbonate. After passing
through a phase separator the organic layer was dried, and evaporated to give a yellow oil.
The oil was purified by flash chromatography (silica, gradient elution from 50-75% thyl
acetate in cyclohexane) to give the title compound as a white solid.
MS (ES\(+\)): 467 [M+Na]\+

T<sub>R</sub> [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%
Formic acid for 5 min, flow 2.0 ml/min]: 3.22 min.

E) N-(trans-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl)pyridazine-3-carboxamide
hydrochloride

Trifluoroacetic acid (1mL) was added to a solution of (trans-1-(3-chlorophenyl)-4-
[(pyridazine-3-carbonyl)-amino]-cyclohexylmethyl)carbamoyl acid tert-butyl ester (75mg,
0.168mmol) in dichloromethane (10mL) and the mixture was stirred at room temperature for
90 mins. The reaction mixture was purified by chromatography (SCX cartridge, eluting
sequentially with dichloromethane, methanol and 0.5M ammonia in methanol) to give the
free base of the title compound. The free base was dissolved in methanol and treated with
excess 1M hydrogen chloride in methanol. Evaporation and drying afforded the title
compound as a white solid.
MS (ES\(+\)): 345 [M+H]\+

T<sub>R</sub> [HPLC, Higgins Clicheus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%
Formic acid for 20 min, flow 2.0 ml/min]: 5.24 min.
Example K2

1-Acetyl-N-rfrans-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexynpiperidine-4-carboxamide hydrochloride

The title compound was prepared analogously as described in Example K1 using 1-acetyl-piperidine-4-carboxylic acid instead pyridazine-3-carboxylic acid.

MS (ES\(^{+}\)): 392 [M+H]\(^{+}\).

TR [HPLC, Higgins Cliepeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.11 min.

Example K3

N-rfrans^-faminomethylM-O-chlorophenyDcvclohexyn- 2-furamide hydrochloride

The title compound was prepared analogously as described in Example K1 using furan-2-carboxylic acid instead pyridazine-3-carboxylic acid.

MS (ES\(^{+}\)): 333 [M+H]\(^{+}\).

TR [HPLC, Higgins Cliepeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.93 min.

Example L1

cfs^-{(AminomethylIM^3^hlorophenyl)-N-r(4-phenyl-1H-pyrazol-5- yDmethyllcvclohexanamine hydrochloride

The title compound was prepared according to Scheme L

A) (c/s-1-(3-Chloro-phenyl)-4-f(4-phenyl-2H-pyrazol-3-ylmethyl)-amino1-cyclohexylmethyl)-carbamic acid tert-butyl ester

A mixture of [c/s-4-amino-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester [Example E1] (130mg, 0.384mmol) and 4-phenyl-2H-pyrazole-3-carbaldehyde (68mg, 0.394mmol) in acetic acid (0.3mL) and dichloromethane (2mL) was stirred in the presence of 4A molecular sieves for 30min. Sodium triacetoxyborohydride (130mg, 0.613mmol) was added in one portion and the reaction mixture was stirred for a further 4hours. The reaction mixture was partitioned between aqueous sodium carbonate (2M, 5ml) and dichloromethane
(2x1 ml) and the combined organic phases were directly applied to a silica cartridge (5g). Sequential elution with dichloromethane, dichloromethane:ethanol:ammonia, 400:8:1 then 200:8:1 then 100:8:1 gave the title product as a colourless oil.

MS (ES\(^{+}\)) \text{:} 495 [M+H]\(^{+}\). 

\(T_R\) [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: split peak 2.2, 2.31 min.

\textbf{B)} \textit{c/s}^-^\textit{AminomethylM-O-chlorophen} \textit{π-N-f}^-^\textit{phenyl-lH-pyrazol-S- vDmethylcyclohexanamine Hydrochloride}

A mixture of the \{c/s-1-(3-Chloro-phenyl)-4-{(4-phenyl-2H-pyrazol-3-ylmethyl)-amino]-cyclohexylmethyl]-carbamic acid tert-butyl ester (124mg, 0.25mmol) trifluoroacetic acid (1mL) and dichloromethane (1mL) was stirred for 2h, then blown down to dryness. The residue was purified by flash chromatography (silica, eluting sequentially with dichloromethane, dichloromethane:ethanol:ammonia, 400:8:1 then 200:8:1 then 100:8:1 ) to afford the free base of the title compound as a colourless oil. The oil was dissolved in methanol (1ml) and treated with concentrated hydrochloric acid (3 drops). The mixture was concentrated in vacuo, triturated with diethyl ether and dried to give the title compound as a white solid.

MS (ES\(^{+}\)) \text{:} 395, 397 [M+H]\(^{+}\). 

\(T_R\) [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.68 min.

\textbf{Example L2} \textit{c/s-4-(Aminomethyl)-N-f(2-benzyl-lH-imidazol-5-yl)methvn-4-(3- chlorophenvDcyclohexanamine Hydrochloride}

The title compound was prepared analogously as described in Example L1 using 2-benzyl-3H-imidazole-4-carbaldehyde instead 4-phenyl-2H-pyrazole-3-carbaldehyde.

MS (ES\(^{+}\)) \text{:} 409, 411 [M+H]\(^{+}\). 

\(T_R\) [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 3.64 min.

\textbf{Example M1}
N-rc/s-4-(Aminomethyl)-(3-chlorophenyl)cyclohexyn-N-benzylpyridazine-3-carboxamide hydrochloride

The title compound was prepared according to Scheme M.

A) A mixture of rc/s-4-Benzylamino-1-(3-chloro-phenyl)-cyclohexylmethyl carbamic acid tert-butyl ester and rfrans-4-benzylamino-1-(3-chloro-phenyl)-cyclohexylmethyl carbamic acid tert-butyl ester

Sodium triacetoxyborohydride (320mg, 1.5mmol) was added in one portion to a mixture of benzylamine (90µL, 0.825mmol), [1-(3-chlorophenyl)-4-oxo-cyclohexylmethyl]-carbamic acid tert-butyl ester (250mg, 0.74mmol) and acetic acid (0.5mL) in dichloromethane (5mL) and the reaction mixture was stirred for 18 hours. The reaction mixture was partitioned between aqueous sodium carbonate (2M, 5ml) and dichloromethane (2x1 ml) and the organic phases were applied directly to a silica cartridge (5g). Sequential elution with dichloromethane, dichloromethane:ethanol:ammonia, 400:8:1 then 200:8:1 then 100:8:1 gave a mixture of the title compounds in the form of a pale yellow oil.


T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 2.31, 3.39 min.

B) fc/s-4-fBenzyl-(pyridazine-3-carbonyl)amino1-1-(3-chloro-phenyl)-cyclohexylmethyln-carbamic acid tert-butyl ester and rfrans-4-fbenzyl-(pyridazine-3-carbonv jamino1-1-(3-chloro-phenylD-cyclohexylmethylH-carbamic acid tert-butyl ester

Pyridazine-3-carboxylic acid (36mg, 0.29mmol) was added to a solution of the foregoing mixture of [c/s-4-benzylamino-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester and [rfrans-4-benzylamino-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (83mg, 0.193mmol) in dimethylformamide (3mL) containing diisopropylethylamine (100µL, 0.58mmol) and O-(7-azabenztiaziol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (110mg, 0.29mmol) under a nitrogen atmosphere. After stirring at room temperature overnight, the mixture was diluted with water and extracted into ethyl acetate (2x50ml). The combined organic phases were washed with water and brine, dried (MgSO₄) and concentrated. The residue was purified by automated flash chromatography.
Cis diastereoisomer:
MS (ES\(^{+}\)): 535, 537 [M+H]\(^{+}\).

\[ T_{R} [\text{HPLC, Phenomenex Luna 3 micron C18}; 5-95\% \text{CH}_{3}\text{CN}+0.1\% \text{Formic acid/H}_{2}\text{O}+0.1\% \text{Formic acid for 5 min, flow 2.0 ml/min}]: 3.95 \text{ min}. \]

Trans diastereoisomer:
MS (ES\(^{+}\)): 535, 537 [M+H]\(^{+}\).

\[ T_{R} [\text{HPLC, Phenomenex Luna 3 micron C18}; 5-95\% \text{CH}_{3}\text{CN}+0.1\% \text{Formic acid/H}_{2}\text{O}+0.1\% \text{Formic acid for 5 min, flow 2.0 ml/min}]: 3.84 \text{ min}. \]

\[ \text{C) N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-N-benzylpyridazine-3-carboxamide hydrochloride} \]

A solution of [c/s-4-[benzyl-(pyridazine-3-carbonyl)amino]-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (48mg, 0.090mmol) in trifluoroacetic acid (0.6mL) and dichloromethane (3mL) was stirred at room temperature for 2 hours. The reaction mixture was applied to an SCX-2 ion exchange column and eluted sequentially with dichloromethane, methanol and a 2M solution of ammonia in methanol to the freebase of the product. The free base was further purified by flash chromatography (silica, eluting with 0-20% methanol in dichloromethane). Treatment with excess hydrogen chloride in methanol and freeze drying afforded the title compound as a beige coloured solid.
MS (ES\(^{+}\)): 435, 437 [M+H]\(^{+}\).

\[ T_{R} [\text{HPLC, Higgins Clipeus 5micron C18}; 5-95\% \text{CH}_{3}\text{CN}+0.1\% \text{Formic acid/H}_{2}\text{O}+0.1\% \text{Formic acid for 20 min, flow 2.0 ml/min}]: 6.14 \text{ min}. \]

**Example M2**

**N-rfra/is^-fAminomethylM-O-chlorophenv πcyclohexyll-N-benzylpyridazine-S-carboxamide hydrochloride**

The title compound was prepared analogously as described in Example M1, step C using [trans-4-[benzyl-(pyridazine-3-carbonyl)amino]-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester instead of [c/s-4-[benzyl-(pyridazine-3-carbonyl)amino]-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester.

Tᵣ [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.03 min.

Example M3
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-(2-phenylethyl)acetamide Hydrochloride

The title compound was prepared according to Scheme M.

A) A mixture of fc/s-1-(3-chloro-phenyl)-4-phenethylamino-cyclohexylmethylT- cat>amic acid tert-butyl ester and [frans-1-(3-chloro-phenyl)-4-phenethylamino-cyclohexylmethyl]carbamic acid tert-butyl ester

Sodium triacetoxyborohydride (350mg, 1.65mmol) was added in one portion to a mixture of 2-phenyl-ethylamine (200µL, 1.59 mmol), [i- (3-chlorophenyl)^-oxo-cyclohexylmethyl]-carbamic acid tert-butyl ester (300mg, 0.89mmol) and acetic acid (0.5ml) in dichloromethane (5mL) and the reaction mixture was stirred for 36 hours. The reaction mixture was partitioned between sodium carbonate (2M, 5ml) and dichloromethane (2x2ml) and the organic phases were directly applied to a silica cartridge (10g). Elution with dichloromethane, then dichloromethane:ethanol:ammonia, 400:8:1 then 200:8:1 then 100:8:1 gave a mixture of the products as a colourless oil.

MS (ES⁺): 443, 445 [M+H]⁺

Tᵣ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 2.46 min.

B) fc/s-4-(Acetyl-phenethyl-amino)-1-(3-chloro-phenyl)-cydohexymethylcarbamic acid tert-butyl ester and [frans-7s-4-(acetyl-phenethyl-amino)-1-Q-chloro-phenvD-cvclohexylmethv π carbamic acid tert-butyl ester

Triethylamine (160µL, 1.13mmol) and acetyl chloride (40µL, 0.57mmol) were added to a solution of the foregoing mixture of [c/s-1-(3-chlorophenyl)-4-phenethylamino-cyclohexylmethyl]-carbamic acid tert-butyl ester and [frans-1-(3-chloro-phenyl)-4-phenethylamino-cyclohexylmethylj-carbamic acid tert-butyl ester (167mg, 0.377mmol) in
dichloromethane (3mL) and the reaction mixture was stirred at room temperature for 3 hours. The mixture was diluted with water and extracted with dichloromethane (2 x 30mL). The combined organic phases were washed with brine, dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography (Silica cartridge (10g), using gradient elution from 30%-50% ethyl acetate in cyclohexane) to give the title compounds as individual diastereoisomers.

**Cis diastereoisomer:**


T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 4.33 min.

**Trans diastereoisomer:**


T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 4.09 min.

**C) N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-N-(2-phenylethyl)acetamide Hydrochloride**

A solution of [c/s-4-(acetyl-phenethyl-amino)-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (71 mg, 0.146mmol) in trifluoroacetic acid (0.6mL) and dichloromethane (3mL) was stirred at room temperature for 2 hours. The reaction mixture was applied to an SCX-2 ion exchange column and eluted sequentially with dichloromethane, methanol and a 2M solution of ammonia in methanol to the freebase of the product. The free base was further purified by automated flash chromatography (silica, eluting with 0-20% methanol in dichloromethane). Treatment with excess hydrogen chloride in methanol and freeze drying afforded the title compound as a beige coloured solid.


T_R [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.85 min.

**Example M4**

**N-rafns-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-N-(2-phenylethyl)acetamide Hydrochloride**
The title compound was prepared analogously as described in Example M3, step C using [frans-4-(acetyl-phenethyl-amino)-1- (3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester instead of [c/s-4-(acetyl-phenethyl-amino)-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester.

**Example M5**

**N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy N-(2-phenylethyl)pyridazine-3-carboxamide hydrochloride**

The title compound was prepared analogously as described in Example M1 using 2-phenylethylamine instead of benzylamine.

**Example M6**

**N-frans-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy N-(2-phenylethyl)pyridazine-3-carboxamide hydrochloride**

The title compound was prepared analogously as described in Examples M1 and M2 using 2-phenylethylamine instead of benzylamine.

**Example M7**

**N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl]-N-(cyclopropylmethyl)pyridazine-3-carboxamide hydrochloride**

The title compound was prepared analogously as described in Example M1 using C-cyclopropyl-methylamine instead of benzylamine.
MS (ES\(^+\)): 399, 401 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clipeus δmicron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.32 min.

**Example M8**

**N-trans-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-N-(cyclopropylmethyl)pyridazine-3-carboxamide hydrochloride**

The title compound was prepared analogously as described in Examples M1 and M2 using C-cyclopropyl-methylamine instead of benzylamine.

MS (ES\(^+\)): 399, 401 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clipeus Smicron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.65 min.

**Example M9**

**N-fc/s-4-(Aminomethyl)-M-(3-chlorophenyl)cyclohexyl-N-(2-phenoxyethyl)pyridazine-3-carboxamide hydrochloride**

The title compound was prepared analogously as described in Example M1 using 2-phenoxyethylamine instead of benzylamine.

MS (ES\(^+\)): 465, 467 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.71 min.

**Example M10**

**N-ftrans-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-(2-phenoxyethyl)pyridazine-3-carboxamide hydrochloride**

The title compound was prepared analogously as described in Examples M1 and M2 using 2-phenoxyethylamine instead of benzylamine.

MS (ES\(^+\)): 465, 467 [M+H]\(^+\).

\(T_R\) [HPLC, Higgins Clipeus 5micron C18; 5-95% CH\(_3\)CN+0.1%Formic acid/H\(_2\)O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.49 min.
Example M11
N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-benzylacetamide hydrochloride

The title compound was prepared analogously as described in Example M3 using benzylamine instead of 2-phenylethylamine.
MS (ES+) : 371, 373 [M+H].
T_R [HPLC, Higgins Clieus 5 micron C18; 5-95% CH3CN+0.1%Formic acid/H2O+0.1%Formic acid for 20 min, flow 2.0 ml/min] : 6.62 min.

Example M12
N-frans-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-benzylacetamide hydrochloride

The title compound was prepared analogously as described in Examples M3 and M4 using benzylamine instead of 2-phenylethylamine.
MS (ES+) : 371, 373 [M+H].
T_R [HPLC, Higgins Clieus 5 micron C18; 5-95% CH3CN+0.1%Formic acid/H2O+0.1%Formic acid for 20 min, flow 2.0 ml/min] : 6.53 min.

Example M13
N-fc,s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexy π-N-(cyclopropylmethyl)acetamide hydrochloride

The title compound was prepared analogously as described in Example M3 using C-cyclopropyl-methylamine instead of 2-phenylethylamine.
MS (ES+) : 335, 337 [M+H].
T_R [HPLC, Higgins Clieus 5micron C18; 5-95% CH3CN+0.1%Formic acid/H2O+0.1%Formic acid for 20 min, flow 2.0 ml/min] : 6.32 min.

Example M14
N-frans^-IAminomethylM-O-chlorophenyDcyclohexy π-N-(cyclopropylmethyl)acetamide hydrochloride
The title compound was prepared analogously as described in Examples M3 and M4 using C-cyclopropyl-methylamine instead of 2-phenylethylamine.


**Example M15**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-benzylmethanesulfonamide hydrochloride and H-Urans 4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-benzylmethanesulfonamide hydrochloride

The title compounds were prepared analogously as described in Examples M3 using methane-sulphonyl chloride instead of acetyl chloride and using benzylamine instead of 2-phenylethylamine and were isolated as a mixture of diastereomers.


**Example M16**

N-rc/s-4-(Aminomethyl)M-(3-chlorophenyl)cyclohexyn-N-(cyclopropylmethyl)methanesulfonamide hydrochloride and N-frans-4-(aminomethy0-4-(3-chlorophenynvcyclohexyn-N-(cyclopropylmethyl)methanesulfonamide hydrochloride

The title compounds were prepared analogously as described in Examples M3 using methane-sulphonyl chloride instead of acetyl chloride and using C-cyclopropyl-methylamine instead of 2-phenylethylamine and were isolated as a mixture of diastereomers.


**Example M17**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-(2-pyridyl-2-ylethyl)acetamide
The title compound was prepared analogously as described in Example M1 using 2-pyridin-2-ylethanamine instead of benzylamine.

**Example M18**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexen-N-(3-pyridyl-2-ylethyl)acetamide

The title compound was prepared analogously as described in Example M1 using 3-pyridin-2-ylethanamine instead of benzylamine.

**Example N1**

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-N-(2-phenylethyl)pyridazine-4-carboxamide hydrochloride

The title compound was prepared by the route shown in Scheme N.

**A)** N-r8-(3-Chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyn-2,2,2-trifluoroacetamide

Trifluoroacetic anhydride (5.5mL, 39.57mmol) was added at 0°C to a stirred solution of C-[8-(3-chlorophenyl)-1,4-dioxo-spiro[4.5]dec-8-yl]-methylamine (7.42, 26.33mmol) and diisopropylethylamine (18.4mL, 105.64mmol) in tetrahydrofuran (20mL) and the resulting mixture stirred overnight, warming to room temperature. The mixture was diluted with ethyl acetate (100 mL) and 0.5N hydrochloric acid (100mL). The aqueous layer was separated and extracted with EtOAc (100 mL x 2). The combined organic phases were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100mL), dried (MgSO4) and evaporated to give the title compound as an orange coloured gum which was used directly in the next step.

**B)** N-[1-(3-Chloro-phenyl)-4-oxo-cyclohexylmethyl]-2,2,2-trifluoroacetamide
The foregoing product, N-[8-(3-chloro-phenyl)-1,4-dioxa-spiro[4.5]dec-8-ylmethyl]-2,2,2-
trifluoroacetamide (10.4g, 26.3mmol), was dissolved in a mixture of acetic acid (10OmL) and
water (2OmL) and the solution stirred at ambient temperature for 68 hours.
The mixture was diluted with ethyl acetate (300 mL) and washed with water (3 x 10OmL), and
saturated aqueous sodium bicarbonate (100 mL) and the pH was adjusted to 9 by addition of
10N sodium hydroxide. The organic layer was collected, washed with brine (50 mL), dried
(MgSO4) and evaporated to give a dark orange oil that solidified on standing. The gum was
purified by automated flash chromatography (Silica (33Og cartridge), gradient elution with 5-
40% ethyl acetate in cyclohexane). Appropriate fractions were combined and evaporated to
give the title compound as an off-white solid.
MS (ES') : 332, 334 [M-H]⁻
T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%
Formic acid for 5 min, flow 2.0 ml/min]: 3.13 min.

C) A mixture of N-fc/s-1-(3-chloro-phenyl)-4-phenethylamino-cyclohexylmethvn-2,2,2-
trifluoroacetamide and N-frans-1-O-chloro-phenylM-phenethylamino-cyclohexylmethvn π-
2,2,2-trifluoroacetamide

Sodium triacetoxyborohydride (216mg, 1.01mmol) and acetic acid (58µL, 1.01mmol) were
added to a solution of N-[1-(3-chloro-phenyl)-4-oxo-cyclohexymethyl]-2,2,2-
trifluoroacetamide (170mg, 0.50mmol) and 2-phenylethylamine (96µL, 0.76mmol) in 1,2-
dichloroethane (2.5mL) and the mixture was stirred at room temperature overnight. The
reaction was quenched with saturated aqueous sodium bicarbonate and extracted with
dichloromethane. The organic phase was washed with saturated aqueous sodium
bicarbonate and water, filtered through a phase separator and concentrated in vacuo. The
residue was purified by automated flash chromatography (silica (4g), gradient elution with
dichloromethane to dichloromethane: methanol 93:7) to give a mixture of the title
compounds as a yellow oil.
MS (ES): 439, 441 [M-H]⁺
T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%
Formic acid for 5 min, flow 2.0 ml/min]: 2.58, 2.68 min.
D) Pyridazine-4-carboxylic acid (c/s-4-(3-chloro-phenyl)-4-[(2,2,2-trifluoro-acetylamino)-methyl]-cyclohexyl)-phenethyl-amide and pyridazine-4-carboxylic acid (c/s-4-(3-chloro-phenyl)-4-[(2,2,2-trifluoro-acetylamino)-methyl]-cyclohexyl)-phenethyl-amide.

Diisopropylethylamine (134 µl, 0.78 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylenuronium hexafluorophosphate (182 mg, 0.47 mmol) were added to a solution of pyridazine-4-carboxylic acid (59.4 mg, 0.47 mmol) and a mixture of N-[c/s-1-(3-chloro-phenyl)-4-phenethylamino-cyclohexylmethyl]-2,2,2-trifluoroacetamide and N-[trans-1-(3-chloro-phenyl^-phenethylamino-cyclohexylmethyl^-trifluoroacetamide (191 mg, 0.43 mmol) in dimethylformamide (3.5 mL). The mixture was stirred at room temperature for 72 hours, and was then quenched by the addition of saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic phase was washed with water (3 times), filtered through a phase separator and concentrated in vacuo. The residue was purified by automated flash chromatography (Silica (12g), gradient elution from neat cyclohexane to 100% ethyl acetate). This gave the title compounds as individual diastereoisomers.

**Cis diastereoisomer:**
MS (ES+): 545, 547 [M+H]+.
T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.77 min.

**Trans diastereoisomer:**
MS (ES+): 545 [M+H]+.
T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.73 min.

E) N-fcAS-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl]-N-(2-phenylethyl)pyridazine-4-carboxamide hydrochloride

A solution of potassium carbonate (107.6 mg, 0.779 mmol) in water (1.5 mL) was added to a solution of pyridazine-4-carboxylic acid (c/s-4-(3-chloro-phenyl)-4-[(2,2,2-trifluoro-acetylamino)-methyl]-cyclohexyl)-phenethyl-amide (85 mg, 0.155 mmol) in methanol (1.5 mL) and the mixture was stirred for 60°C for 2 hours. After diluting with ethyl acetate, the organic phase was separated, washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by ion exchange chromatography (SCX-2 column, eluting with vacuo. The residue was purified by ion exchange chromatography (SCX-2 column, eluting with dichloromethane/methanol 1:1 then 1.25M ammonia in methanol) to afford the freebase of
the title compound which was converted to the hydrochloride salt by treatment with 1.25M hydrogen chloride in methanol and drying in vacuo.


TR [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH3CN+0.1%Formic acid/H2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.73 min.

**Example N2**

N-fc/s-4-(Aminomethyl)-(3-chlorophenyl)cyclohexyl N-(cyclopropylmethyl)pyrazidine^-carboxamide hydrochloride

The title compound was prepared analogously as described in Examples N1 using C-cyclopropyl-methylamine instead of 2-phenylethylamine.


TR [HPLC, Higgins Cliqueus Smicron C18; 5-95% CH3CN+0.1%Formic acid/H2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.05 min.

**Example N3**

N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl-N-methylpyridazine-4-carboxamide hydrochloride

The title compound was prepared analogously as described in Examples N1 using methylamine instead of 2-phenylethylamine.


TR [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH3CN+0.1%Formic acid/H2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.05 min.

**Example N4**

N-rc/s-4-(Aminomethyl)-(3-chlorophenyl)cyclohexyl1-N-methylpyridazine-3-carboxamide hydrochloride

The title compound was prepared analogously as described in Examples N1 using methylamine instead of 2-phenylethylamine and pyridazine-3-carboxylic acid instead of pyridazine-4-carboxylic acid.

Example N5

N-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-N-(4-pyridyl-2-ylethyl)acetamide

The title compound was prepared analogously as described in Example N1 using 4-pyridin-2-ylethanolamine instead of 2-phenylethylamine and using acetyl chloride instead of pyridazine-4-carboxylic acid.

MS (ES⁺): 386 [M+H]⁺

Example O1

N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyl π-3-(trifluoromethyl)1,2,3-triazolo[4,3-b]pyrazine-β-amine hydrochloride

The title compound was prepared according to Scheme O.

A) tert-Butylc/s-1-(3-chlorophenyl)-4-ir3-trifluoromethyl)ri).2,41triazolo[4,3-b]pyridazine-6-ylaminol-cyclohexyl πmethyltoarbamate

A solution of [c/s-4-amino-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester [Example E1] (50mg, 0.147mmol), 6-chloro-S^-rifluoromethyOII^\$.triazolo^\$.S-bpyridazine (34.5mg, 0.15mmol) and DIPEA in DMA was heated under microwave irradiation in a Smith Synthesiser at 130°C for 45 min. The reaction mixture was diluted with EtOAc (100 mL) and washed successively with water (2 x 10 mL) and brine (10 mL), then dried (Na₂SO₄) and concentrated in vacuo. Purification by a silica-gel cartridge, eluting from DCM to DCM/MeOH afforded the title compound.

MS (ES⁺): 525[M+H]⁺

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 4.18 min.
B) N-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexyn-3-(trifluoromethyl)-1,2,3-triazolo[4,3-b]pyridazine-6-amine hydrochloride

A solution of tert-butyl[(c/s-4-(3-chlorophenyl)-4-[[3-trifluoromethyl]1,2,4]triazolo[4,3-b]pyridazine-β-yl]amino)cyclohexylmethyl]carbamate (54mg, 0.102mmol) in trifluoroacetic acid (2mL) and dichloromethane (3mL) was stirred at room temperature for 0.5 hours. The reaction mixture was concentrated in vacuo and the residue was purified by ion exchange chromatography (SCX-2 column, eluting with dichloromethane/methanol 1:1 then 1.25M ammonia in methanol) to afford the freebase of the title compound, which was converted to the hydrochloride salt by treatment with 1.25M hydrogen chloride in methanol and drying in vacuo.

MS (ES⁺): 425 [M+H⁺].

T_R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 6.88 min.

**Example P1**

1-rc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexynpiperidine-2-one

The title compound was prepared according to Scheme P.

A) tert-Butyl[(c/s-4-[(5-chloropentanoyl)amino]-1(3-chlorophenyl)cyclohexyl)methy]carbamic acid tert butyl ester (300mg, 0.88mmol) in chloroform (3mL) was treated with saturated aqueous sodium carbonate (2.5mL) then 5-chlorovaleryl chloride (143mg, 0.88mmol). After 0.75 hours the reaction mixture was poured onto a hydrophobic phase separator and the aqueous layer further washed with DCM (3 x 5mL). The combined organic extracts were concentrated in vacuo to afford the title compound.


T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.91 min.
As solution of tert-butyl((c/s-4-[(5-chloropentanoyl)amino]1-(3-chlorophenyl)cyclohexyl)methyl) carbamate (211mg, 0.440mmol) in DMF (1mL) was added drop-wise to a solution in DMF (0.5mL) of sodium hydride (1.4 eq, 26mg, 0.618mmol). The reaction mixture was stirred for 18 hours then quenched via addition of water (20mL) and extracted into ethyl acetate (2 x 20 mL). The combined organic extracts were washed further with water (10mL) and brine (10mL) before drying (Na₂SO₄), filtering and concentrating in vacuo. The residue was purified by flash silica-gel cartridge, eluting with ethyl acetate/cyclohexane (2:3) to give the title compound.


Tᵣ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.70 min.

C) 1-fc/s-4-(Aminomethyl)-4-(3-chlorophenyl)cyclohexylpiperidine-2-one  
   bipyridazine-6-amine hydrochloride

A solution of tert-butyl([c/s-1-(3-chlorophenyl)-4-(2-oxopiperidin-1-yl)cyclohexyl]methyl)carbamate (142mg, 0.337mmol) in trifluoroacetic acid (2mL) and dichloromethane (3mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was purified by ion exchange chromatography (SCX-2 column, eluting with dichloromethane/methanol 1:1 then 1.25M ammonia in methanol) to afford the freebase of the title compound, which was converted to the hydrochloride salt by treatment with 1.25M hydrogen chloride in methanol and drying in vacuo.


Tᵣ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.06 min.

Example P2

1-fc/s-4-(3-Chlorophenyl)-4-piperidin-1-ylcyclohexylmethanamine

The title compound was prepared according to Scheme P.

A solution of 1-[c/s-4-(aminomethyl)-4-(3-chlorophenyl)cyclohexyl]piperidine-2-one
b) pyridazine-6-amine hydrochloride (50 mg, 0.155 mmol) in THF (1.5 ml) was treated drop-wise with borane (1 M in THF) and then heated to reflux for 18 hours. A further quantity of borane (3 eq, 0.47 ml, 0.465 mmol) was added and refluxing continued for 24 hours. The crude reaction mixture was concentrated in vacuo, then re-dissolved in MeOH (1 ml) and treated with aqueous 1 N HCl (1 ml) prior to refluxing for 7 hours. The reaction mixture was cooled and partitioned between aqueous 3 N NaOH (50 ml) and ethyl acetate (3 x 75 ml). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The residue was purified by flash silica-gel chromatography, eluting with DCM/MeOH (1:1) to give the free-base of the title compound. The addition of 1.25 N HCl in MeOH and concentration in vacuo afforded the title compound.


TR [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH$_3$CN+0.1% Formic acid/H$_2$O+0.1% Formic acid for 20 min, flow 2.0 ml/min]: 1.08 & 3.63 min.

**Example Q1**

**Pyridazine-3-carboxylic acid f4-aminomethyl-4-(3-chloro-phenyl)-1-methyl-cyclohexylamide**

A) f8-(3-Chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyl-carbamic acid benzyl ester

A solution of C-[8-(3-chlorophenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethylamino] (9.9 g, 35.13 mmol), N-(benzoxycarbonyloxy)succinimide (9.65 g, 38.72 mmol) and DIPEA (12.25 mL, 70.33 mmol) in DMF (25 mL) is stirred at rt during 4 h before evaporation of the solvent. The residue is dissolved with ethyl acetate and an aqueous 1 N HCl solution, the aqueous phase is extracted with ethyl acetate, the combined organic phases are washed with water, dried and evaporated to give the title compound.


TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1% Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.94 min.

B) f1-(3-Chloro-phenyl)-4-oxo-cyclohexylmethyl-carbamic acid benzyl ester

The title compound was prepared analogously as described in Example N1 step B using 8-(3-Chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyl-carbamic acid benzyl ester instead of N-[8-(3-chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyl]-2,2,2-trifluoroacetamide.


\[ \text{Example Q1} \]

**Pyridazine-3-carboxylic acid f4-aminomethyl-4-(3-chloro-phenyl)-1-methyl-cyclohexylamide**

A) f8-(3-Chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyl-carbamic acid benzyl ester

A solution of C-[8-(3-chlorophenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethylamino] (9.9 g, 35.13 mmol), N-(benzoxycarbonyloxy)succinimide (9.65 g, 38.72 mmol) and DIPEA (12.25 mL, 70.33 mmol) in DMF (25 mL) is stirred at rt during 4 h before evaporation of the solvent. The residue is dissolved with ethyl acetate and an aqueous 1 N HCl solution, the aqueous phase is extracted with ethyl acetate, the combined organic phases are washed with water, dried and evaporated to give the title compound.


TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH$_3$CN+0.1% Formic acid/H$_2$O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.94 min.

B) f1-(3-Chloro-phenyl)-4-oxo-cyclohexylmethyl-carbamic acid benzyl ester

The title compound was prepared analogously as described in Example N1 step B using 8-(3-Chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyl-carbamic acid benzyl ester instead of N-[8-(3-chloro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-ylmethyl]-2,2,2-trifluoroacetamide.


\[ \text{Example Q1} \]
To 1-(3-Chloro-phenyl)-4-oxo-cyclohexylmethyl]-carbamic acid benzyl ester (5.58 g, 15.01 mmol) and 2-methyl-2-propanesulfinamide (2 g, 16.5 mmol) in THF (60 mL) is added titanium tetraethoxide (6.3 mL, 30.05 mmol) before stirring at 70-75°C during 40h. The mixture is poured in Rochelle's salt, filtered and extracted with ethyl acetate. The combined organic phases are washed with brine, dried and evaporated before purification by flash chromatography on silica gel (cyclohexane/Ethyl acetate 8/2 to 4/6) to give the title compound.

MS (ES⁺): 475 [M+H]⁺.

To [1-(3-Chloro-phenyl)-4-oxo-cyclohexylmethyl]-carbamic acid benzyl ester (300 mg, 0.63 mmol) in DCM (6 mL) is added at 0°C a 3M methylmagnesium bromide solution in ether (0.842 mL, 2.52 mmol) before stirring at rt over night. The reaction is quenched with an aqueous saturated NH₄Cl solution, extracted with DCM and the combined organic phases are dried and evaporated before purification by flash chromatography on silica gel (cyclohexane/Ethyl acetate 9/1 to 25/75) to give the title compound.

MS (ES⁺): 491 [M+H]⁺.

To [1-(3-Chloro-phenyl)-4-methyl-4-(2-methyl-propane-2-sulfinylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (145 mg, 0.295 mmol) in dioxane / methanol (0.472 mL/ 1 mL) is added a 1.25M HCl solution in methanol (0.472 mL, 0.59 mmol) before stirring at rt during
3h. The solvent is evaporated before purification onto a SCX-2 cartridge (DCM/MeOH 1/1 and 2N NH3 in MeOH) to give the title compound.

TLC (DCM / 2N NH3 in MeOH 94/6): 0.16.

F) 1-(3-Chloro-phenyl)-4-methyl-4-f(Pyridazine-3-carbonyl)-amino1-cyclohexylmethyl>-carbamic acid benzyl ester

The title compound was prepared analogously as described in Example E1 step H using [4-Amino-1-(3-chloro-phenyl)-4-methyl-cyclohexylmethyl]-carbamic acid benzyl ester instead of [c/s-4-Amino-1-(3-chlorophenyl)-cyclohexylmethyl]-carbamic acid tert butyl ester.

Isomer 1: MS (ES⁺): 493 [M+H]⁺

Tₚ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.40 min.

Isomer 2: MS (ES⁺): 493 [M+H]⁺

Tₚ [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 3.60 min.

G) Pyridazine-3-carboxylic acid r4-aminomethyl-4-(3-chloro-phenyl)-1-methyl-cyclohexy π-amide

The title compound was prepared analogously as described in Example D60 using 1-(3-Chloro-phenyl)-4-methyl-4-[(pyridazine-3-carbonyl)-amino]-cyclohexylmethyl]-carbamic acid benzyl ester instead of 4-[4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-piperazine-1-carboxylic acid benzyl ester.

Isomer 1: MS (ES⁺): 359 [M+H]⁺

Tₚ [HPLC, Higgins Clipeus 6micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: min.

Isomer 2: MS (ES⁺): 359 [M+H]⁺

Tₚ [HPLC, Higgins Clipeus 5micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: min.

Example Q2

Pyridazine-4-carboxylic acid r4-aminomethyl-4-(3-chloro-phenyl)-1-methyl-cyclohexyl-
amide
The title compound was prepared analogously as described in Example Q1 using pyridazine-3-carboxylic acid instead of pyridazine-2-carboxylic acid.

**Isomer 1**: MS (ES⁺): 359 [M+H]⁺

T_R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: min.

**Isomer 2**: MS (ES⁺): 359 [M+H]⁺

T_R [HPLC, Higgins Clipeus 5 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: min.

**Example R1**

_C-ri-(3-Chloro-phenyl)-4-phenyl-cyclohex-3-en-vn-methylamine_

A) **Trifluoro-methanesulfonic acid 4-aminomethyl-4-(3-chloro-phenyl)-cyclohex-1-enyl ester**

To [1-(3-Chlorophenyl)-4-oxo-cyclohexylmethyl]-carbamic acid tert-butyl ester (507 mg, 1.5 mmol) in THF (15 mL) is added at -78°C a 1.8M LDA solution in THF/hexane (1.77 mL, 3.18 mmol). After stirring at this temperature during 1h, N-phenyl-bis(trifluoromethanesulfonimide (810 mg, 2.267 mmol) in THF (6 mL) is added before warming slowly at rt and stirring overnight. The mixture is poured into water, extracted with ethyl acetate, the combined organic phases are washed with brine, dried and evaporated to give the title compound.

B) **C-ri-(3-Chloro-phenyl)-4-phenyl-cyclohex-3-en-vn-methylamine**

To a mixture of -methanesulfonic acid 4-aminomethyl-4-(3-chloro-phenyl)-cyclohex-1-enyl ester (340 mg, 0.724 mmol), phenylboronic acid (140 mg, 1.15 mmol) and an aqueous 1N Na₂CO₃ solution (4.4 mL, 4.4 mmol) in DME (10 mL) is added tetrakis(triphenylphosphine)palladium (84 mg, 0.078 mmol) before stirring at 80°C during 16h. The reaction is quenched with water, extracted with ethyl acetate, the combined organic phases are washed with an aqueous saturated NaHCO₃ solution, dried and evaporated to give a crude compound. The protected amine is dissolved with DCM (5 mL) and TFA (0.5 mL) before stirring at rt during 16h. The solvent are evaporated before purification by flash chromatography on silica gel (DCM / ethylacetate / methanol 78/20/2) to give the title compound.

MS (ES⁺): 298-300 [M+H]⁺.

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH₃CN+0.1%Formic acid/H₂O+0.1% Formic acid for 5 min, flow 2.0 ml/min]: 2.46 min.
Example R2
C-ri-(3-Chloro-phenyl)-4-pyridin-3-yl-cyclohex-3-enyl-methylamine

The title compound was prepared analogously as described in Example R1 using 3-pyridineboronic acid instead of phenylboronic acid.

MS (ES+): 299 [M+H]+

T_R [HPLC, Higgins Cliqueus 5micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 4.23 min.

Example S1
C-ri-(3-Chloro-benzyl)-4-(3-trifluoromethyl-5,6-dihydro-8H-ri,2,4-triazole-7-yl)-cyclohexyl-π-methylamine

A) 8-(3-Chloro-benzyl)-1.4-dioxa-spiro[4.5]decane-8-carbonitrile

To a solution of diisopropylamine (1.21 mL, 8.66 mmol) in THF (50 mL) is added at -78°C a 1.6M BuLi solution in hexane (4.94 mL, 7.91 mmol) before stirring at -78°C during 15 min. A solution of 1,4-Dioxa-spiro[4.5]decane-8-carbonitrile (1.26 g, 7.53 mmol) in THF (25 mL) is added, the mixture is stirred at -78°C during 1h before addition of 3-chlorobenzylbromide (1.09 mL, 8.29 mmol) and warming to rt for a stirring during 3h. The reaction is quenched with water, extracted with Et2O, the combined organic phases are washed with H2O, dried and evaporated before purification by flash chromatography on silica gel (cyclohexane / ethylacetate 1/0 to 85/15) to give the title compound.

MS (ES+): 291 [M+H]+

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 3.7 min.

B) 1-(3-Chloro-benzyl)-4-oxo-cyclohexanecarbonitrile

The title compound was prepared analogously as described in Example D1 step G using 8-(3-Chloro-benzyl)-1,4-dioxa-spiro[4.5]decane-8-carbonitrile instead of [8-(3-chlorophenyl)-1,4-dioxa-spiro[4.8]dodec-β-ylmethyl-carbamic acid tert-butyl ester.

MS (ES+): 246 [M+H]+

T_R [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 3.33 min.
C) 1-(3-Chloro-benzyl)-4-(3-trifluoromethyl-5,6-dihydro-8H-π.2,4-triazolo[4,3-a]pyrazin-7-yn-cyclohexanecarbonitrile

The title compound was prepared analogously as described in Example C1 step A using 1-(3-Chloro-benzyl)-4-oxo-cyclohexanecarbonitrile instead of 4-oxo-1-phenyl-cyclohexanecarbonitrile.

MS (ES^+): 465 [M+CH_3CN+H]^+

TR [HPLC, Phenomenex Luna 3 micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 5 min, flow 2.0 ml/min]: 3.43 min.

D) C-f-1-(3-Chloro-benzyl)-4-(3-trifluoromethyl-5,6-dihydro-8H-π.2,4-triazolo[4,3-a]pyrazin-7-yn-vD-cyclohexyll-methylamine

The title compound was prepared analogously as described in Example H1 step E using 1-(3-Chloro-benzyl)-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclohexanecarbonitrile instead of cis-4-(3-Chlorophenyl)-cyano-cyclohexanecarboxylic acid 2-trifluoromethyl-benzylamide.

MS (ES^+): 428 [M+H]^+

TR [HPLC, Higgins Clipeus 5micron C18; 5-95% CH_3CN+0.1%Formic acid/H_2O+0.1%Formic acid for 20 min, flow 2.0 ml/min]: 5.52 min.

Example T1

C-K1S.3RH -m-Tolyl-3-f-13-trifluoromethyl-5,6-dihydro-8H-H .2.41triazolo[4,3-a]pyrazin-7-yn-vD-cyclohexyll-methylamine

A) S-m-Tolyl-cyclohexyl-enone

To a 1M m-toluenemagnesium bromide solution in THF (8.56 mL) is added at 0°C 3-Ethoxy-cyclohex-2-enone (1g, 7.13 mmol) in THF (1 mL) before stirring at t during 1h. The reaction is quenched with an aqueous saturated NH4Cl solution, extracted with DCM, the organic phase is dried and evaporated before purification by flash chromatography on silica gel (cyclohexane / ethylacetate 9/1 to 2/1) to give the title compound.

MS (ES^+): 187 [M+H]^+

HPLC (Zorbax SB C18, 2min method (0-0.8min 10-95%ACN, 0.8-1.5min 95%ACN, 1.5-1.6min 95-10%ACN, 1.6-2min 10%ACN): 1.367 min.
B) 3-Oxo-J-m-tolyl-cyclohexanecarbonitrile

To S-m-Tolyl-cyclohex-\(^{\Delta}\)-enone (550 mg, 2.95 mmol) in DMF/H\(_2\)O (10 mL, 1.75 mL) are added KCN (385 mg, 5.9 mmol) and trimethylamine hydrochloride (425 mg, 4.42 mmol) before stirring at 95°C during 6h. The reaction is quenched with an aqueous saturated NaHCO\(_3\) solution, extracted with ethyl acetate, the organic phase is dried and evaporated before purification by flash chromatography on silica gel (cyclohexane / ethylacetate 9/1 to 1/1) to give the title compound.

MS (ES\(^{+}\)): 214 [M+H]\(^{+}\)

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.6 min.

C) C-f(1.S.3R)-1-m-Tolyl-3-(3-trifluoromethyl-5,6-dihydro-8H-1,2,4-triazol-4-yl)-cyclohexyl-methylamine

The title compound was prepared analogously as described in Example S1 step C-D using 3-Oxo-J-m-tolyl-cyclohexanecarbonitrile instead of 1-(3-Chloro-benzyl)-4-oxo-cyclohexane carbonitrile.

MS (ES\(^{+}\)): 394 [M+H]\(^{+}\)

HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.608 min.

Example U1

1-ftrans-1-Aminomethyl-4-(3-trifluoromethyl-5,6-dihydro-8H-f1 .2.41triazolor4.3-alpyrazin-7-vD-cyclohexyl-methylamine
dihydrochloride

The title compound was prepared according to Scheme U.

A) 8-Nitromethyl-1,4-dioxaspiro4.51decan-8-ol

A mixture of Cyclohexanedione monoethylene acetal (1.0g, 6.4mmol), 1,4-Diazabicyclo[2.2.2]octane (730mg, 6.31 mmol), Lithium bromide (270mg, 3.12mmol) and Nitromethane (0.86ml, 14.8mmol) was immediately melted by heating at 100°C. The resulting solution was stirred at 100°C for 20 minutes. The reaction mixture was partitioned between water and dichloromethane. The organic phase was washed with brine, dried over Sodium sulfate and concentrated in vacuo. The residue was purified by silica ge!
chromatography using gradient elution from 100% dichloromethane to dichloromethane / methanol 96:4. Fractions containing the product were concentrated in vacuo. The residue was purified by silica gel chromatography using gradient elution from 100% cyclohexane to cyclohexane / ethylacetate 1:1. Fractions containing the product were concentrated in vacuo to give the title compound as an amorphous white solid.

MS (ES\(^+\)): 218 [M+H]\(^+\).

B) 8-Nitromethylene-1,4-dioxa-spiro4.5decane

To a solution of 8-Nitromethyl-1,4-dioxa-spiro[4.5]decan-8-ol (7.94g, 36.6mmol) in dichloromethane (100ml) was added Triethylamine (12.7ml, 91.4mmol) at -40°C. The resulting mixture was stirred at -40°C for 5 minutes, then Methane sulfonyl chloride (4.27ml, 54.8mmol) was added dropwise. The resulting mixture was stirred at -40°C for 2h, then again Triethylamine (12.7ml, 91.4mmol) and Methane sulfonyl chloride (4.27ml, 54.8mmol) were added dropwise at -40°C. The resulting mixture was stirred at -40°C for 1h. The reaction mixture was diluted with dichloromethane then the organic phase was washed sequentially with 1N Hydrochloric acid, water and brine, dried over Sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography using gradient elution from cyclohexane / ethylacetate 4:1 to cyclohexane / ethylacetate 1:1. Fractions containing the product were concentrated in vacuo to give the title compound as a pale yellow oil.

MS (ES\(^+\)): 201 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN)): 3.35min.

C) 4-Methyl-(8-nitromethyl-1,4-dioxa-spiro4.5dec-8-yl)-pyrrolidin-2-one

4-Methyl-pyrrolidin-2-one (268mg, 2.70mmol), Potassium tert-butoxide (303mg, 2.70mmol) and 18-Crown-6 (715mg, 2.70mmol) were dissolved in tetrahydrofuran (22ml) at 0°C. The resulting solution was stirred at 0°C for 1h, then 8-Nitromethylene-1,4-dioxa-spiro[4.5]decane (539mg, 2.70mmol) was added at -78°C. The mixture was allowed to warm up to room temperature over 2h of stirring. The reaction mixture was quenched with saturated aqueous Ammonium chloride solution and extracted 3x into ethyl acetate. The combined organic phases were washed with brine, dried over Sodium sulfate and
concentrated in vacuo. The residue was purified by silica gel chromatography using elution with cyclohexane / ethylacetate 1:1. Fractions containing the product were concentrated in vacuo to give the title compound as a colourless oil.


D) 4-Methyl-1-(1-nitromethyl-oxo-cyclohexyl-pyrrolidin-^n^-one

To a solution of 4-Methyl-(8-nitromethyl-1,4-dioxa-spiro[4.5]dec-8-yl)-pyrrolidin-2-one (489mg, 1.51mmol) in acetic acid (10ml) was added water (3ml). The resulting mixture was stirred at room temperature for 6Oh, then at 50°C for 5h and finally at 60°C for 4.5h. The mixture was diluted with ethylacetate and washed 3x with water. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed sequentially with 1N Sodium hydroxide solution, water and brine. The product remains in aqueous phase. All the combined aqueous phases were neutralized with 1N Hydrochloric acid and concentrated in vacuo. The residue was taken up in Acetonitrile, the suspension was filtered and the filtrate was concentrated in vacuo to give the title compound as crystalline needles.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.84 min.

E) 4-Methyl-1-(3-trifluoromethyl-5,6-dihydro-8H-f1,2,41triazolo[4,3-a]pyrazin-7-yl)-cis-cyclohexyl1-pyrrolidin-2-one formate and 4-Methyl-1-ri-nitromethyl-4-(3-trifluoromethyl-5,6-dihydro-8H-f1,2,41triazolo[4,3-aipyrazin-7-yl)-trans-cyclohexyn-pyrrolidin-2-one formate

To a solution of 4-Methyl-1-(1-nitromethyl-4-oxo-cyclohexyl)-pyrrolidin-2-one (95mg, 0.374mmol) in 1,2-Dichloroethane (6ml) was added 3-Trifluoromethyl-5,6,7,8-tetrahydro-1H-1,2,4-triazolo[4,5-a]pyrazine (135mg, 0.591mmol), N,N-Diisopropylethylamine (0.1ml, 0.584mmol) and acetic acid (20µl, 0.393mmol). The resulting mixture was stirred at room temperature for 30 minutes, then Sodium triacetoxyborohydride (167mg, 0.788mmol) was added. The resulting mixture was stirred at room temperature for 6h. The mixture was quenched with water, then concentrated in vacuo to give the title compound as a mixture of diastereomeric isomers, which were separated and purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20mi/π, ISrnin method (0-2.5min 20%ACN, 2.5-
17.5min 20-50%ACN, 17.5-20.0min 50%ACN). Fractions containing the products were lyophilized individually to give the individual title compounds as white solids as formic acid salts.

MS (ES\(^{+}\)): 431 [M+H\(^{+}\)] (trans) and MS (ES\(^{+}\)): 431 [M+H\(^{+}\)] (cis)

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.00 min (trans) and 3.11min (cis).

F) 1-trans-1-Aminomethyl-4-(3-trifluoromethyl-5,6-dihydro-8H-f 1,2,4triazolof4,3-a]pyrazin-7-yl)-cyclohexyl]-4-methyl-pyrrolidin-2-one dihydrochloride

4-Methyl-1-[1-nitromethyl-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-trans-cyclohexyl]-pyrrolidin-2-one formate (15mg, 0.031mmol) was dissolved in 4N Hydrochloric acid (2ml) and lyophilized. The obtained 4-Methyl-1-[1-nitromethyl-4-(3-trifluoromethyl-δ6-dihydro-δH-f^\(\text{ii}\)triazolo [4,S-alpyrazin^-yl-trans-cyclohexy1]-pyrrolidin-2-one hydrochloride was dissolved 1N Hydrochloric acid (4ml), then 10% Palladium on charcoal (10mg, 0.009mmol) was added. The resulting mixture was stirred at room temperature for 16h under hydrogen atmosphere. The mixture was filtered and the filtrate was lyophilized to give the title compound as a beige solid.

MS (ES\(^{+}\)): 401 [M+H\(^{+}\)].

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.62 min.

Example U2

1-cis-1-Aminomethyl-4-(3-trifluoromethyl-5,6-dihydro-8H-n,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclohexyl]-4-methyl-pyrrolidin-2-one dihydrochloride

The title compound was prepared analogously as described in Example U1, step F from 4-MethyM-[1-nitromethyl-4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-trans-cyclohexyl]-pyrrolidin-2-one formate.

MS (ES\(^{+}\)): 401 [M+H\(^{+}\)].

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.49 min.
Example V1

C-ri-m-Tolyl-S-O-trifluoromethyl-S.6-dihydro-SH-n.Z^i^triazolor^a-aipyrazin-y-v π-cyclopentyl-methylamine hydrochloride

The title compound was prepared according to Scheme V.

A) 2-Allyl-2-m-tolyl-pent-4-enenitrile

To a mixture of 3-Methylbenzylcyanide (5g, 37.4mmol) and Hexadecyltributylphosphonium bromide (391 mg, 0.747mmol) in 50% aqueous Sodium hydroxide solution (15ml) was added slowly retaining temperature below 50°C Allyl bromide (8.3ml, 86mmol). When the addition was complete, the reaction mixture was stirred at room temperature for 24h. The reaction mixture was extracted into toluene. The combined organic phases were dried and concentrated in vacuo to give the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 4.20 min.

B) 1-m-Tolyl-cyclopent-S-enecarbonitrile

2-Allyl-2-m-tolyl-pent-4-enenitrile (3.Og, 13.9mmol) was dissolved in dichloromethane (300ml) under nitrogen atmosphere. The resulting mixture was heated to 40°C, then (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium (Grubbs Catalyst, 2nd Generation) (1.15g, 1.39mmol) was added. The resulting mixture was stirred at 40°C for 16h. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (Silica cartridge) using gradient elution from 100% cyclohexane to cyclohexane / ethylacetate 1:1. Fractions containing the product were concentrated in vacuo to give the title compound as a black oil.

C) C-(1-m-Tolyl-cyclopent-3-enyl)-methylamine hydrochloride

A solution of i-m-Tolyl-cyclopent-S-enecarbonitrile (2.25g, H.Ommol) in tetrahydrofuran (10ml) was added to a stirred solution of Lithium aluminium hydride (1.3g, 33.1mmol) in tetrahydrofuran (10ml) at 0°C over a period of 30 minutes. After the addition was complete, the mixture was stirred for 1h at 0°C, then heated to 40°C and stirred for 16h at 40°C. After
cooling, the reaction mixture was quenched carefully with a mixture of water and 10% aqueous Sodium hydroxide solution and extracted into ethyl acetate. The organic phase was filtered, then the filtrate was dried and concentrated in vacuo. The residue was dissolved in diethylether (2ml) and treated with 2M Hydrogen chloride in diethylether (6.1ml, 12mmol) at 0°C. The precipitate was filtered and dried to give the title compound as a white solid.

MS (ES⁺): 188 [M+H]⁺.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.66 min.

D) (1-m-Tolyl-cyclopent-3-ениlmethyl)-карбамидная кислота tert-butyl ester

To a solution of C-(1-m-Tolyl-cyclopent-3-енил)-метиламин гидрохлорид (1.0g, 4.47mmol) and Triethylamine (1.87ml, 13.4mmol) in dichloromethane (10ml) was added a solution of Ditert-Butyl dicarbonate (2.93g, 13.4mmol) in dichloromethane (5ml). The resulting mixture was stirred at room temperature for 4h. The mixture was partitioned between dichloromethane and saturated aqueous Sodium bicarbonate solution. The organic phase was dried and concentrated in vacuo. The residue was purified by flash chromatography. Fractions containing the product were concentrated in vacuo to give the title compound as a yellow oil.

MS (ES⁺): 232 [M-tBu+H]⁺.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 5.47 min.

E) (3-гидрокси-1-m-tolyl-cyclopentilmethyl)-карбамидная кислота tert-butyl ester

To a solution of Borane dimethyl sulfide complex solution (2.0 M in tetrahydrofuran, 3.7ml, 7.4mmol) in tetrahydrofuran (25ml) was added a solution of (1-m-Tolyl-cyclopent-3-енилмethyl)-карбамидная кислота tert-butyl ester (1.81g, 6.17mmol) in tetrahydrofuran (5ml) at 0°C under nitrogen atmosphere. After the addition was complete, the mixture was stirred at room temperature for 16h. The reaction mixture was cooled to 0°C, then 3N Sodium hydroxide solution (2.5ml, 7.4mmol) was added dropwise, followed by addition of 30% solution of hydrogen peroxide in water (3.5ml, 34.0mmol). The resulting mixture was stirred at 40°C for 1h. After cooling, the mixture was treated with 10% aqueous sodium thiosulfate solution. The separated organic layer was diluted with dichloromethane and washed with 1N Hydrochloric
acid. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a colourless oil as a mixture of diastereomers.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.34 min + 3.47 min.

F) (3-Oxo-1-m-tolyl-cyclopentylmethyl)-carbamic acid tert-butyl ester

A solution of (3-Hydroxy-1-m-tolyl-cyclopentylmethyl)-carbamic acid tert-butyl ester (120mg, 0.393mmol) in dichloromethane (1ml) was added to a suspension of Pyridinium chlorochromate (144mg, 0.668mmol) and molecular sieves in dichloromethane (1ml). The resulting mixture was stirred at 40°C for 2h. The mixture was partitioned between dichloromethane and saturated aqueous Sodium bicarbonate solution. The organic phase was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a colourless oil.

MS (ES⁺): 326 [M+Na]⁺

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.57 min.

G) f1-m-Tolyl-3-(3-trifluoromethyl-5,6-dihydro-8H-π.2.41triazolo4.3-aipyraxin-7-yl)-cyclopentylmethyl-carbamic acid tert-butyl ester

To a solution of (3-Oxo-1-m-tolyl-cyclopentylmethyl)-carbamic acid tert-butyl ester (55mg, 0.181mmol) in dichloromethane (2ml) was added 3-Trifluoromethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine (52mg, 0.272mmol) and acetic acid (10µl, 0.181mmol). The resulting mixture was stirred at room temperature for 1h, then Sodium triacetoxyborohydride
(61 mg, 0.272mmol) was added. The resulting mixture was stirred at room temperature for 16h. The mixture concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

MS (ES+): 480 [M+H]+

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.1 1 min.

H) C-f1-m-Tolyl-3-(3-trifluoromethyl-5,6-dihydro-8H-M.2.41triazolor4.3-alPyrazin-7-yl)-cyclopentyl-methylamine hydrochloride

Trifluoroacetic acid (468µl) was added to a solution of [1-m-Tolyl-3-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-cyclopentylmethyl] carbamic acid tert-butyl ester (63mg, 0.122mmol) in dichloromethane (1mL). The reaction mixture was stirred at room temperature for 2h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.71 min.

Example W 1
2-rcis-4-Aminomethyl-4-(3-chioro-phenyl)-cyclohexyn-6-phenyl-2H-pyridazin-3-one hydrochloride
The title compound was prepared according to Scheme W.

A) 1-(cis-3-Chloro-phenyl)-4-(6-oxo-3-phenyl-6H-Dyridazin-1-yl)-cyclohexylmethyl-carbamic acid tert-butyl ester

To a solution of a mixture of [1-(cis-3-Chloro-phenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester and [1-(trans-3-Chloro-phenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester (200mg, 1.16mmol), 6-Phenyl-3-pyridazinone (481 mg, 1.39mmol) and Triphenylphosphine polymer bound (3mmol/g, 620mg, 1.86mmol) in tetrahydrofurane (5ml), was added dropwise Diethyl azodicarboxylate (298 µl, 1.86mmol) at 0°C under argon atmosphere. The reaction mixture was stirred for 4h at 0°C. The mixture was filtered, then the filtrate was partitioned between ethyl acetate and 2N aqueous Hydrochloric acid. The organic layer was dried and concentrated in vacuo to give a mixture of [1-(cis-3-Chloro-phenyl)-4-(6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester and [1-(trans-3-Chloro-phenyl)-4-(6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 20%ACN, 2.5-12.5min 20-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo, then partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.28 min.

B) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-6-phenyl-2H-pyridazin-3-one hydrochloride

Trifluoroacetic acid (0.9ml) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (90mg, 0.179mmol) in dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep CIS ODB Sµtrs 19 x 50mm, flow
20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

MS (ES\(^+\)): 394 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.72 min.

**Example W2**

2,r\textsuperscript{t}-trans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-phenyl-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example W1, step B from [1-(trans-3-Chloro-phenyl)-4-(6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester.

MS (ES\(^+\)): 394 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.78 min.

**Example W3**

2,S-Bromo-pyridin-2-yloxyM-O-chloro-phenvD-cvclohexyn-methylamine

The title compound was prepared analogously as described in Example W1, using 5-Bromopyridin-2-one instead of 6-Phenyl-3-pyridazinone.

MS (ES\(^+\)): 395 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.19 min.

**Example W4**

2-r\textsuperscript{t}trans-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-\(\pi\)-2H-pyridazin-3-one hydrochloride
The title compound was prepared analogously as described in Example W2, using 3(2H)-
Pyridazinone instead of 6-Phenyl-3-pyridazinone.
HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-
5%ACN, 5.55-6min 5%ACN): 4.01 min.

**Example W5**  
2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2H-pyridazin-3-one hydrochloride  

The title compound was prepared analogously as described in Example W1, using 3(2H)-
Pyridazinone instead of 6-Phenyl-3-pyridazinone.
HPLC (Nucleosil, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-
5%ACN, 5.55-6min 5%ACN): 3.97 min.

**Example W6**  
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π-6-methyl-2H-pyridazin-3-one hydrochloride  

The title compound was prepared analogously as described in Example W1, using 6-Methyl-
3-pyridazinone instead of 6-Phenyl-3-pyridazinone.
MS (ES$^+$): 332 [M+H]$^+$. 
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.87 min.

**Example W7**  
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2.3-dihydro-
pyridazine-4-carboxylic acid amide  

The title compound was prepared analogously as described in Example W1, using 3-Oxo-6-
phenyl-2,3-dihydro-pyridazine-4-carboxylic acid amide instead of 6-Phenyl-3-pyridazinone.

Example W8
2-f4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-3-oxo-6-phenyl-2,3-dihydro-
pyridazine-4-carboxylic acid ethyl ester

The title compound was prepared analogously as described in Example W1, using 3-Oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester instead of 6-Phenyl-3-pyridazinone.
MS (ES\(^+\)): 466 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.33 min.

Example W9
3-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyloxy1-6-phenyl-pyridazine-4-
carboxylic acid ethyl ester

The title compound was prepared analogously as described in Example W1, using 3-Oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester instead of 6-Phenyl-3-pyridazinone.
MS (ES\(^+\)): 466 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.40 min.

Example W10
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-β-phenyl-2,3-dihydro-
pyridazine-4-carboxylic acid

The title compound was prepared analogously as described in Example W1, step A using 3-Oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester instead of 6-Phenyl-3-pyridazinone to afford 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester followed by step
B) 2-f4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl-3-oxo-6-
phenyl^-S-dihydro-pyridazine^-carboxylic acid

To a solution of 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-
3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (100mg, 0.177mmol) in
tetrahydrofurane (1ml) and water (1ml) was added Lithium hydroxide hydrate (37mg, 0.883mmol). The mixture was stirred at 60°C for 3h. The mixture was partitioned between
dichloromethane and 1N Hydrochloric acid. The organic layer was dried and concentrated in
cavuo to give the title compound as an orange solid.
MS (ES^+): 560 [M+Na]^+
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.71 min.

C) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylV3-oxo-6-phenyl-2,3-dihydro-
pyridazine-4-carboxylic acid

Trifluoroacetic acid (21µl) was added to a solution of 2-[4-(tert-Butoxycarbonylamino-
methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-
carboxylic acid (15mg, 0.028mmol) in dichloromethane (1mL). The reaction mixture was
stirred at room temperature for 1h. The mixture was concentrated in cavuo. The residue was
purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min,
15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN).
Fractions containing the product were partitioned between dichloromethane and saturated
aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in
cavuo to give the title compound as a yellow solid.
MS (ES^+): 438 [M+H]^+
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.03 min.

Example WA1
2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(3-methanesulfonyl-phenyl)-
2H-pyridazin-3-one
The title compound was prepared according to Scheme W.

A) f4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl-1-carbamic acid tert-butyl ester

To a solution of 1-(cis-3-Chloro-phenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester (1.11g, 3.21mmol), 6-Bromo-2H-pyridazin-3-one (510mg, 2.91mmol) and Triphenylphosphine (917mg, 3.50mmol) in tetrahydrofurane (40ml), was added dropwise Diethyl azodicarboxylate (750µl, 4.66mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 16h at room temperature. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give a mixture of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester and [4-(6-Bromo-pyridazin-3-yloxy)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester which was separated by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 30 x 100mm, flow 40ml/min, 45min method (0-2.5min 20%ACN, 2.5-42.5min 20-100%ACN, 42.5-45.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid. MS (ES+): 519 [M+Na]+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.55-6min 95-20%ACN, 5.55-6min 20%ACN): 4.06 min.

B) (1-(cis-3-Chloro-phenyl)-4-f3-(3-methanesulfonyl-phenyl)-6-oxo-6H-pyridazin-1-yl1-cyclohexylmethyl]-carbamic acid tert-butyl ester

To a suspension of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (50mg, 0.101mmol) in 1,2-Dimethoxyethane (1ml) were added 3-Methylsulfonylphenylboronic acid (23mg, 0.111mmol), Tetrakis(triphe πylphosphine)palladium(0) (6mg, 0.005mmol) and 10% aqueous sodium carbonate solution (0.5ml, 0.19mmol) under nitrogen atmosphere. The reaction mixture was stirred for 16h at 80°C. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x
50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

MS (ES?): 595 [M+Na]-

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.91 min.

C) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-π-6-(3-methanesulfonyl-phenyl)-2H-pyridazin-3-one

Trifluoroacetic acid (0.5ml) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-[3-(3-methanesulfonyl-phenyl)-6-oxo-6H-pyridin-1-yl]-cyclohexylmethyl]-carbamic acid tert-butyl ester (10mg, 0.017mmol) in dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a colourless solid.

MS (ES?): 472 [M+H]-

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a colourless solid.

Example WA2

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-π-6-(3-methanesulfonyl-phenyl)-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A followed by step

B) f1-(cis-3-Chloro-phenyl)-4-(6-oxo-3-pyridin-3-yl-6H-pyridazin-1-yl)-cyclohexylmethyl-carbamic acid tert-butyl ester
A mixture of [4-(3-Brpmo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (36mg, 0.072mmol), 3-Pyridineboronic acid (27mg, 0.217mmol), Bis(triphenylphosphine)palladium(II) chloride (5mg, 0.007mmol) and Cesium carbonate (47mg, 0.145mmol) in Dimethylacetamide/water/ethanol 7:3:2 (1ml) was treated with microwave at 150°C for 150 seconds. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.16 min.

C) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-pyridin-3-yl-2H-pyridazin-3-one hydrochloride

Trifluoroacetic acid (21 µl) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(6-oxo-3-pyridin-3-yl-H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (15mg, 0.027mmol) in dichloromethane (1mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.70 min.

Example WA3
2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-β-o-tolyl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using o-Tolylboronic acid instead of 3-Pyridineboronic acid.

MS (ES⁺): 408 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.25 min.

Example WA4
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-pyridin-4-yl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using A-Pyridineboronic acid instead of 3-Pyridineboronic acid.


HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.71 min.

Example WA5
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-pyrimidin-5-yl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using Pyrimidine-5-boronic acid instead of 3-Pyridineboronic acid.

MS (ES⁺): 396 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5μm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.12 min.

Example WA6
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(2-dimethylamino-pyrimidin-5-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 1,2-Dimethyaminopyrimidine-5-boronic acid pinacol ester instead of 3-Pyridineboronic acid.
Example WA7
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-m-tolyl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using m-Tolyboronic acid instead of 3-Pyridineboronic acid.

MS (ES⁺): 408 [M+H]⁺.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.85 min.

Example WA8
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-p-tolyl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using p-Tolyboronic acid instead of 3-Pyridineboronic acid.

MS (ES⁺): 408 [M+H]⁺.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.90 min.

Example WA9
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-cyclopropyl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using Cyclopropylboronic acid instead of 3-Pyridineboronic acid.

MS (ES⁺): 358 [M+H]⁺.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.03 min.

Example WA10
4-(1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexy π -6-oxo-1,6-dihydro-pyridazin-
3-yl)-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example WA2, step A to B using 4-Ethoxycarbonylphenylboronic acid instead of 3-Pyridineboronic acid followed by step C)

4-(1-r4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl1-6-oxo-1,6-
dihydro-pyridazin-3-yl-V-benzoic acid

To a solution of 4-{1-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-
cyclohexyl]-β-oxo-i. β-dihydro-pyridazin-S-ylJ-benzoic acid ethyl ester (30mg, 0.053mmol) in tetrahydrofurane (0.5ml) and water (0.5ml) was added Lithium hydroxide hydrate (5.6mg, 0.132mmol). The mixture was stirred at 60°C for 3h. The mixture was partitioned between dichloromethane and 1N Hydrochloric acid. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.82 min.

D) 4-|1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl1-6-oxo-1,6-dihydro-pyridazin-3-ylV-
benzoic acid hydrochloride

Trifluoroacetic acid (29µl) was added to a solution of 4-{1-[4-(tert-Butoxycarbonylamino-
methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-6-oxo-1,6-dihydro-pyridazin-3-yl}-benzoic acid (20mg, 0.037mmol) in dichloromethane (1mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo. The residue was treated with 4M hydrogen chloride in dioxane. Lyophilization of the volatiles gave the title compound as a white solid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.54 min.
**Example WAH**

3-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazin-3-yl}-benzoic acid hydrochloride

The title compound was prepared analogously as described in Example WA10, using 3-Methoxycarbonylphenylboronic acid instead of 4-Ethoxycarbonylphenylboronic acid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.60 min.

**Example WA12**

5-(1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-β-oxo-1,6-dihydro-pyridazin-3-yl)-pyridine-2-carboxylic acid hydrochloride

The title compound was prepared analogously as described in Example WA10, using 2-Methylcarboxy-pyridine-5-boronic acid pinacol ester instead of 4-Ethoxycarbonylphenylboronic acid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.87 min.

**Example WA13**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 4-Methanesulfonylphenyl boronic acid instead of 3-Pyridineboronic acid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.54 min.

**Example WA14**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(6-morpholin-4-yl-pyridin-3-yl)-2H-pyridazin-3-one
The title compound was prepared analogously as described in Example WA2, using 6-(Morpholin-4-yl)pyridine-3-boronic acid pinacol ester instead of 3-Pyridineboronic acid.

MS (ES\(^+\)) : 481 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.01 min.

**Example WA15**

2-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-quinolin-3-yl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 3-Quinolineboronic acid pinacol ester instead of 3-Pyridineboronic acid.

MS (ES\(^+\)) : 439 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.87 min.

**Example WA16**

2-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-isoquinolin-4-yl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 4-Isoquinolineboronic acid pinacol ester instead of 3-Pyridineboronic acid.

MS (ES\(^+\)) : 439 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.87 min.

**Example WA17**

2-r cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(2-amino-pyrimidin-5-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 2-Aminopyrimidine-5-boronic acid instead of 3-Pyridineboronic acid.

MS (ES\(^+\)) : 411 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.78 min.

Example WA18
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(β-methoxy-pyridin-3-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 2-Methoxy-5-pyridineboronic acid instead of 3-Pyridineboronic acid.

MS (ES⁺): 426 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.04 min.

Example WA19
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(β-methoxy-pyridin-3-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 2-Aminopyridine-5-boronic acid pinacol ester instead of 3-Pyridineboronic acid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.62 min.

Example WA20
3-(1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1.β-dihydro-pyridazin-3-vU-N,N-dimethyl-benzamide

The title compound was prepared analogously as described in Example WA2, using 3-Dimethylcarbamoylphenylboronic acid instead of 3-Pyridineboronic acid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.47 min.

Example WA21
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(5-methyl-pyridin-3-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 5-Methylpyridine-3-boronic acid instead of 3-Pyridineboronic acid.
MS (ES\(^+\)): 410 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 1.85 min.

Example WA22
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(5-methanesulfonyl-pyridin-3-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 5-Methanesulfonylpyridine-3-boronic acid instead of 3-Pyridineboronic acid.
MS (ES\(^+\)): 473 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.36 min.

Example WA23
3-1-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1.\(\beta\)-dihydro-pyridazin-3-yl]-benzamide

The title compound was prepared analogously as described in Example WA2, using 3-Carbamoylphenylboronic acid instead of 3-Pyridineboronic acid.
MS (ES\(^+\)): 465 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.39 min.

Example WA24
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(5-methoxy-pyridin-3-ven-2H-pyridazin-3-one
The title compound was prepared analogously as described in Example WA2, using 3-Methoxypyridine-5-boronic acid pinacol ester instead of 3-Pyridineboronic acid.

MS (ES⁺): 426 [M+H]⁺.

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.84 min.

Example WA25

2-rcis4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(3-amino-phenyl)-2H-pyridazine-3-one tetrahydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-Aminophenylboronic acid monohydrate instead of 3-Pyridineboronic acid.


HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.91 min.

Example WA26

5-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazine-3-yl}nicotinic acid dihydrochloride

The title compound was prepared analogously as described in Example WA2, using 5-(Methoxycarbonyl)pyridine-3-boronic acid instead of 3-Pyridineboronic acid.


HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.97 min.

Example WA27

4-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazine-3-yl}benzenesulfonamide dihydrochloride

The title compound was prepared analogously as described in Example WA2, using 4-Aminosulfonylpyridine-3-boronic acid instead of 3-Pyridineboronic acid.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.40 min.

**Example WA28**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one trihydrochloride

The title compound was prepared analogously as described in Example WA2, using 1-Pyrazole-5-boronic acid instead of 3-Pyridineboronic acid. 


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.28 min.

**Example WA29**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1-benzyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one dihydrochloride

The title compound was prepared analogously as described in Example WA2, using 1-Benzyl-1H-pyrazole-4-boronic acid instead of 3-Pyridineboronic acid. 


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.74 min.

**Example WA30**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(3-morpholin-4-yl-phenyl)-2H-pyridazin-3-one dihydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-Morpholinophenylboronic acid pinacol ester instead of 3-Pyridineboronic acid. 


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.64 min.

**Example WA31**
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 1-Methylpyrazole-4-boronic acid pinacol ester instead of 3-Pyridineboronic acid. MS (ES+): 398 [M+H]+.
HPLC (Waters Symmetry C18 3.5µm 2 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.11 min.

Example WA32
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 4-Pyrazoleboronic acid pinacol ester instead of 3-Pyridineboronic acid. MS (ES+): 384 [M+H]+.
HPLC (Waters Symmetry C18 3.5µm 2 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.06 min.

Example WA33
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1-oxy-pyridin-3-yl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, step A to B followed by step

CHHcis-S-Chloro-phenylM-f 6-oxo-S-(1-oxy-pyridin^vO-eH-pyridazin-i-yll-cyclohexylmethylVcarbamic acid tert-butyl ester

To a solution of [1-(cis-3-Chloro-phenyl)-4-(6-oxo-3-pyridin-4-yl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (50mg, 0.101mmol) in dichloromethane (2ml) was added m-Chloroperbenzoic acid (25mg, 0.101mmol). The mixture was stirred at room temperature for 4h, then concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-
2.5 min 5% ACN, 2.5-1 2.5 min 5-100% ACN, 12.5-1 5.0 min 100% ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.

MS (ES\(^+\)) : 511 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6 min method (0-3 min 20-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-20% ACN, 5.55-6 min 20% ACN): 3.53 min.

D) 2-[4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1-oxy-pyridin-4-yl)]-2H-pyridazin-3-one

Trifluoroacetic acid (35µl) was added to a solution of [1-(cis-3-Chloro-phenyl)]-4-[6-oxy-3-[1-oxy-pyridin-4-yl]-6H-pyridazin-1-yl]-cyclohexylmethyl]-carbamic acid tert-butyl ester (23mg, 0.045mmol) in dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15 min method (0-2.5 min 5% ACN, 2.5-12.5 min 5-100% ACN, 12.5-15.0 min 100% ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.

MS (ES\(^+\)) : 411 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6 min method (0-3 min 5-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 2.94 min.

**Example WA34**

3-{1-(cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazin-3-yl)}-benzenesulfonamide

The title compound was prepared analogously as described in Example WA2, using 3-Aminosulfonylbenzenem boronic acid instead of 3-Pyridineboronic acid.

MS (ES\(^+\)) : 473 [M+H]\(^+\).

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6 min method (0-3 min 5-95% ACN, 3.5-5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 3.16 min.
Example WA35
2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(3-hydroxy-phenyl)-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WA2, using 3-Hydroxybenzeneboronic acid instead of 3-Pyridineboronic acid.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.26 min.

Example WA36
3-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1.6-dihydro-pyridazin-3-yl}->benzonitrile

The title compound was prepared analogously as described in Example WA2, using 3-Hydroxybenzeneboronic acid instead of 3-Pyridineboronic acid.
MS (ES+): 419 [M+H].
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.36 min.

Example WA37
3-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-β-3-(morpholine-4-carbonyl>-phenyl1-2H-pyridazin-3-one dihydrochloride

The title compound was prepared analogously as described in Example WA2, using N-[2-hydroxyethyl]benzamide-3-boronic acid pinacol ester instead of 3-Pyridineboronic acid.
MS (ES+): 481 [M+H]+.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.99 min.

Example WA38
2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-β-r3-(morpholine-4-carbonyl>-phenyl1-2H-pyridazin-3-one dihydrochloride
The title compound was prepared analogously as described in Example WA2, using 3-(Morpholine-4-carbonyl)phenylboronic acid instead of 3-Pyridineboronic acid.

**MS (ES+):** 507 [M+H]+.

**HPLC** (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.1 1 min.

**Example WA39**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-3-(4-methyl-piperazine-1-carbonyl)-phenyl-2H-pyridazin-3-one dihydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-(4-methylpiperazine-1-carbonyl)phenylboronic acid pinacol ester instead of 3-Pyridineboronic acid.

**MS (ES+):** 520 [M+H]+.

**HPLC** (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.83 min.

**Example WA40**

3-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazin-3-yl>-N-methyl-benzamide trihydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-(N-Methylaminocarbonyl)phenyl boronic acid instead of 3-Pyridineboronic acid.

**MS (ES+):** 451 [M+H]+.

**HPLC** (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.05 min.

**Example WA41**

3-{1-fcis-4-Aminomethyl-4-f3-chloro-phenyl)-cyclohexyn \( \pi \)-6-oxo-1,6-dihydro-pyridazin-3-yl>-N-(3-methoxy-propyl)-benzamide trihydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-(3-methoxypropylcarbamoylphenyl)boronic acid instead of 3-Pyridineboronic acid.

**MS (ES+):** 509 [M+H]+.
HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.16 min.

**Example WA42**

3-\{(1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1.6-dihydro-pyridazin-3-yl)-N-(2-methoxy-ethyl)-benzamide trihydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-(2-methoxyethylaminocarbonyl)benzene boronic acid instead of 3-Pyridineboronic acid. MS (ES^+): 495 [M+H]^+.

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.11 min.

**Example WA43**

3-(1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1.6-dihydro-pyridazin-3-yl)-N-(2H-tetrazol-5-yl)-benzamide trihydrochloride

The title compound was prepared analogously as described in Example WA2, using 3-(1H-tetrazol-5-yl-carbomoyl)benzene boronic acid instead of 3-Pyridineboronic acid. MS (ES^-): 505 [M+H]^+.

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.99 min.

**Example WB1**

4-Amino-2-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-π-6-phenyl-2H-pyridazinone

The title compound was prepared analogously as described in Example W10, step A to B to afford 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid followed by step C) f4-(5-Amino-6-oxo-3-phenyl-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyT-carbamic acid tert-butyl ester
To a solution of 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid (30mg, 0.056mmol) in toluene (250µl) was added Diphenyl phosphoryl azide (9µl, 0.056mmol) and Triethylamine (8µl, 0.056mmol). The mixture was stirred at 80°C for 2h, then water (50µl) was added and the resulting mixture was stirred at 80°C for 5h. The mixture was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN)). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.66 min.

D) 4-Amino-2-[cis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-phenyl-2H-pyridazin-3-one

Trifluoroacetic acid (9µl) was added to a solution of [4-(5-Amino-6-oxo-3-phenyl-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (6mg, 0.012mmol) in dichloromethane (1mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN)). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.46 min.

Example WC1

2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid dimethylamide formate
The title compound was prepared analogously as described in Example W10, step A to B to afford 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid followed by step C) 1-(cis-3-Chloro-phenyl)-4-(5-dimethylcarbamoyl-6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl-carbamic acid tert-butyl ester.

To a solution of 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid (20mg, 0.037mmol) in Tetrahydrofuran (150µl) was added N-Methyl morpholine (12µl, 0.07mmol) and Isobutylchloroformate (6µl, 0.044mmol) at 0°C. The mixture was stirred at 0°C for 30 minutes, then Dimethylamine hydrochloride (4mg, 0.044mmol) was added and the resulting mixture was stirred at 0°C for 1h, then at room temperature for 16h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 20-100%ACN, 2.5-12.5min 100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a colourless gum. MS (ES+): 588[M+Na]+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.32 min.

D) 2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid dimethylamide formate

Trifluoroacetic acid (38µl) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(5-dimethylcarbamoyl-6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (4mg, 0.007mmol) in dichloromethane (250µL). The reaction mixture was stirred at room temperature for 2h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo to give the title compound as a white solid. MS (ES+): 465 [M+H]+.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.94 min.

**Example WC2**

2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-(morpholine-4-carbonyl)-6-phenyl-2H-pyridazin-3-one formate

The title compound was prepared analogously as described in Example WC1, using Morpholine instead of Dimethylamine hydrochloride.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.10 min.

**Example WC3**

2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid methylamide formate

The title compound was prepared analogously as described in Example WC1, using Methylamine (2M solution in Tetrahydrofurane) instead of Dimethylamine hydrochloride.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.44 min.

**Example WC4**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid cyclopropylamide formate

The title compound was prepared analogously as described in Example WC1, using Methylamine (2M solution in Tetrahydrofurane) instead of Dimethylamine hydrochloride.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.65 min.

**Example WC5**
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-
pyridazine-4-carboxylic acid (2-methoxy-ethyl)-amide

The title compound was prepared analogously as described in Example WC1, using 2-
Methoxyethylamine instead of Dimethylamine hydrochloride.
MS (ES\(^+\)) : 496 [M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 2.99 min.

**Example WC\(\beta\)**
2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-
pyridazine-4-carboxylic acid carboxamoylmethyl-amide formate

The title compound was prepared analogously as described in Example WC1, using 2-Amino
acetamide instead of Dimethylamine hydrochloride.
MS (ES\(^+\)) : 495[M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.14 min.

**Example WC7**
2-r4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-4-(3-oxo-piperazine-1-carbonyl)-6-
phenyl-2H-pyridazin-3-one formate

The title compound was prepared analogously as described in Example WC1, using 2-
Piperazin-2-one instead of Dimethylamine hydrochloride.
MS (ES\(^+\)) : 520[M+H]\(^+\).
HPLC (Waters Symmetry C18 3.5\(\mu\)m 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-
5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 3.07 min.

**Example WC8**
2-r4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-6-phenyl-4-(piperazine-1-carbonyl)-
2H-pyridazin-3-one diformate
The title compound was prepared analogously as described in Example WC1, using Boc-piperazine instead of Dimethylamine hydrochloride.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.91 min.

**Example WD1**

2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid hydrazide

The title compound was prepared analogously as described in Example W8, step A to afford 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester followed by step B) f1-(cis-3-Chloro-phenyl)-4-(5-hydrazinocarbonyl-6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl-carbamic acid tert-butyl ester

To a solution of 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-phenyl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (55mg, 0.097mmol) in Ethanol (1ml) was added Hydrazine hydrate (96µl, 1.94mmol). The mixture was refluxed for 2h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 4.37 min.

C) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylV3-oxo-6-phenyl-2,3-dihydro-Pyridazine-4-carboxylic acid hydrazide

Trifluoroacetic acid (56µl) was added to a solution of [1-(cis-3-Chloro-phenyl)-4-(5-hydrazinocarbonyl-6-oxo-3-phenyl-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (40mg, 0.072mmol) in dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was
purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.

MS (ES⁺): 452 [M+H]

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95-20%ACN, 5.55-6min 20%ACN): 3.18 min.

**Example WE1**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1H-tetrazol-5-yl)-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A to afford [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexymethyl]-carbamic acid tert-butyl ester followed by step

B) ff1-(cis-S-Chloro-phenylM-O-cvano-β-oxo-βH-pyridazin-i-yl)-cyclohexymethyl1-carbamic acid tert-butyl ester

To a solution of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexymethyl]-carbamic acid tert-butyl ester (50mg, 0.101mmol) in Dimethylformamide (1ml) was added Tetrakis(triphenylphosphine)palladium(0) (3.5mg, 0.003mmol) and Zinc cyanide (12mg, 0.101mmol) under argon atmosphere. The mixture was treated with microwave at 120°C for 120 seconds. The mixture was filtered. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 5.60 min.
C) (1-(cis-3-Chloro-phenyl)-4-f6-oxo-3-(1 H-tetrazol-5-yl)-6H-pyridazin-1 -yll-
cyclohexymethyl carbamic acid tert-butyl ester

To a solution of [(1-(cis-3-Chloro-phenyl)-4-(3-cyano-6-oxo-6H-pyridazin-1-y)]-
cyclohexymethyl] carbamic acid tert-butyl ester (27mg, 0.061 mmol) in Dimethylformamide
(1ml) was added Sodium azide (48mg, 0.732mmol) and Ammonium chloride (39mg, 0.731 mmol) under argon atmosphere. The mixture was treated with microwave at 120°C for
15 minutes. The mixture was filtered. The filtrate was concentrated in vacuo to give the title
compound.

D) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylH-6-(1H-tetrazol-5-yl)-2H-pyridazin-3-one hydrochloride

To {1-(cis-3-Chloro-phenyl)-4-[6-oxo-3-(1 H-tetrazol-5-yl)-6H-pyridazin-1 -yl]-
cyclohexymethyl] carbamic acid tert-butyl ester (29mg, 0.080mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room
temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min
5%ACN, 2.0-7.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN).
Fractions containing the product were lyophilized in vacuo to give the formate salt of the title
compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.
MS (ES^+): 386 [M+Hf .
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min
20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.45 min.

**Example WF1**

6-Amino-2-fcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A to
afford [4-(3-Bromo-6-oxo-6H-pyridazin-1 -yl)-1-(cis-3-chloro-phenyl)-cyclohexymethyl]-
carbamic acid tert-butyl ester followed by step
B) f4-(3-Amino-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl-carbamic acid tert-butyl ester trifluoroacetate

To a solution of 4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (50mg, 0.101mmol) in a mixture of Ethanol (1.4ml) and water (0.6ml) was added Sodium Azide (13mg, 0.202mmol), Copper iodide (2mg, O.010mmol), Sodium ascorbate (1mg, 0.005mmol) and N-N-Dimethylethylenediamine (1.6µl, 0.015mmol) under argon atmosphere. The mixture was treated with microwave at 100°C for 30 minutes. The mixture was filtered. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 4.50 min.

C) 6-Amino-2-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-2H-pyridazin-3-one hydrochloride

To [4-(3-Amino-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbarnic acid tert-butyl ester trifluoroacetate (33mg, 0.076mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 1.76 min.

Example v*v* F 2
N-{1-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-oxo-1. β -dihvdro-pyrida2in-
3-yl>-acetamide hydrochloride

The title compound was prepared analogously as described in Example WF1, step A to B to afford [4-(3-Amino-6-oxo-6H-pyridazin-1 -yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-
carbamic acid tert-butyl ester trifluoroacetate followed by step C) 4-(3-Acetylamino-6-oxo-6H-pyridazin-1 -yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl-
carbamic acid tert-butyl ester

To a solution of [4-(3-Amino-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-
cyclohexylmethyl]-carbamic acid tert-butyl ester trifluoroacetate (18mg, 0.042mmol) in Dichloromethane (1.5ml) was added Triethylamine (29µl, 0.21mmol) and Acetylchloride (3.5µl, 0.05mmol). The mixture was stirred at room temperature for 2h. The mixture was filtered. The filtrate was concentrated in vacuo to give the title compound.

D) N-(1-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-oxo-1.6-dihvdro-pyrida3-
yl/Vacetamide hydrochloride

To [4-(3-Acetylamino-6-oxo-6H-pyridazin-1 -yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-
carbamic acid tert-butyl ester (20mg, 0.042mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40mL/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.
HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.12 min.

Example WF3
The title compound was prepared analogously as described in Example WF1, step A to B to afford [4-(3-Amino-6-oxo-6H-pyridazin-1-yl)-1-(3-chloro-phenyl)cyclohexylmethyl]carbamic acid tert-butyl ester trifluoroacetate followed by step C)

C) f4-(3-Benzoyl-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]carbamic acid tert-butyl ester.

To a solution of [4-(3-Amino-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)cyclohexylmethyl]carbamic acid tert-butyl ester trifluoroacetate (61 mg, 0.141 mmol) in Dichloromethane (3 ml) was added Benzoic acid (26 mg, 0.211 mmol), N-(3-Dimethylaminopropyl)-N’-ethylcarbodiimide (51 µL, 0.282 mmol), 1-Hydroxybenzotriazole hydrate (42 mg, 0.310 mmol) and Triethylamine (98 µL, 0.705 mmol). The mixture was stirred at 40°C for 48h. The mixture was filtered. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40 ml/min, 21 min method (0-2.0 min 5% ACN, 2.0-17.5 min 5-100% ACN, 17.5-19.5 min 100% ACN, 19.5-21.0 min 100-5% ACN). Fractions containing the product were concentrated in vacuo to give title compound.

MS (ES-): 537 [M+H]-

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5 ml/min, 8 min method (0-6.0 min 20-100% ACN, 6.0-7.5 min 100% ACN, 7.5-8.0 min 100-20% ACN): 5.68 min.

D) 2-f4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-benzoyl-2H-pyridazin-3-one hydrochloride

To [4-(3-Benzoyl-6-oxo-6H-pyridazin-1-yl)-1-(3-chloro-phenyl)cyclohexylmethyl]carbamic acid tert-butyl ester (6 mg, 0.065 mmol) was added 4N hydrogen chloride solution in dioxane (5 ml). The reaction mixture stirred at room temperature for 2 h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40 ml/min, 21 min method (0-2.0 min 5% ACN, 2.0-17.5 min 5-100% ACN, 17.5-19.5 min 100% ACN, 19.5-21.0 min 100-5% ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and...
treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

MS (ES\textsuperscript{+}): 437 [M+H]+.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN)): 3.02 min.

**Example WG1**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1-r2-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-M.2,31triazol-4-yl)-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A to afford [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester followed by step B) f1-(cis-S-Chloro-phenyl]-M-P-ethynyl-\beta-oxo-6H-pyridazin-i -vD-cyclohexylmethylT-carbamic acid tert-butyl ester.

To a solution of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (50mg, 0.101mmol) in Dimethylformamide (1ml) was added Trimethylsilylacetylene (15µl, 0.111mmol), Copper iodide (1mg, 0.005mmol), trans-Dichlorobis(triphenylphosphine)palladium(II) (3.5mg, 0.005mmol), Triphenylphosphine (5.3mg, 0.02mmol) and Diethylamine (157µl, 1.51mmol) under argon atmosphere. The mixture was treated with microwave at 120°C for 30 minutes. The mixture was filtered. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5μm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.

MS (ES\textsuperscript{+}): 442 [M+H]+.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 5.61 min.

C) f1-(cis-3-Chloro-phenyl)-4-(3-f_1-r2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethy \pi 1H-f1,2,31triazol-
4-yl)-6-oxo-6H-pyridazin-1-yl)-cyclohexylmethyn-carbamic acid tert-butyl ester
To [1-(cis-3-Chloro-phenyl)-4-(3-ethynyl-6-oxo-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (25mg, 0.057mmol) in a mixture of Dichloromethane (1ml) and water (1ml) was added 4-(2-Azidoethyl)-3,5-dimethyl-1H-pyrazole (9.3mg, 0.057mmol), Copper sulfate (0.05mg, 0.003mmol) and Sodium ascorbate (1.7mg, 0.005mmol). The mixture was stirred at room temperature for 16h. The mixture was filtered. The filtrate was concentrated in vacuo to give the title compound.

D) 2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1-r2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl1-1H-1,2,3-triazol-4-yl)-2H-pyridazin-3-one hydrochloride

To [1-(cis-3-Chloro-phenyl)-4-(3-{1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)-ethyl]-1H-[1,2,3]triazol-4-yl]-6-oxo-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (34mg, 0.056mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.30 min.

Example WG2

(4-{1-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazin-3-vi>-n.2,31triazol-1-yl)-acetic acid ethyl ester hydrochloride

The title compound was prepared analogously as described in Example WG1, using Ethylazidoacetate instead of 4-(2-Azidoethyl)-3,5-dimethyl-1 H-pyrazole.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.98 min.
Example WG3

(4-{1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-oxo-1,6-dihydro-pyridazin-3-ylH1.2.3triazol-1-yl)-acetic acid hydrochloride

The title compound was prepared analogously as described in Example WG2 followed by step:

E) (4-{1-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-6-oxo-1,6-dihydro-pyridazin-3-ylH1.2.3triazol-1-yl)-acetic acid ethyl ester hydrochloride

To (4-{1-[cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl]-6-oxo-1,6-dihydro-pyridazin-3-ylH1.2.3triazol-1-yl)-acetic acid ethyl ester hydrochloride (6mg, 0.013mmol) in dioxane (2ml) was added 1M aqueous potassium hydroxide solution (1ml). The mixture was treated with microwave at 120°C for 5min. The mixture was evaporated. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

MS (ES?): 443 [M+H]

HPLC (Agilent Eclipse XDB-C18 4.6°50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.44 min.

Example WG4

(4-{1-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-oxo-1,6-dihydro-pyridazin-3-ylH1.2.3triazol-1-vD-acetic acid hydrochloride

The title compound was prepared analogously as described in Example WG2 step A to C followed by step:

D) (4-11-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyn-6-oxo-1,6-dihydro-pyridazin-3-ylH1.2.3triazol-1-yl)-acetic acid
To (4-{1-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-6-oxo-1,6-dihydro-pyridazin-3-yl]-[1,2,3]triazol-1-yl})-acetic acid ethyl ester (22mg, 0.039mmol) in dioxane (2ml) was added 1M aqueous potassium hydroxide solution (1.5ml). The mixture was treated with microwave at 120°C for 5min. The mixture was evaporated. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 4.54 min.

E) f4-r3-π-Carbamoylmethyl-1H-[1,2,3]triazol-4-yl)-6-oxo-6H-Dyridazin-1-vn-1-(cis-3-chloro-phenyl)-cyclohexylmethyl carbamic acid tert-butyl ester

To (4-{1-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-6-oxo-1,6-dihydro-pyridazin-3-yl]-[1,2,3]triazol-1-yl})-acetic acid (15mg, 0.028mmol) in acetonitrile (1ml) was added O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (16mg, 0.041mmol) at 0°C. The mixture was stirred at 0°C for 5min, then Ammonium carbonate (4mg, 0.055mmol) in Triethylamine (0.25ml) was added to the mixture. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was treated with saturated aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give the title compound.

F) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1-r2-(3,5-dimethyl-1-H-pyrazol-4-yl)-ethyl1-1H.2.31triazol-4-yl)-2H-Dyridazin-3-one hydrochloride

To [4-3-{1-Carbamoymethyl-1 H-[1,2,3]triazol-4-yl]}-6-oxo-6H-pyridazin-1 -yl]-1-(cis-3-chloro-phenyl)-cyclohexylmethyl carbamic acid tert-butyl ester (15mg, 0.028mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-1S.91mir 100%ACN, 19.5-21.0mir. 100-5%ACN).
Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN)): 2.28 min.

**Example WG5**

2-r4-Aminomethyl-4-(3-chloro-phenyO-cvclohexy π-6-ri -f2-piperidin-1 -yl-ethyl)-1 H-
li ,2,31triazol-4-vn-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WG1, using 2-Piperidino-ethylazide instead of 4-(2-Azidoethyl)-3,5-dimethyl-1 H-pyrazole.

MS (ES⁺): 496 [M+H]⁺.

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN)): 1.93 min.

**Example WG6**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-{1H-f1,2,31triazol-4-yl)-2H-
pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WG2 step A to C using 2,2-Dimethyl-propionic acid azidomethyl ester instead of 4-(2-Azidoethyl)-3,5-dimethyl-1H-pyrazole to afford 2,2-Dimethyl-propionic acid 4-{1-[4-(tert-butoxycarbonylamino-methyl)]-4-(cis-3-chloro-phenyl)-cyclohexyl]-6-oxo-1,6-dihydro-pyridazin-3-yl]-[1,2,3]triazol-1-ylmethyl ester followed by step:

D),(1-(cis-3-Chloro-phenyl)-4-r6-oxo-3-{1 H-f1,2,31triazol-4-vn-6H-pyridazin-1 -yli-
cyclohexylmethylVcarbamic acid tert-butyl ester

To 2,2-Dimethyl-propionic acid 4-{1-[4-(tert-butoxycarbonylamino-methyl)]-4-(cis-3-chloro-
phenyl)-cyclohexyl]-6-oxo-1 ,6-dihydro-pyridazin-3-yl]-[1,2,3]triazol-1-ylmethyl ester (24mg, 0.040mmol) in Methanol (1ml) was added 1M aqueous sodium hydroxide solution (1ml). The
mixture was stirred at room temperature for 30 min. The mixture was filtered and concentrated in vacuo to give the title compound.

E) 2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1H-M,2,3triazol-4-yl)-2H-pyridazin-3-one hydrochloride

To {1-(cis-3-Chloro-phenyl)-4-[6-oxo-3-(1H-[1,2,3]triazol-4-yl)-6H-pyridazin-1-yl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (20mg, 0.041 mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.


HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5mL/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 2.48 min.

**Example WH1**

2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(1H-M,2,3triazol-4-yl)-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A to afford [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester followed by step

B) r4-(3-Azido-6-oxo-6H-pyridazin-1-yl)-1-(3-chloro-phenyl)-cyclohexylmethyl carbamic acid tert-butyl ester

To a solution of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (40mg, 0.081 mmol) in a mixture of Ethanol (1.4ml) and water (0.6ml) was added Sodium Azide (10.5mg, 0.161mmol), Copper iodide (1.5mg, 0.008mmol), Sodium ascorbate (1mg, 0.004mmol) and N-N-
Dimethylethylenediamine (1.3 µl, 0.012 mmol). The mixture was stirred at room temperature for 1h, then treated with microwave at 60°C for 15 seconds. The mixture was extracted into dichloromethane. The organic phase was dried and concentrated in vacuo to give the title compound.

MS (ES\(^+\)): 403 [M-t-Bu+H]\(^+\).

**3D-O-Chloro-phenyl-4-f6-oxo-S-C\(^\text{propyl}\)-S-dihydro-fi\(^\text{S-triazol-1-vD-eH-pyridazin-i-yll-cyclohexymethylIV-carbamic acid tert-butyl ester**

To [4-(3-Azido-6-oxo-6H-pyridazin-1-yl)-1-(3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (37mg, 0.081 mmol) in a mixture of Dichloromethane (1ml) and water (1ml) was added 1-Pentyne (7.9 µl, 0.081 mmol), Copper sulfate (0.6mg, 0.004 mmol) and Sodium ascorbate (2.4mg, 0.012 mmol). The mixture was stirred at room temperature for 16h. The mixture was filtered. The filtrate was concentrated in vacuo to give the title compound.

**D) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-(4-propyl-f 1,2,3triiazol-1-yl)-2H-pyridazin-3-one hydrochloride**

To (1-(3-Chloro-phenyl)-4-[6-oxo-3-(4-propyl-2,3-dihydro-[1,2,3]triazol-1-yl]-6H-pyridazin-1-yl]-cyclohexylmethyl]-carbamic acid tert-butyl ester (42mg, 0.08 mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was purified by prep. HPLC (Macherey-Nagel Nucleosil 100-10 C18, flow 40ml/min, 21min method (0-2.0min 5%ACN, 2.0-17.5min 5-100%ACN, 17.5-19.5min 100%ACN, 19.5-21.0min 100-5%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salt of the title compound, which was dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the title compound as a white solid.

MS (ES\(^+\)): 427 [M+H]\(^+\).

HPLC (Agilent Eclipse XDB-C18 4.6*50mm, 1.8µm, flow 1.5ml/min, 8min method (0-6.0min 20-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-20%ACN): 3.23 min.

**Example WM**

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-β-pyridin-3-yl-2,3-dihydro-pyridazine-4-carboxylic acid amide
The title compound was prepared according to Scheme W.

A) 2-f4-(tert-Butoxycarbonylamino-methyl π-4-(cis-3-chloro-phenyl)-cyclohexyn-3-oxo-6-pyridin-3-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester

To a solution of [1-(cis-3-Chloro-phenyl)-4-hydroxy-cyclohexylmethyl]-carbamic acid tert-butyl ester (35mg, 0.101mmol), 3-Oxo-6-pyridin-3-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (37mg, 0.151mmol) and Triphenylphosphine (32mg, 0.121mmol) in tetrahydrofurane (40ml), was added Diethyl azodicarboxylate (26µl, 0.161mmol) at room temperature. The reaction mixture was stirred for 3 days at room temperature. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-20%ACN, 5.55-6min 20%ACN): 3.45 min.

B) f4-(5-Carbamoyl-6-oxo-3-pyridin-3-yl-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethylT-carbamic acid tert-butyl ester

2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-pyridin-3-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (20mg, 0.035mmol) was dissolved in 2M ammonia in Methanol (350µL, 0.69mmol). The mixture was stirred at room temperature for 12h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow oil.

MS (ES⁺): 538[M+H]⁺.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-20%ACN, 5.55-6min 20%ACN): 3.26 min.
C) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyl-3-oxo-6-pyridin-3-yl-2,3-dihydro-
pyridazine-4-carboxylic acid amide

Trifluoroacetic acid (56 µl) was added to a solution of [4-(5-Carbamoyl-6-oxo-3-pyridin-3-yl-
6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester
(19 mg, 0.034 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room
temperature for 1 h. The mixture was concentrated in vacuo. The residue was purified by
prep. HPLC (Waters SunFire Prep C18 ODB 5 µm 19 x 50 mm, flow 20 mL/min, 15 min method
(0-2.5 min 5% ACN, 2.5-12.5 min 5-100% ACN, 12.5-15 min 100% ACN). Fractions containing
the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title
compound.

HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50 mm, 6 min method (0-3 min 5-95% ACN, 3.5-
5.5 min 95% ACN, 5.5-5.55 min 95-5% ACN, 5.55-6 min 5% ACN): 2.81 min.

Example WI2

2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-3-oxo-6-(1-oxy-pyridin-3-yl)-2,3-
dihydro-pyridazine-4-carboxylic acid amide

The title compound was prepared analogously as described in Example WH, step A to B
followed by step

C) f4-r5-Carbamoyl-6-oxo-3-(1-oxy-pyridin-3-yl)-6H-pyridazin-1-yli-1-(cis-3-chloro-phenyl)-
cyclohexymethylcarbamic acid tert-butyl ester

To a solution of [4-(5-Carbamoyl-6-oxo-3-pyridin-3-yl-6H-pyridazin-1-yl)-1-(cis-3-chloro-
phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (50 mg, 0.093 mmol) in
dichloromethane (2 mL) was added m-Chloroperbenzoic acid (23 mg, 0.093 mmol). The
mixture was stirred at room temperature for 16 h. The mixture was partitioned between
dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was
dried and concentrated in vacuo to give the title compound as a white solid.
MS (ES⁺): 554 [M+H]⁺.
HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.42 min.

D) 2-rcis-4-Aminomethyl-4-(3-chloro-phenyl)-cvclohexyll-3-oxo-6-(1-oxy-pyridin-3-yl)-2.3-dihvdro-pyridazine-4-carboxylic_acid amide

Trifluoroacetic acid (35µl) was added to a solution of [4-[5-Carbamoyl-6-oxo-3-(1-oxy-pyridin-3-yl)-6H-pyridazin-1-yl]-1-(cis-3-chloro-phenyl)-cyclohexymethyl]-carbamic acid tert-butyl ester (23mg, 0.045mmol) in dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.

MS (ES+) : 454 [M+H]+.

HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.87 min.

Example WJ1

4-Amino-2-rcis-4-aminomethyl-4-(3-chloro-phenyl)-cvclohexyn-6-pyridin-3-yl-2H-pyridazin-3-one

The title compound was prepared analogously as described in Example WH, step A followed by step

B) 2-f4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cvclohexyl1-3-oxo-6-pyridin-S-yl^-S-dihvdro-pyridazine^-carboxylic acid

To 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cvclohexyl]-3-oxo-6-pyridin-3-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester (250mg, 0.442mmol) in Tetrahydrofurane (2ml) and water (2ml) was added Lithium hydroxide hydrate (93mg, 2.2mmol). The mixture was stirred at 60°C for 3h. The mixture was partitioned between
dichloromethane and 1N Hydrochloric acid. The organic layer was dried and concentrated in vacuo to give the title compound as an orange solid.

MS (ES\textsuperscript{+}): 540[M+Na\textsuperscript{+}].

HPLC (Waters Symmetry C18 3.5\mu m 2.1 x 50mm, 6min method (0-3min 20-95\%ACN, 3.5-5.5min 95\%ACN, 5.5-5.55min 95-20\%ACN, 5.55-6min 20\%ACN): 3.55 min.

C) [4-(5-Amino-6-oxo-3-pyridin-3-yl-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester

To a solution of 2-[4-(tert-Butoxycarbonylamino-methyl)-4-(cis-3-chloro-phenyl)-cyclohexyl]-3-oxo-6-pyridin-3-yl-2,3-dihydro-pyridazine-4-carboxylic acid (200mg, 0.372mmol) in Tetrahydrofuran (10ml) was added at 0\degree C N-Methylmorpholine (49\mu L, 0.445mmol) and Isobutylchloroformate (58\mu L, 0.445mmol). The mixture was stirred at 0\degree C for 0.5h, then Sodium azide (36mg, 0.557mmol) was added. The mixture was stirred at 0\degree C for 1h, then at room temperature for 16h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give [4-(5-Azidocarbonyl-6-oxo-3-pyridin-3-yl-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester which was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5\mu m 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5\%ACN, 2.5-12.5min 5-100\%ACN, 12.5-15.0min 100\%ACN). Fractions containing the azide were kept at room temperature for 16h to form the amine. Then they were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.

MS (ES\textsuperscript{+}): 510 [M+H\textsuperscript{+}].

HPLC (Waters Symmetry C18 3.5\mu m 2.1 x 50mm, 6min method (0-3min 20-95\%ACN, 3.5-5.5min 95\%ACN, 5.5-5.55min 95-20\%ACN, 5.55-6min 20\%ACN): 3.21 min.

D) 4-Amino-2-fcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyll-6-Pyridin-3-yl-2H-pyridazin-3-one

Trifluoroacetic acid (28\mu l) was added to a solution of [4-(5-Amino-6-oxo-3-pyridin-3-yl-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (20mg, 0.036mmol) in dichloromethane (2mL). The reaction mixture was stirred at room
temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-5%ACN, 5.55-6min 5%ACN): 2.79 min.

Example WJ2

\(^{\text{Amino-2-r^2aminomethyM-O-chloro-phenv}} \pi\-cyclohexy \pi\-6-d-\text{oxy-pyridin-a-v} \pi\-2H-pyridazin-3-one\)

The title compound was prepared analogously as described in Example WJ1, step A to C followed by step

D) f4-f5-Amino-6-oxo-3-(1-oxy-pyridin-3-yl)-6H-pyridazin-1-yl-1-(cis-3-chloro-phenyl)-cyclohexylmethylcarbamic acid tert-butyl ester

To a solution of [4-(5-Amino-6-oxo-3-pyridin-3-yl)-6H-pyridazin-1-yl]-1-(cis-3-chloro-phenyl)-cyclohexylmethyl][carbamic acid tert-butyl ester (50mg, 0.090mmol) in dichloromethane (2ml) was added m-Chloroperoxybenzoic acid (22mg, 0.090mmol). The mixture was stirred at room temperature for 16h. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a white solid.


HPLC (Waters Symmetry C18 3.5µm 2.1 x 50mm, 6min method (0-3min 20-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.55min 95-20%ACN, 5.55-6min 20%ACN): 3.47 min.
Trifluoroacetic acid (34 µl) was added to a solution of [4-(5-Amino-6-oxo-3-(1-oxy-pyridin-3-yl)-6H-pyridazin-1-yl]-1-(3-chloro-phenyl)-cyclohexymethyl]-carbamic acid tert-butyl ester (25mg, 0.044mmol) in dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5 µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the title compound as a yellow solid.


HPLC (Waters Symmetry C18 3.5 µm 2.1 x 50mm, 6min method (0-3min 5-95%ACN, 3.5-5.5min 95%ACN, 5.5-5.5min 95-5%ACN, 5.5-6min 5%ACN): 2.88 min.

**Example WK1**

2-rcis-4-Aminomethyl-4-f3-chloro-phenyl)-cvclohexy π-6-morpholin-4-yl-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A to afford [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexymethyl]-carbamic acid tert-butyl ester followed by step B) H-(cis-S-Chloro-phenylIM-O-morpholin^-yl- 6-oxo-βH-pyridazin-i ,yl)-cyclohexymethyl1- carbamic acid tert-butyl ester

To a solution of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexymethyl]-carbamic acid tert-butyl ester (30mg, 0.06mmol) in toluene (0.9ml) was added Morpholine (32µl, 0.362mmol), (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene (1mg, 0.001 δmmol), Tris(dibenzyldieneacetone)dipalladium(0) (1mg, 0.0012mmol) and Sodium tert.butoxide (8mg, 0.085mmol). The mixture was stirred at 120°C for 20min. To the mixture was added Morpholine (16µl, 0.181mmol), (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene (0.5mg, 0.0009mmol), Tris(dibenzyldieneacetone)dipaiia αium(0) (0.0mg,
O.OOO β mmol). The mixture was treated with microwave at 120°C for 10 minutes. The mixture was filtered over a ChemElut Extraction column (VARIAN) eluting with Ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.

MS (ES⁺): 503 [M+H⁺].

C) 2-tcis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-morpholin-4-yl-2H-pyridazin-3-one hydrochloride

To [1-(cis-3-Chloro-phenyl)-4-(3-morpholin-4-yl-6-oxo-6H-pyridazin-1-yl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (33mg, 0.076mmol) was added 4N hydrogen chloride solution in dioxane (5ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was treated with diethyl ether in ultrasonic bath. The etheric phase was removed with a pipette. The residue was lyophilized in vacuo to give the title compound as a white solid.

MS (ES⁺): 403 [M+H⁺].

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.82 min.

Example WK2

6-(4-Acetyl-piperazin-1-yl)-2-tcis-4-aminomethyl-4-(3-chloro-phenyl)-cyclohexyn π-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WK1, using 1-Acetylpiperazine instead of Morpholine.

MS (ES⁺): 444[M+H⁺].

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.71 min.

Example WK3

4-{1-(4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-oxo-1.6-dihydro-pyridazin-3-yl)-morpholine-2-carboxylic acid methylamide hydrochloride
The title compound was prepared analogously as described in Example WK1, using Morpholine-2-carboxylic acid methylamide instead of Morpholine.

MS (ES⁺): 460[M+H]⁺.

HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.79 min.

Example WK4

2-r4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexyn-6-piperidin-1-y1-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WK1, using Piperidine instead of Morpholine.


HPLC (Nucleosil C-18HD 4x70mm 3μm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 4.35 min.

Example WL1

2-cis-4-Aminomethyl-4-(3-chloro-phenyl)-cyclohexylβ-(3-oxo-piperazin-1-vi)-2H-pyridazin-3-one hydrochloride

The title compound was prepared analogously as described in Example WA1, step A to afford [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester followed by step B) (1-(cis-3-Chloro-phenyl)-4-f6-oxo-3-(3-oxo-piperazin-1 -yl)-6H-pyridazin-1 -yl]-cyclohexylmethyl]-carbamic acid tert-butyl ester

To a solution of [4-(3-Bromo-6-oxo-6H-pyridazin-1-yl)-1-(cis-3-chloro-phenyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (30mg, 0.06mmol) in Dimethylsulfoxide (0.72ml) was added Piperazin-2-one (18mg, 0.181mmol), Copper(I)iodide (2.3mg, 0.012mmol), L-Proline (2.8mg, 0.024mmol) and Potassium carbonate (17mg, 0.121mmol). The mixture was stirred at 90°C for 16h. The mixture was directly purified by prep. HPLC (Waters SunFire Prep C18 ODB 5μm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min
5%ACN, 2.5-1 2.5min 5-100%ACN, 12.5-1 5.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the title compound.

MS (ES+) : 516 [M+H]+.

C) 2-fcis-4-Aminomethyl-4-(3-chloro-phenyO-cyclohexyll-6-(3-oxo-piperazin-1-yl)-2H-pyridazin-3-one

To {1-(cis-3-Chloro-phenyl)-4-[6-oxo-3-(3-oxo-piperazin-1-yl)-6H-pyridazin-1-yl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (9mg, 0.017mmol) was added 4N hydrogen chloride solution in dioxane (4ml). The reaction mixture stirred at room temperature for 2h, then it was concentrated in vacuo. The residue was treated with diethyl ether in ultrasonic bath. The etheric phase was removed with a pipette. The residue was lyophilized in vacuo to give the title compound as a white solid.

MS (ES+) : 416 [M+H]+.

HPLC (Nucleosil C-18HD 4x70mm 3µm, 8min method (0-6min 5-100%ACN, 6.0-7.5min 100%ACN, 7.5-8.0min 100-5%ACN): 3.56 min.

Example Y1
C-rcis-4-(5,β,7,8-Tetrahvdro-naphthalen-1-yl)-1-m-tolyl-cyclohexy π-methylamine hydrochloride

The title compound was prepared according to Scheme Y.

A) 4-Cvano-4-m-tolyl-heptanedioic acid dimethyl ester

To a solution of Triton B (25.5mL, 61mmol of a 40% solution in methanol) in t-butanol (30mL) was added a solution of 3-Methylbenzylycyanide (25ml, 185mmol) and Methyl acrylate (47.2mL, 519mmol t-butanol (70ml). When the addition was complete, the reaction mixture was stirred at 80°C for 16h. After cooling, the reaction mixture was treated with 4N Hydrochloric acid to pH2, then concentrated in vacuo. The residue aqueous phase was extracted 2x with ethyl acetate. The combined organic phases were dried over Magnesium sulfate and concentrated in vacuo. The residue was recrystallised from diethyl ether: pentane 1:1 to give the title compound as a white solid.

MS (ES+) : 321 [M+H2O]
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 6.29 min.

B) 5-Cvano-2-oxo-5-m-tolyl-cyclohexanecarboxylic acid methyl ester

To a solution of 4-Cyano-4-m-tolyl-heptanedioic acid dimethyl ester (10.4g, 34.3mmol) in tetrahydrofurane (100ml) was added Potassium tert-butoxide (9.4g, 78.7mmol). The resulting mixture was stirred at 70°C for 2h. The reaction mixture was cooled (0°C) and treated with a solution of acetic acid (12ml) in water (60mL). The mixture was extracted with diethyl ether and the organic phase was washed with 2N aqueous sodium bicarbonate solution and water, then dried over Magnesium sulfate and concentrated in vacuo to give the title compound as a white solid. MS (ES⁺): 289 [M+H2O]⁺.

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 6.66 min.

C) 4-Oxo-1-m-tolyl-cyclohexanecarbonitrile

A mixture of 5-Cyano-2-oxo-5-m-tolyl-cyclohexanecarboxylic acid methyl ester (7.4g, 27.3mmol) in 10% aqueous sulphuric acid (40mL) and acetic acid (80mL) was stirred for 16h at 110°C. After cooling to room temperature, the reaction mixture was diluted with water and extracted into ethyl acetate. The organic phase was washed with 2N aqueous sodium bicarbonate solution and water, then dried over Magnesium sulfate and concentrated in vacuo to give the title compound as an orange oil. MS (ES⁺): 426 [2xM+H].

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 6.02 min.

D) Trifluoro-methanesulfonic acid 4-cyano-4-m-tolyl-cyclohex-1-enyl ester
To a solution of Lithium diisopropylamide solution (2.8ml, 5.6mmol of a 2.0 M solution in tetrahydrofuran/heptane/ethylbenzene) in tetrahydrofuran (10ml) was added dropwise a solution of 4-Oxo-1-m-tolyl-cyclohexanecarbonitrile (1.0g, 4.64mmol) in tetrahydrofuran (5ml) at -78°C. The resulting mixture was stirred at -78°C for 30 minutes, then a solution of N-Phenyl-bis(trifluoromethansulfonimide) (1.99g, 5.57mmol) in tetrahydrofuran (5ml) was added. The reaction mixture was stirred at 0°C for 5h. The mixture was concentrated in vacuo. The residue was partitioned between dichloromethane and 1N Hydrochloric acid. The organic phase was dried over Magnesium sulfate and concentrated in vacuo to give the title compound.


HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 6.66 min.

E) 4-Naphthalen-1-yl-1-m-tolyl-cyclohex-5-enecarbonitrile

To a solution of Trifluoro-methanesulfonic acid 4-cyano-4-m-tolyl-cyclohex-1-enyl ester (1.25g, 2.32mmol) in 1,2-Dimethoxyethane (10ml) was added 1-Naphthaleneboronic acid (558mg, 3.24mmol), Lithium chloride (295mg, 6.96mmol), Tetrakis(triphenylphosphine)palladium(0) (135mg, 0.116mmol) and 2N aqueous sodium carbonate solution (3ml). The reaction mixture was stirred for 3h at 90°C. After cooling, the mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried over Magnesium sulfate and concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were concentrated in vacuo to give the title compound.


HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 7.97 min.
F) C-fcis-4-(5,6,7,8-Tetrahydro-naphthalen-1-yl)-1-m-tolyl-cyclohexylmethylamine hydrochloride and C-ftrans-4-(5,6,7,8-Tetrahydro-naphthalen-1-yl)-1-m-tolyl-cyclohexymethylamine hydrochloride

To a solution of 4-Naphthalen-1-yl-1-m-tolyl-cyclohex-3-enecarbonitrile (260mg, 0.804mmol) in Ethanol (25ml) and cone. Hydrochloric acid (5ml, 37%) was added Platinum(IV)oxide hydrate (18.3mg, 0.081mmol). The reaction mixture was stirred at room temperature for 3h under hydrogen atmosphere. The mixture was filtered, then the filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salts of the individual title compounds, which were dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the individual title compounds as white solids.

MS (ES⁺): 334 [M+H]⁺ (cis) and MS (ES⁺): 334 [M+H]⁺ (trans)
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 6.55 min (cis) and 6.44 min (trans).

Example Y2
C-rcis-4-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-1-m-tolyl-cyclohexyn-methylamine hydrochloride

The title compound was prepared analogously as described in Example Y1, using 2-Naphthaleneboronic acid instead of 1-Naphthaleneboronic acid.

MS (ES⁺): 334 [M+H]⁺
HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 6.66 min

Example Y3
C-(cis-4-Naphthalen-1-yl-1-m-tolyl-cyclohexyl)-methylamine hydrochloride
The title compound was prepared analogously as described in Example Y1, step A to E followed by step F.

F) C-(4-Naphthalen-1-yl-1-m-tolyl-cyclohex-3-enyl)-methylamine

To a solution of 4-Naphthalen-1-yl-1-m-tolyl-cyclohex-3-enecarbonitrile (280mg, 0.866mmol) in Diethylether (10ml), was added Lithiumaluminium hydride (85mg, 2.16mmol). The resulting mixture was stirred at room temperature for 2h. The mixture was treated with aqueous Potassium sodium tartrate solution and extracted 2x into ethyl acetate. The combined organic phases were dried over Magnesium sulfate and concentrated in vacuo to give the title compound.

**MS (ES⁺): 328 [M+H]+**

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5ml/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 8.32 min.

G) C-(cis-4-Naphthalen-1-yl-1-m-tolyl-cyclohexyl)-methylamine hydrochloride and C-(trans-4-Naphthalen-1-yl-1-m-tolyl-cyclohexyl)-methylamine hydrochloride

To a solution of C^-^-Naphthalen-1-yl-1-m-tolyl-cyclohex-3-enyl-methylamine (250mg, 0.687mmol) in Ethanol (5ml) was added 10% Palladium on charcoal (73mg, 0.069mmol). The reaction mixture was stirred at room temperature for 16h under hydrogen atmosphere. The mixture was filtered, then the filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (Waters SunFire Prep C18 ODB 5µm 19 x 50mm, flow 20ml/min, 15min method (0-2.5min 5%ACN, 2.5-12.5min 5-100%ACN, 12.5-15.0min 100%ACN). Fractions containing the product were lyophilized in vacuo to give the formate salts of the individual title compounds, which were dissolved in methanol and treated with an excess of 2M hydrogen chloride in methanol. Removal of the volatiles gave the individual title compounds as white solids.

**MS (ES⁺): 330 [M+H]+ (cis) and MS (ES⁺): 330 [M+H]+ (trans)**

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5ml/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.30 min (cis) and 5.18 min (trans).
Example Y4
C-(cis-4-Naphthalen-2-yl-1-m-tolyl-cyclohexyl)-methylamine hydrochloride

The title compound was prepared analogously as described in Example Y3, using 2-Naphthaleneboronic acid instead of 1-Naphthaleneboronic acid.

MS (ES+): 330 [M+H]+

HPLC (Macherey-Nagel LiChrospher 100-5 RP18 Flow 1.5mL/min, 12min method (0-1.5min 10%ACN, 1.5-6.5min 10-100%ACN, 6.5-9.0min 100%ACN, 9.0-12.0min 100-10%ACN): 5.38 min

Example AA: Activity Assay

Various Example compounds were tested for their inhibitory activity to human DPP-IV.

Materials

Human DPP-IV consisting of amino acids 39 to 766 followed by a C-terminal Streptavidin-tag was expressed using the baculovirus system and purified to >80% purity. The enzyme was stored in 25 mM Tris buffer, pH 9.0, containing 300 mM NaCl at -80°C.

The fluorogenic substrates H-Gly-Pro-AMC was purchased from Bachem AG (Bubendorf, Switzerland). The substrate was kept as a 5 mM stock solution in DMSO at -20°C. All other chemicals were purchased from Sigma (Buchs, Switzerland).

The assay buffer for the DPP-IV reaction was 25 mM Tris/HCl, pH 7.5, containing 140 mM NaCl, 10 mM KCl and 0.05% (w/v) CHAPS.

Compound and liquid handling

The test compounds were dissolved in 90% DMSO/10% H2O (v/v). Serial dilutions of the compounds from 3 mM to 0.03 μM in 90% DMSO/10% H2O (v/v) followed by a 1:33.3 dilution in assay buffer was done in 96-well polypropylene plates using a CyBio Dilus 8-channel pipettor (CyBio AG, Jena, Germany) with tip change after each pipetting step. The compound solutions as well as the substrate and the enzyme solutions were transferred to the assay plates (384-well black Cliniplate; cat. no. 95040020 Labsystems Oy, Finland) by means of a CyBi-Well 96-channel pipettor (CyBio AG, Jena, Germany).
Kinetic measurements

Enzyme kinetics were measured by mixing 10 µl of a 3-fold concentrated substrate solution in assay buffer (final substrate concentration was 10 µM) with 10 µl of the corresponding compound solution. The reactions were initiated by addition of 10 µl of a 3-fold concentrated solution of the enzyme in assay buffer. Final enzyme (active site) concentrations in the assay was 10 pM for DPP-IV. Fluorescence product (AMC) formation was monitored for 1 hour at room temperature at 35 second intervals by measuring the fluorescence emission at 500 nm using an excitation wavelength of 350 nm in a TECAN Ultra fluorescence reader (TECAN, Maennedorf, Switzerland). The fluorescence in each well was excited by one flash per measurement. The Origin software package (Origin 7.5 Mircocal, Northampton, MA, USA) was used to generate all graphs and to perform the IC50 calculations.

Results

The inhibitory activities (IC$_{50}$ values) of the compounds to human DPP-IV were found to be 50 µM or less and in many cases 10 µM or less. The activity data of selected compounds are shown in the table below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>0.4</td>
</tr>
<tr>
<td>D78</td>
<td></td>
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<tr>
<td>D81</td>
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<tr>
<td>Compound</td>
<td>Structure</td>
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<tr>
<td>WG1</td>
<td><img src="image" alt="WG1 structure" /></td>
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</table>
Claims

1. A compound of Formula (I):

wherein

one of V and W is selected from a bond, -(CH$_2$)$_n$-, -O-, -NH- and -N(R$_8$)-; and the other is selected from a bond, -(CH$_2$)$_n$- and -O-;

X is a bond or a linker having 1 to 5 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_n$-N(R$_8$)- and hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R$_{10}$; with the proviso that, when at least one of V and W is -O-, -NH- or -N(R$_8$)-, X is a bond;

Y is a bond; or Y and an R$_7$ moiety taken together with the atom(s) to which they are attached form a carbocycle or a heterocycle, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$_{10}$;

Z is a bond or a linker having 1 to 12 in-chain atoms and comprising one or more linkages selected from -O-, -C(O)-, -S(O)$_n$-N(R$_8$)-, hydrocarbylene optionally substituted with 1, 2, 3, 4 or 5 R$_{10}$, and heterocyclylene optionally substituted with 1, 2, 3, 4 or 5 R$_{10}$;

R$_3$ and R$_4$ are each independently hydrogen or R$_{10}$; or R$_3$ and R$_4$ taken together with the carbon atom to which they are attached form carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R$_{10}$;
R^6 is selected from hydrogen, except when X is a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{10}; and -(CH_2)_k-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{10};

R^6 is selected from hydrogen, except when Y and Z are each a bond; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{10}; and -(CH_2)_k-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{10};

R^7 is independently selected from R^{10};

or two R^7 moieties taken together may form a bridge between the atoms to which they are attached, wherein the bridge is a hydrocarbylene or -(CH_2)_i-O-(CH_2)_j- bridge, wherein i and j are each independently 0, 1 or 2;

R^8 is selected from R^9, -OR^9, -(O)R^9, -(C)OR^9 and -(S)O,R^9;

R^9 is selected from hydrogen; hydrocarbyl optionally substituted with 1, 2, 3, 4 or 5 R^{10}; and -(CH_2)_k-heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^{10};

each R^{10} is independently selected from halogen, trifluoromethyl, cyano, nitro, oxo, =NR^{11}, -OR^{11}, -(C)OR^{11}, -(OC)OR^{11}, -(S)O,R^{11}, -(N)R^{11}R^{12}, -(C)O,N(R^{11})R^{12}, -(S)O,N(R^{11})R^{12} and R^{13};

R^{11} and R^{12} are each independently hydrogen or R^{13};

R^{13} is selected from hydrocarbyl and -(CH_2)_k-heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halogen, cyano, amino, hydroxy, C_{1-6} alkyl and C_{1-6} alkoxy;

k is 0, 1, 2, 3, 4, 5 or 6;

l is 0, 1 or 2;

m is 0, 1, 2, 3, 4, 5 or 6; and
n is 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof;

for use in the treatment or prevention of a disease or condition selected from non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, calcitonin-osteoporosis, heart failure, impaired glucose metabolism or impaired glucose tolerance, neurodegenerative diseases, renal diseases, neurodegenerative or cognitive disorders, hyperglycemia, insulin resistance, lipid disorders, dyslipidemia, hypertriglyceridemia, hypercholesterolemia, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, retinopathy, nephropathy, neuropathy, syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), type 2 diabetes, growth hormone deficiency, neutropenia, neuronal disorders, tumor metastasis, benign prostatic hypertrophy, gingivitis, hypertension and osteoporosis; or for producing a sedative or anxiolytic effect, attenuating post-surgical catabolic changes or hormonal responses to stress, reducing mortality and morbidity after myocardial infarction.

2. A compound according to claim 1, wherein the compound is of the Formula (VII):

![Chemical Structure](image)

(VII)

or a pharmaceutically acceptable salt or prodrug thereof.

3. A compound according to any preceding claim, X is a bond, -CH₂- or -CH₂O--; and R⁵ is phenyl optionally substituted with 1, 2, 3, 4 or 5 R¹⁰.

4. A compound according to claim 3, wherein the compound is of the formula (XVIII):
wherein $p$ is 0, 1, 2, 3, 4 or 5; or a pharmaceutically acceptable salt or prodrug thereof.

5. A compound according to claim 4, wherein, when $p$ is 1, 2, 3, 4 or 5, at least one $R^{10}$ is halogen or $C_{1-6}$ alkyl.

6. A compound according to claim 5, wherein, when $p$ is 1, 2, 3, 4 or 5, at least one $R^{10}$ is halogen.

7. A compound according to claim 6, wherein, when $p$ is 1, 2, 3, 4 or 5, at least one $R^{10}$ is fluorine or chlorine.

8. A compound according to any preceding claim, wherein $R^3$ and $R^4$ are each hydrogen.

9. A compound according to claim 8, wherein the compound is of the formula (XXXVI):

or a pharmaceutically acceptable salt or prodrug thereof.
10. A compound according to claim 9, wherein, when \( p \) is 1, 2, 3, 4 or 5, at least one \( R^{10} \) is halogen or alkyl.

11. A compound according to claim 10, wherein, when \( p \) is 1, 2, 3, 4 or 5, at least one \( R^{10} \) is halogen.

12. A compound according to claim 11, wherein, when \( p \) is 1, 2, 3, 4 or 5, at least one \( R^{10} \) is fluorine or chlorine.

13. A compound according to any preceding claim, \( m \) is 0 or 1.

14. A compound according to any preceding claim, wherein \( Y \) is a bond.

15. A compound according to any of claims 1 to 13, wherein \( Y \) and an \( R^{7} \) moiety taken together with the atom(s) to which they are attached form a carbocycle or a heterocycle, either of which is optionally substituted with 1, 2, 3, 4 or 5 \( R^{10} \).

16. A compound according to claim 15, wherein \( Y \) and said \( R^{7} \) moiety are attached to adjacent ring carbon atoms.

17. A compound according to claim 16, wherein \( Y \) and said \( R^{7} \) moiety are attached to the same carbon atom.

18. A compound according to claim 1, wherein the compound is of the Formula (XXXVII):

![Chemical structure](image)

(XXXVII)

or a pharmaceutically acceptable salt or prodrug thereof.
19. A compound according to claim 18, wherein the compound is of the Formula (XXXVII):

\[
\begin{align*}
R^6 & \\
Z & \\
\text{H}_2\text{N} & \\
\text{X} & \\
\text{Ar} & \left(\text{R}^{10}\right)_p
\end{align*}
\]

(XXXVII)

wherein \( p \) is 0, 1, 2, 3, 4 or 5;

or a pharmaceutically acceptable salt or prodrug thereof.

20. A compound according to claim 19, wherein the compound is of the Formula (XXXIX):

\[
\begin{align*}
R^6 & \\
Z & \\
\text{H}_2\text{N} & \\
\text{X} & \\
\text{Ar} & \left(\text{R}^{10}\right)_p
\end{align*}
\]

(XXXIX)

or a pharmaceutically acceptable salt or prodrug thereof.

21. A compound according to any preceding claim, wherein \( Z \) is a bond or a linker comprising 1, 2, 3 or 4 linkages selected from \( -\text{O}, -\text{C}(-\text{O}), -\text{S}(-\text{O})_\text{R}, -\text{N}(\text{R}^8)_\text{R}, -\text{CH}_2, \) and \(-\text{CH}=-\text{CH}; \) and \( R^6 \) is hydrogen or is selected from \( \text{C}_{1-6} \) alkyl, cycloalkyl, aryl (e.g. phenyl) and heterocyclyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 \( \text{R}^{10} \).

22. A compound according to claim 21, wherein \( Z \) is selected from \( -\text{O}, -\text{O}(-\text{C}(-\text{O})_6 \text{alkylene}- \) and \(-\text{Q}-\text{C}_{1-6} \text{alkylene}- \).
23. A compound according to claim 21, wherein \(-Z-R^6\) is selected from \(R^1-\), \(-OR^1\), \(-C(O)R^1\), \(-C(O)OR^1\), \(-C(O)N(R^5)R^6\), \(-N(R^1)R^6\), \(-N(R^1)C(O)R^1\), \(-N(R^1)J(S(O))R^1\), \(-S(O)R^1\), \(-S(O)\) \(\{-1, 2, 3, 4, 5\} R^1\) and \(-S(O)\) \(\{-1, 2, 3, 4, 5\} R^1\); wherein \(R^1\) is hydrogen or is selected from hydrocarbyl or \(-(CH_2)\) \(k\) heterocyclyl, either of which is optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\); and wherein \(R^1\) and \(R^6\) are each independently selected from \(R^5\), \(-OR^5\), \(-C(O)R^5\), \(-C(O)OR^5\) and \(-S(O)\) \(R^9\); or \(R^1\) and \(R^6\) taken together with a nitrogen atom to which they are attached form heterocyclyl optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\).

24. A compound according to claim 23, wherein \(R^1\), \(R^5\) and \(R^6\) are each independently selected from hydrogen; \(C_i\) \(\{1, 2, 3, 4\}\) alkyl optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\); and \(-(CH_2)\) \(k\) aryl optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\).

25. A compound according to claim 24, wherein \(R^1\), \(R^5\) and \(R^6\) are each independently selected from hydrogen; \(C_i\), \(C_2\), \(C_3\) or \(C_4\) alkyl optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\); and phenyl or benzyl, either of which is optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\).

26. A compound according to any preceding claim, wherein \(Z\) comprises at least one moiety selected from \(-N(R^9)\), \(-C(O)\) and \(-S(O)\).

27. A compound according to any preceding claim, wherein \(Z\) is attached to the ring shown in formula (I) via a nitrogen atom.

28. A compound according to claim 27, wherein \(Z\) is attached to said ring via an \(-N(R^8)\)-moiety or via a nitrogen atom present in a heterocyclic moiety.

29. A compound according to claim 27, wherein \(Z\) is a linker selected from \(-N(R^8)\), \(-N(R^8)C(O)\), \(-N(R^8)\) \(\{-1, 2, 3, 4\}\) alkylene and \(-N(R^8)C(O)\) \(\{-1, 2, 3, 4\}\) alkylene, wherein \(-Z-R^6\) is attached to the remainder of the compound via the nitrogen atom of said linker and wherein any \(C_1\) \(\{-1, 2, 3, 4\}\) alkylene group is optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\).

30. A compound according to claim 29, wherein \(Z\) is \(-N(R^8)C(O)\).

31. A compound according to any of claims 1 to 20, wherein \(Z\) comprises at least one carbocyclyl or heterocyclyl moiety, either of which is optionally substituted with \(1, 2, 3, 4\) or \(5\) \(R^1\).
32. A compound according to claim 31, wherein Z-R^6 is a carbocyclylene or heterocyclylene moiety, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

33. A compound according to claim 31 or claim 32, wherein Z comprises a moiety selected from 2H-pyridazin-3-onylene, oxazolidin-2-onylene, imidazolidin-2-onylene, 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylene, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

34. A compound according to any of claims 1 to 20, wherein Z is a bond and R^6 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

35. A compound according to claim 34, wherein R^6 is heterocyclyl optionally substituted with 1, 2, 3, 4 or 5 R^10.

36. A compound according to claim 35, wherein R^6 is selected from 2H-pyridazin-3-onyl, oxazolidin-2-onyl, imidazolidin-2-onyl, 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinyl and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onyl, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

37. A compound according to any of claims 1 to 20, wherein Z is a linker selected from -N(R^6)-, -N(R^6)C(O)-, -N(R^6)-C_{1-6} alkylene- and -N(R^6)C(O)-C_{1-6} alkylene-, wherein -Z-R^6 is attached to the remainder of the compound via the nitrogen atom of said linker and wherein any C_{1-6} alkylene group is optionally substituted with 1, 2, 3, 4 or 5 R^10; and R^6 is carbocyclyl or heterocyclyl, either of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.

38. A compound according to any of claims 1 to 20, wherein Z and R^6 each independently comprise a carbocyclic or heterocyclic group, and are each optionally substituted with 1, 2, 3, 4 or 5 R^10.

39. A compound according to claim 38, wherein Z comprises a moiety selected from 2H-pyridazin-3-onylene, oxazolidin-2-onylene, imidazolidin-2-onylene, 5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazinylene and 6,7-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-8-onylene, any of which is optionally substituted with 1, 2, 3, 4 or 5 R^10.
40. A compound according to any preceding claim, wherein the disease or condition is Alzheimer's disease, Parkinson's disease, Crohn's disease or ulcerative colitis.

41. A compound according to claim 40, wherein the disease or condition is diabetic cardiomyopathy, left or right ventricular hypertrophy, hypertrophic medial thickening in arteries and/or in large vessels, mesenteric vasculature hypertrophy or mesangial hypertrophy.

42. A method of treating or preventing a disease or condition in a patient selected from non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, calcitonin-osteoporosis, heart failure, impaired glucose metabolism or impaired glucose tolerance, neurodegenerative diseases, renal diseases, neurodegenerative or cognitive disorders, hyperglycemia, insulin resistance, dyslipidemia, hypertriglyceridemia, hypercholesterolemia, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, retinopathy, nephropathy, neuropathy, syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), type 2 diabetes, growth hormone deficiency, neutropenia, neuronal disorders, tumor metastasis, benign prostatic hypertrophy, gingivitis, hypertension and osteoporosis; or for producing a sedative or anxiolytic effect, attenuating post-surgical catabolic changes or hormonal responses to stress, reducing mortality and morbidity after myocardial infarction, said method comprising administering a therapeutically effective amount of a compound as defined in any of claims 1 to 39.

43. A method according to claim 42, wherein the disease or condition is as defined in claim 40 or claim 41.

44. A pharmaceutical formulation comprising a compound as defined in any of claims 1 to 39 and a therapeutic agent selected from anti-diabetic agents, hypolipidemic agents, anti-obesity or appetite-regulating agents, anti-hypertensive agents, HDL-increasing agents, cholesterol absorption modulators, Apo-A1 analogues and mimetics, thrombin inhibitors, aldosterone inhibitors, inhibitors of platelet aggregation, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, chemotherapeutic agents, and 5-HT\textsubscript{3} or 5-HT\textsubscript{4} receptor modulators; or pharmaceutically acceptable salts or prodrugs thereof.
45. A formulation according to claim 44, wherein the agent is tegaserod, imatinib, vildagliptin, metformin, a thiazolidone derivative, a sulfonylurea receptor ligand, aliskiren, valsartan, orlistat or a statin, or pharmaceutically acceptable salts or prodrugs.

46. A product comprising a compound as defined in any of claims 1 to 39 and an agent as defined in claim 44; as a combined preparation for simultaneous, separate or sequential use in therapy.

47. A product according to claim 46, wherein the agent is as defined in claim 45.

48. A compound of formula (XVIII) or a pharmaceutically acceptable salt or prodrug thereof:

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{V} \\
\text{W} \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\text{R}^6 \\
\text{Y} \\
\text{Z} \\
\text{R}^7 \\
\text{(R}^7)_{\text{m}} \\
\text{R}^{10} \\
\text{(R}^{10})_{\text{p}}
\end{array}
\]

(XVIII)

wherein

\[V, W, Y, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{10}, \text{p}, \text{m}\]

are as defined in claim 1;

\[p \text{ is 0, 1, 2, 3, 4 or 5;}
\]

and when \(p\) is 1, 2, 3, 4 or 5, at least one \(R^{10}\) is halogen or \(C_{1-6}\) alkyl;

and wherein the compound is not one of the following compounds:
or a pharmaceutically acceptable salt or prodrug thereof.

49. A compound according to claim 48, which is as defined in any of claims 6 to 39.

50. A compound according to claim 48 or claim 49, wherein R³ and R⁴ are each hydrogen.
51. A compound according to any of claims 48 to 50, wherein, when \( p \) is 1, 2, 3, 4 or 5, at least one \( R^{10} \) is halogen.

52. A compound according to any of claims 48 to 51, wherein \( m \) is 0.

53. A compound according to any of claims 48 to 52, for use in therapy.

54. A pharmaceutical formulation comprising a compound of any of claims 48 to 52.

55. A formulation according to claim 54, which further comprises a pharmaceutically acceptable excipient or carrier.

56. A formulation according to claim 54 or claim 55, which further comprises a therapeutic agent selected from anti-diabetic agents, hypolipidemic agents, anti-obesity or appetite-regulating agents, anti-hypertensive agents, HDL-increasing agents, cholesterol absorption modulators, Apo-A1 analogues and mimetics, thrombin inhibitors, aldosterone inhibitors, inhibitors of platelet aggregation, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, chemotherapeutic agents, and 5-HT\(_3\) or 5-HT\(_4\) receptor modulators; or pharmaceutically acceptable salts or prodrugs thereof.

57. A formulation according to claim 56, wherein the agent is tegaserod, imatinib, vildagliptin, metformin, a thiazolidone derivative, a sulfonyleurea receptor ligand, aliskiren, valsartan, orlistat or a statin, or pharmaceutically acceptable salts or prodrugs.

58. A product comprising a compound of any of claims 48 to 52 and an agent as defined in claim 61; as a combined preparation for simultaneous, separate or sequential use in therapy.

59. A product according to claim 58, wherein the agent is as defined in claim 57.

60. A compound of any of claims 48 to 52 for use in the treatment or prevention of a disease or condition selected from non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, calcitonin-osteoporosis, heart failure, impaired glucose metabolism or impaired glucose tolerance, neurodegenerative diseases, cardiovascular or renal diseases, and neurodegenerative or cognitive disorders, hyperglycemia, insulin resistance,
lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, retinopathy, nephropathy, neuropathy, syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), type 2 diabetes, growth hormone deficiency, neutropenia, neuronal disorders, tumor metastasis, benign prostatic hypertrophy, gingivitis, hypertension and osteoporosis; or for producing a sedative or anxiolytic effect, attenuating post-surgical catabolic changes or hormonal responses to stress, reducing mortality and morbidity after myocardial infarction, modulating hyperlipidemia or associated conditions, or lowering VLDL, LDL or Lp(a) levels.

61. Use of a compound of formula (I) as defined in any of claims 1 to 39 or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the treatment or prevention of a disease or condition as defined in claim 1.

62. Use of a compound of any of claims 48 to 52 or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the treatment or prevention of a disease or condition as defined in claim 60.
**INTERNATIONAL SEARCH REPORT**

**Form PCT/ISA/210 (second sheet) (April 2005)**

**A. CLASSIFICATION OF SUBJECT MATTER**


According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
A61K - C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, EMBASE, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>Y</td>
<td>RUMMEY ET AL: &quot;In silico fragment-based discovery of DPP-IV S1 pocket binders&quot;</td>
<td>1-62</td>
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<tr>
<td></td>
<td>BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 16, no. 5, 1 March 2006 (2006-03-01), pages 1405-1409, XP005263963</td>
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<td></td>
<td>ISSN: 0960-894X compound 4</td>
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</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search: 30 April 2008

Date of mailing of the international search report: 23/05/2008

Name and mailing address of the ISA/Authorized officer:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>Y</td>
<td>WO 2005/121089 A (SANThERa PHARmaCEUTICALS DEUTS [DE]; EDWARDS PAUL JOHN [DE]; ROSENBAUM) 22 December 2005 (2005-12-22) claim 1</td>
<td>1-62</td>
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<tr>
<td>Category</td>
<td>Citation of document with indication where appropriate of the relevant passages</td>
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<tr>
<td>X</td>
<td>BE 616 646 A (PERCK AG) 16 August 1982 (1382-08-16) examples S. 10</td>
<td>46-55</td>
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<tr>
<td>X</td>
<td>ELLIOTT JASON M ET AL: &quot;4, 4-di substituted cyclohexyl amine NK1 receptor antagonists I&quot; BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 12, no. 13, 8 July 2002 (2002-07-08) pages 1755-1758, XP002478907 ISSN: 0960-894X scheme 4, page 1756</td>
<td>48-52</td>
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<td>Category</td>
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<td>Relevant to claim No</td>
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<td>WO 01/87866 A (MERCK SHARP &amp; DOHME [GB]; CASTRO PINEIRO JOSE LUIS [GB]; DINNELL KEVIN) 22 November 2001 (2001-11-22) page 37</td>
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