Title: HETEROCYCLIC PHENYL CARBAMATES AS NOVEL FAAH-INHIBITORS

(57) Abstract: Fatty acid amide hydrolase inhibitors of the Formula (I) are provided, wherein R is a heterocyclic or heterocyclic carbonyl moiety and R' is a group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Pharmaceutical compositions and methods comprising compounds of Formula (I) may be used for the treatment of disease states, disorders, and conditions mediated by fatty acid amide hydrolase (FAAH) activity. Thus, the compounds may be administered to treat, anxiety, epilepsy, depression, pain, inflammation, appetite disorders, glaucoma and insomnia.
Heterocyclic phenyl carbamates as novel FAAH-inhibitors

Field of the invention

The present invention relates to inhibitors of fatty acid amide hydrolase and/or monoglyceride lipase. More particularly, the invention relates to inhibitors of fatty acid amide hydrolase employing a heterocyclic phenyl carbamate pharmacophore.

Background

Fatty acid amide hydrolase (FAAH) is an intracellular serine hydrolase, which catalyzes the hydrolysis of endocannabinoid N-arachidonoyl-ethanolamide (AEA) to arachidonic acid and ethanolamine. FAAH is also able to hydrolyze another endocannabinoid, 2-arachidonoylglycerol (2-AG), and a sleep-inducing endogenous lipid, oleamide. However, the enzymatic hydrolysis of 2-AG has been assumed to occur in vivo by monoglyceride lipase (MGL). Inhibition of FAAH or MGL prevents degradation of endocannabinoids (AEA, 2-AG and oleamide) which activate the cannabinoid receptors and therefore causes beneficial effects in many physiological disorders such as pain, inflammation, anxiety, epilepsy, depression, appetite disorders, glaucoma and insomnia.

Introduction

Arachidonoylethanolamide and 2-arachidonoylglycerol are endogenous compounds called endocannabinoids and they are considered to be the most important endogenous agonists for the G protein-coupled cannabinoid receptors, CB1 and CB2. (Lambert J. Med. Chem. 2005, 48, 5059-5087). CB1 receptors are predominantly located on presynaptic terminals in the central nervous system (CNS), whereas CB2 receptors are located mainly
in peripheral tissues (Facci, Proc. Natl. Acad. Sci. USA 1995, 92, 3376-3380; Galiegue, Eur. J. Biochem. 1995, 232, 54-61; Ishac, Br. J. Pharmacol. 1996, 118, 2023-2028). However, very recently it has been reported that CB2 receptors are also expressed in CNS (Gong, Brain Res. 2006, 1071, 10-23). The endocannabinoids are inactivated rapidly by cellular re-uptake followed by the intracellular hydrolysis by specific enzymes (Goparaju, Biochem. Pharmacol. 1999, 57, 417-423; Schmid, J. Biol. Chem. 1985, 260, 14145-14149). AEA is assumed to be transported into a cell by a specific transporter and rapidly hydrolyzed by the enzyme fatty acid amide hydrolase (FAAH) (Fowler, Leukotrienes Essent. Fatty Acids, 2002, 66, 193-200). Also, like AEA, 2-AG is thought to be removed from its sites of action by cellular uptake and then hydrolyzed enzymatically. Although 2-AG can be hydrolyzed by FAAH (Ueda, Chem. Phys. Lipids 2000, 108, 107-121), the main enzyme responsible for 2-AG hydrolysis in vivo is probably monoacyl glycerol lipase (MGL; EC 3.1.1.23) or MGL-like enzyme (Dinh, Proc. Natl. Acad. Sci. USA 2002, 99, 10819-10824; Saario, Biochem. Pharmacol. 2004, 67, 1381-1387).


The enzyme inhibition could be a convenient way to elevate endocannabinoid levels and thus increase the receptor activity (Cravatt, Curr. Opin.
Endocannabinoids are biosynthesized upon demand and removed from their sites of action by cellular uptake and intracellular enzymatic hydrolysis. By inhibiting FAAH or MGL, it is possible to potentiate the actions of endocannabinoids at their site of biosynthesis.


Additionally, the series of carbamates including highly active compound URB597 with promising pharmacological features have been developed (WO 2004/033422, WO 2005/090322, WO2005/089759, WO 2005/090347, WO 2005/090292, WO 2005/077898, WO 2006/088075, WO 2007/0791 80, WO 2008/024139). Certain oxazolyl piperidines (WO 2007/140005), piperazinyl and piperidinyl ureas (WO 2007/005510, WO 2006/074025) have been also reported as inhibitors of FAAH. Further, Saario et al (J. Med. Chem. 2006, 49, 4650-4656) have performed virtual screening of MGL inhibitors and found five compounds inhibiting FAAH. The most potent FAAH inhibitor found by Saario and co-workers was a 4-substituted dihydrothiazolylphenyl N-butyl carbamate which, however, had an IC_{50} value of only 0.52 µM. Consequently, there still exists a need for potential effective inhibitors of the fatty acid amide hydrolase enzyme.

**Summary of the invention**

The invention relates to novel heterocyclic phenyl carbamates and heterocyclic carbonyl phenyl carbamates represented by the formula I:
wherein \( Z \) is CH or N.

\( R' \) is selected from the group consisting of H, substituted or unsubstituted alkyl of 1 to 24 carbon atoms, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, and

\( R \) is a cyano, carboxyl, (C1-4 alkoxy)carbonyl, mono-C1-4 aliphatic amino-carbonyl, di-C1-4 aliphatic aminocarbonyl, N-hydroxycarbamimidoyl, N-alkoxycarbamimidoyl, acyloxy carbamimidoyl, a heterocyclic moiety or heterocyclic carbonyl moiety. The novel compounds of formula I are useful as inhibitors of fatty acid amide hydrolase and/or monoglyceride lipase.

The heterocyclic moiety \( R \) in the novel compounds of formula I is represented by the following structures:
wherein X is O, S, NH or NCH₃,
and
R₁, R₂, R₃, R₄ are individually H, halogen, alkyl, cycloalkyl, alkenyl, alkythio, hydroxyalkyl, carboxy, alkoxy, alkoxycarbonyl, acyloxy, acylamino, acyloxyalkyl, acylaminoalkyl, hydroxyacyl, sulphonate, alkylsulphonyl, arylsulphonyl, nitro, cyano, amino, -NR₅R₆, aminomethyl, -(CH₂)ₙ-NR₅R₆, aminoacyl, -CO-(CH₂)ₙ-NR₅R₆, carbamoyl, -CO-NR₅R₆, carbamoyloxy, -O-CO-NR₅R₆, sulphonamide -SO₂NR₅R₆, wherein n represents an integer from 1 to 4 and wherein R₅ and R₆ are selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyalkyl and wherein optionally R₅ and R₆ together with the N atom to which they are attached form a 5-7 membered cyclic ring.

The invention also relates to pharmaceutical compositions which contain a compound of the formula I, and to the use of the compounds of the formula I for the therapeutic treatment of a human or animal body or for the preparation of pharmaceutical compositions.

A further object of the invention is a method of inhibiting fatty acid amid hydrolase and/or monoglyceride lipase in a mammal, said method comprising administering an effective amount of a compound of the formula I to a subject in need of inhibition of FAAH or MGL.

A still further object of the invention is a method of treating pain, inflammation, anxiety, epilepsy, depression, appetite disorders, glaucoma, insomnia or other disease states, disorders and conditions mediated by fatty acid amide hydrolase activity in a mammal, said method comprising administering an effective amount of a compound of the formula I to a subject in need of such treatment.
Detailed Description of the Invention

In the context of the present application, the general terms used above and below preferably have the following meanings:

Alkyl is a saturated hydrocarbon radical containing 1-24, preferably 3-12 carbon atoms. It is for example ethyl, methyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, decyl, dodecyl, tetradecyl, hexadecyl, octadecyl, octenyl, octadecenyl, etc preferably propyl, butyl, pentyl, hexyl, octyl, decyl or dodecyl. Substituted alkyl is preferably chloroalkyl or fluoroalkyl.

In the meaning of the group R1, R2, R3 and R4 alkyl preferably contains 1-6 carbon atoms, preferably 1-4 carbon atoms. It is for example ethyl, methyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl.

Cycloalkyl contains 3-8, preferably 5 or 6 atoms. It is for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopentyl or cyclohexyl.

Heteroalkyl means a straight or branched chain hydrocarbon radical, containing 1-22, preferably 3-12 carbon atoms and at least one heteroatom selected from the group consisting of O, N and S. Examples of heteroalkyl include, but are not limited to hydroxyalkyl (e.g., 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl), alkoxyalkyl (e.g., methoxyalkyl, ethoxyalkyl, propoxyalkyl, butoxyalkyl, pentoxyalkyl), acyloxyalkyl (e.g., acetoxyalkyl, propionyloxyalkyl, benzoxyloxyalkyl), mercaptoalkyl, alkylthioalkyl, acythioalkyl, aminoalkyl (e.g., amino, mono- and di-d-C3 alkanylaminoalkyl).
Aryl means a polyunsaturated, aromatic hydrocarbon substituent. Heteroaryl refers to aryl groups that contain from one to four heteroatoms selected from N, O and S. Non-limiting examples of aryl and heteroaryl include phenyl, benzyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, furyl, thienyl, pyridyl or pyrimidyl. Preferred aryls are substituted or unsubstituted phenyl or benzyl, especially substituted benzyl.

When the group $R'$ is a substituted group as defined, especially a substituted cycloalkyl, aryl or heteroaryl group, suitable substituents include those defined for $R_1, R_2, R_3$ and $R_4$, in particular alkyl, alkoxy, halogen, alkylthio, hydroxy, hydroxyalkyl, carboxy, alkoxycarbonyl, acyloxy, acylamino, aminoalkyl, aminoacyl, carbamoyl, carbamoyloxy or sulfonamide.

Preferred substituents of a substituted benzyl are e.g. 2-methyl and 3-methyl.

If heteroaryl is substituted, preferred substituents are e.g. methyl, ethyl, and acetyl.

Halogen is chlorine, bromine, fluorine or iodine.

In this description alkenylene contains 2-24, preferably 2-8 carbon atoms. It is for example ethylene, methylene, thmethylene, tetramethylene or pentamethylene.

In this description alkoxy contains 1-6, preferably 1-2 carbon atoms. It is for example methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy or ethyloxy, preferably methoxy.
In this description acyl contains 1-6, preferably 1-2 carbon atoms. It is, for example, formyl, acetyl, propionyl or pivaloyl.

In this description alkyne preferably contains 2-6 carbon atoms. It is for example acetylene, propyne or 1- or 2-butyne.

If R5 and R6 together with the N atom to which they are attached form a 5-7 membered cyclic ring, said ring is for example, but not limited to, pyrrolidinyl, piperidyl, or morpholinyl.

The compounds of the invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the inventive compounds.

The compounds of the invention include the diastereoisomers of pairs of enantiomers. Diastereomers, for example, can be obtained by fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of such a compound of the invention may be obtained by stereosepecific synthesis using optically pure starting materials of known configuration.

In the compounds of formula I, the substituent R' is preferably H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl. More preferably R' is substituted or unsubstituted alkyl (preferably an unsubstiti-
tuted alkyl of 5 to 12 carbon atoms), cycloalkyl (preferably cyclopentyl or cyclohexyl), or substituted or unsubstituted benzyl. Preferred substituents are e.g. H and methyl.

In one embodiment, R' is selected from the group consisting of unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted aryl or unsubstituted heteroaryl.

The substituent Z is preferably CH.

The substituent R is preferably selected from the group consisting of cyano, carboxyl, \((C1-4\text{-alkoxy})\text{carbonyl}\), N-hydroxycarbamimidoyl, N-alkoxycarbamimidoyl, acyloxy carbamimidoyl, a heterocyclic moiety or heterocyclic carbonyl moiety, wherein the heterocyclic moiety is selected from the group represented by the following structures:

![Chemical Structures](image)

wherein X is O, S, NH or NCH₃, and
R1, R2, R3, R4 are individually H, halogen, alkyl, cycloalkyl, alkylene, acyl, aroyl, aryl, phenoxy, alkoxy, alkoxyalkyl, alkythio, hydroxy, hydroxyalkyl, carboxy, alkoxyacarbonyl, acyloxy, acylamino, acyloxyalkyl, acylaminoalkyl, hydroxyacyl, sulfonate, alkylsulfonyl, arylsulfonyl, nitro, cyano, amino - NR5R6, aminoalkyl -(CH₂)ₙ-NR5R6, aminoacyl - CO-(CH₂)ₙ-NR5R6, carbamoyl - CO-NR5R6, carbamoyloxy - O-CO-NR5R6, sulfonamido - SO₂NR5R6, wherein n represents an integer from 1 to 4 and wherein R5 and R6 are selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyalkyl and wherein optionally R5 and R6 together with the N atom to which they are attached form a 5-7 membered cyclic ring.

Even more preferably the substituent R is selected from the group consisting of

![Chemical structures](image)

wherein

R1, R2, R3 and R4 are independently of each other hydrogen, alkyl, aryl, acyl, alkoxyacarbonyl, aminoacyl, or dialkylaminoacyl.

Most preferably, R1, R2, R3 and R4 are independently of each other hydrogen, alkyl (especially methyl), acetyl or ethoxycarbonyl.

The substituent R is even more preferably methoxycarbonyl, oxazolyl, tetrazolyl, thiadiazolyl, benoxazole-carbonyl or benzothiazolecarbonyl.

The invention relates particularly to the compounds of the formula I.
wherein \( Z \) is CH or N, preferably CH,

\( R' \) is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted benzyl, and

\( R \) is selected from the group consisting of the following structures:

wherein

\( R_1, R_2, R_3 \) and \( R_4 \) are individually hydrogen, alkyl, aryl, acyl, alkoxy carbonyl, aminoacyl, or dialkylaminoacyl, preferably hydrogen, alkyl, acyl, acetyl or ethoxycarbonyl.

In a further, preferred embodiment the invention relates to the compounds of the following formula

wherein \( Z \) is CH or N, preferably CH,

\( R' \) is substituted or unsubstituted alkyl (preferably an unsubstituted alkyl of 5 to 12 carbon atoms), cycloalkyl (preferably cyclopentyl or cyclohexyl), or substituted or unsubstituted benzyl,

\( R \) is methoxycarbonyl, oxazolyl, tetrazolyl, thiadiazolyl, benzoxazole carbonyl or benzothiazole carbonyl.
The instant compounds may be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Such acids may include hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function can be in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be derivatives of the present compounds that are readily convertible in vivo into a functional compound of the invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. The invention also encompasses active metabolites of the present compounds.

The invention also relates to pharmaceutical compositions which contain a compound of formula I or a pharmaceutically acceptable salt thereof as active ingredient. The pharmaceutical compositions usually contain the pharmacologically active ingredient together with customary pharmaceutical excipients and optionally with other therapeutical ingredients.

The pharmaceutical compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, subdermal, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inha-
lation), or nasal administration. In some embodiments, administration is transdermal. The most suitable route in any given case will depend in part on the nature and severity of the conditions being treated and on the nature of the active ingredient. An exemplary route of administration is the oral route. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of the invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations can contain at least 0.1 percent of the active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such
therapeutically useful compositions is such that a therapeutically effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor. To prevent breakdown during transit through the upper portion of the GI tract, the composition may be an enteric coated formulation.

Although the preferred route of administration is the oral route, the compounds of the invention may also be administered for example parenterally. Solutions or suspensions of the active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous
preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The dose of the active ingredient can depend on various factors, such as the efficacy of the active ingredient, severity of the disease to be treated or its symptoms, administration procedure, sex, age, weight and/or individual condition of the subject in need of the treatment. In a normal case, for a human adult, one daily dose of about 1 mg to about 500 mg, in particular from about 5 mg to about 200 mg, or from about 1 to 100 mg is to be estimated. Doses of from about 0.05 to about 100 mg, and more preferably from about 0.1 to about 100 mg, per day may be used. This can be administered as a single dose or in several sub-doses.

Generally, the compounds of the present invention can be dispensed in unit dosage form comprising preferably from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage. Usually dosage forms suitable for oral, nasal, pulmonary or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds admixed with a pharmaceutically acceptable carrier or diluent. For storage and use, these preparations preferably contain a preservative to prevent the growth of microorganisms.

Formulations suitable for oral administration can consist of (i) liquid solutions, such as an effective amount of the active ingredient suspended in
diluents, such as water, saline or PEG 400; (ii) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (iii) suspensions in an appropriate liquid; and (iv) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents; and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g. sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like, containing, in addition to the active ingredient, carriers known in the art.

Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described. Formulations suitable for parenteral administration, such as, for example, by intraarticular, intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

With respect to transdermal routes of administration, methods for transdermal administration of drugs are disclosed in Remington's Pharmaceutical Sciences, Gennaro A R ed. 20 th edition, 2000, USA. Dermal or skin patches are one means for transdermal delivery of the compounds of the invention.
Preferred patches include those that control the rate of drug delivery to the skin. Patches may provide a variety of dosing systems including a reservoir system or a monolithic system, respectively. The reservoir design may, for example, have four layers: the adhesive layer that directly contacts the skin, the control membrane, which controls the diffusion of drug molecules, the reservoir of drug molecules, and a water-resistant backing. Such a design delivers uniform amounts of the drug over a specified time period, the rate of delivery has to be less than the saturation limit of different types of skin.

The monolithic design, for example, typically has only three layers: the adhesive layer, a polymer matrix containing the compound, and a water-proof backing. This design brings a saturating amount of drug to the skin. Thereby, delivery is controlled by the skin. As the drug amount decreases in the patch to below the saturating level, the delivery rate falls.

Compounds of the invention may be used in combination with other compounds of the invention or with other drugs that may also be useful in the treatment, prevention or suppression of a neurological or psychological disorder. In one embodiment, the second drug is not a FAAH inhibitor and is directed toward the same disorder as the fatty acid amide inhibitor. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound is preferred. When used in combination with one or more other active ingredients, the compound of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain
one or more other active ingredients, in addition to the compounds disclosed above. For example, a FAAH inhibitor according to formula I may be formulated with an anxiolytic agent which is not a FAAH inhibitor. For example, a FAAH inhibitor according to formula I may be formulated with an antidepressant. Further, a FAAH inhibitor according to formula I may be used in a combination with an analgetic drug/compound. A further embodiment is to formulate a FAAH inhibitor according to formula I with an immunosuppressant drug/compound.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle, by itself or in association with another active principle, can be administered to animals and humans in unit forms of administration mixed with conventional pharmaceutical carriers. The appropriate unit forms of administration include oral forms such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, sublingual and buccal forms of administration, aerosols, implants, subcutaneous, intramuscular, intravenous, intranasal or intraocular forms of administration and rectal forms of administration.

When used to treat e.g. glaucoma, direct application to the eye is preferred. Ocular carrier formulations for such ocular application are taught in Remington’s Pharmaceutical Sciences, ed. Gennaro A.R., 20th edition, 2000.

The invention also provides a method of inhibiting fatty acid amid hydrolase in a mammal, said method comprising administering an effective amount of a compound of the formula I to a subject in need of inhibition of FAAH.
The invention also provides a method for inhibiting monoglyceride lipase in a mammal, said method comprising administering an effective amount of a compound of the formula I to a subject in need of inhibition of MGL.

A still further object of the invention is a method of treating, preventing or ameliorating pain, inflammation, anxiety, epilepsy, depression, appetite disorders, glaucoma, insomnia or other disease states, disorders and conditions mediated by fatty acid amide hydrolase activity in a mammal, said method comprising administering an effective amount of a compound of the formula I to a subject in need of such treatment.

The invention further relates to the use of compounds of the formula I for the preparation of medicaments for the treatment, prevention or amelioration of disease states, disorders, and conditions mediated by fatty acid amide hydrolase activity and/or monoglyceride lipase activity of a human or animal body. Among such disease states, disorders and conditions may be mentioned for example anxiety, epilepsy, depression, pain, inflammation, appetite disorders, glaucoma and insomnia. More specifically, among such diseases, disorders or conditions may be mentioned pain, nociceptive pain, neuropathic pain, inflammatory pain, non-inflammatory pain, painful hemorrhagic cystitis, pain associated with the herpes virus, pain associated with diabetes, peripheral neuropathic pain, central pain, deafferentiation pain, chronic nociceptive pain, stimulus of nociceptive receptors, phantom and transient acute pain, diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, neuralgia, pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions, Parkinson's disease, muscle spasticity, epilepsy, obesity, hyperlipidemia, insulin resistance syndrome, fatty liver disease, atherosclerosis, arteriosclerosis, metabolic disorders, feeding and fasting, alteration of appetite, hypertension, septic shock, cardiogenic shock, intestinal inflammation and motility, irritable bowel syndrome, colitis,
diarrhea, ileitis, ischemia, cerebral ischemia, hepatic ischemia, myocardial infarction, arthritis, rheumatoid arthritis, spondylitis, shoulder tendonitis or bursitis, gouty arthritis, aolymyalgia rheumratica, thyroiditis, hepatitis, inflammatory bowel diseases, asthma, multiple sclerosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and cardiovascular diseases.

Preferred examples of compounds of the present invention are selected from the group consisting of:

<table>
<thead>
<tr>
<th>Example</th>
<th>Compound</th>
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<tbody>
<tr>
<td>1</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl ethylcarbamate (1e)</td>
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<tr>
<td>2</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl propylcarbamate (2)</td>
</tr>
<tr>
<td>3</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl butylcarbamate (3)</td>
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<tr>
<td>4</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl cyclopentylcarbamate (4)</td>
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<tr>
<td>5</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl cyclohexylcarbamate (5)</td>
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<td>6</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl benzylcarbamate (6)</td>
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<td>7</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)-phenyl 4-methoxy-benzylcarbamate (7)</td>
</tr>
<tr>
<td>8</td>
<td>3-(Benzo[d]oxazole-2-carbonyl)phenyl 3-methyl-benzylcarbamate (8)</td>
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<td>9</td>
<td>3-(Benzo[d]othiazole-2-carbonyl)-phenyl ethylcarbamate (9c)</td>
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<td>3-(Benzo[d]thiazole-2-carbonyl)-phenyl propylcarbamate (10)</td>
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<td>3-(Benzo[d]thiazole-2-carbonyl)-phenyl butylcarbamate (11)</td>
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<td>3-(Benzo[d]thiazole-2-carbonyl)-phenyl cyclopentylcarbamate (12)</td>
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<td>3-(Benzo[d]thiazole-2-carbonyl)-phenyl cyclohexylcarbamate (13)</td>
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<td>3-(Benzo[d]thiazole-2-carbonyl)-phenyl benzyl carbamate (14)</td>
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<td>3-(Benzo[d]thiazole-2-carbonyl)-phenyl 3-methyl-benzylcarbamate (16)</td>
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<td>17</td>
<td>3-(4,5-Dihydrooxazol-2-yl)phenyl n-propylcarbamate (17b)</td>
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<td>18</td>
<td>3-(4,5-Dihydrooxazol-2-yl)phenyl cyclopentylcarbamate (18)</td>
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<td>19</td>
<td>3-(Oxazol-2-yl)phenyl cyclopentylcarbamate (19c)</td>
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<td>20</td>
<td>3-(Oxazol-2-yl)phenyl cyclohexylcarbamate (20)</td>
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<td>21</td>
<td>3-(Oxazol-2-yl)phenyl 2-methyl-benzylcarbamate (21)</td>
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<td>22</td>
<td>3-(Oxazol-2-yl)phenyl phenethylcarbamate (22)</td>
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<tr>
<td>23</td>
<td>Cyclopentyl-carbamic acid 3-(2H-tetrazol-5-yl)-phenyl ester (23)</td>
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<tr>
<td>24</td>
<td>3-(2-Methyl-2H-tetrazol-5-yl)phenyl cyclopentylcarbamate (24)</td>
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<td>3-(2-Benzyl-2H-tetrazol-5-yl)phenyl cyclopentylcarbamate (25)</td>
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<td>26</td>
<td>Methyl 3-((cyclopentylcarbamoyloxy)benzoate (26)</td>
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<td>27</td>
<td>Methyl 3-((cyclohexylcarbamoyloxy)benzoate (27)</td>
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<td>3-Cyanophenyl cyclohexylcarbamate (28)</td>
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<td>3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl cyclopentylcarbamate (29)</td>
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<td>(S)-3-(4-methyl-4,5-dihydrooxazol-2-yl)phenyl cyclopentylcarbamate (30)</td>
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<td>31</td>
<td>(S)-3-(4-methyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (31)</td>
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<td>32</td>
<td>(R)-3-(4-methyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (32)</td>
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<td>33</td>
<td>(S)-3-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (33)</td>
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<td>34</td>
<td>(R)-3-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (34)</td>
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<td>35</td>
<td>(S)-3-(4-(((1H-Indol-3-yl)methyl)-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (35)</td>
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<tr>
<td>36</td>
<td>3-(1,2,3-Thiadiazol-4-yl)phenyl cyclohexylcarbamate (36c)</td>
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<td>37</td>
<td>3-(1,2,3-Thiadiazol-4-yl)phenyl cyclopentylcarbamate (37)</td>
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<td>38</td>
<td>3-(1,2,3-Thiadiazol-4-yl)phenyl butylcarbamate (38)</td>
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<td>3-(1,2,3-Thiadiazol-4-yl)phenyl benzylcarbamate (39)</td>
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<td>3-(1,2,3-Thiadiazol-4-yl)phenyl phenylcarbamate (40)</td>
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<td>3-(1,2,3-Thiadiazol-4-yl)phenyl isopropylcarbamate (41)</td>
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<td>42</td>
<td>3-(1,2,3-Thiadiazol-4-yl)phenyl dodecylcarbamate (42)</td>
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<tr>
<td>43</td>
<td>3-(1,2,3-Thiadiazol-4-yl)phenyl hexylcarbamate (43)</td>
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</table>
More preferred compounds of the invention are selected from the group consisting of:

<table>
<thead>
<tr>
<th></th>
<th>Formula</th>
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<tr>
<td>44</td>
<td>3-(1,2,3-Thiadiazol-4-yl)phenyl (4-phenyl-butyl)carbamate <strong>(44)</strong></td>
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<tr>
<td>45</td>
<td>3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl cyclohexylcarbamate <strong>(45f)</strong></td>
</tr>
<tr>
<td>46</td>
<td>3-(5-(2-Cyclopentyl-ethyl)-1,2,4-oxadiazol-3-yl)phenyl cyclohexylcarbamate <strong>(46d)</strong></td>
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<tr>
<td>47</td>
<td>3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)phenyl cyclohexylcarbamate <strong>(47d)</strong></td>
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<tr>
<td>48</td>
<td>3-(3-Cyclohexylcarbamoyloxy-phenyl)-1,2,4-oxadiazole-5-carboxylic ethyl ester <strong>(48c)</strong></td>
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<tr>
<td>49</td>
<td>3-Carbamoylphenyl cyclohexylcarbamate <strong>(49b)</strong></td>
</tr>
<tr>
<td>50</td>
<td>3-(Oxazol-4-yl)phenyl cyclohexylcarbamate <strong>(50c)</strong></td>
</tr>
<tr>
<td>51</td>
<td>3-(Thiazol-2-yl)phenyl cyclohexylcarbamate <strong>(51c)</strong></td>
</tr>
<tr>
<td>52</td>
<td>3-(1-(Cyclohexylcarbamoyl)-1H-imidazol-4-yl)phenyl cyclohexylcarbamate <strong>(52c)</strong></td>
</tr>
<tr>
<td>53</td>
<td>(S)-Methyl 2-(3-(cyclohexylcarbamoyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate <strong>(53c)</strong></td>
</tr>
<tr>
<td>54</td>
<td>(R)-Methyl 2-(3-(cyclohexylcarbamoyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate <strong>(54b)</strong></td>
</tr>
<tr>
<td>55</td>
<td>Dimethyl 4-(cyclohexylcarbamoyloxy)phthalate <strong>(55)</strong></td>
</tr>
<tr>
<td>56</td>
<td>3-(N-hydroxycarbamimidoyl)phenyl cyclohexylcarbamate <strong>(56)</strong></td>
</tr>
<tr>
<td>57</td>
<td>2-Cyclohexylcarbamoyloxy-isonicotinic acid methyl ester <strong>(57b)</strong></td>
</tr>
</tbody>
</table>

3-(Oxazol-2-yl)phenyl cyclohexylcarbamate;
3-(Oxazol-2-yl)phenyl cyclopentylcarbamate;
3-(2-Methyl-2H-tetrazol-5-yl)phenyl cyclopentylcarbamate;
Methyl 3-(cyclohexylcarbamoyloxy)benzoate;
3-(1,2,3-Thiadiazol-4-yl)phenyl cyclohexylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl cyclopentylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl benzylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl dodecylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl hexylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl (4-phenyl-butyl)carbamate; and
3-(Thiazol-2-yl)phenyl cyclohexylcarbamate.
The compounds of the formula I can be prepared as described below, using commercially available starting materials and following the methods described in the literature.

**Synthesis**

The carbamic acid esters (1e, 2-8, 9c, 10-16, 17b, 18, 19c, 20-22, 23, 26-35, 36c, 37-44, 45f, 46d, 47d, 48c, 49-54, 56, 57b) were obtained by treatment of heterocyclic phenol (examples 1d, 9b, 17a, 19b, 36b, 45e, 46c, 47c, 48b, 49a, 50b, 51b, 52b, 53b, 54a, 55, 57a) and commercial substances) with a suitable isocyanate in the presence of a catalytic amount of triethylamine in toluene at rt or heating up to 93°C (Scheme 1).

![Scheme 1](image)

The synthesis of carbamate derivatives of 2-benoxazolyl- and 2-benzothiazolyl-(3-hydroxyphenyl)-methanones (examples 1e, 2-8, 9c, 10-16) were started from 3-hydroxybenzoic acid (Scheme 2). The phenol functionality was protected as benzyl ether and then the acids were converted to acid chlorides. The acid chlorides were then coupled with benoxazole following the method described by Harn et al. (*Tetrahedron Lett.* 1995, 36; 9453-9456). The benzothiazole was coupled with 3-benzyloxybenzoic acid chloride in a similar way. Deprotection of phenolic hydroxyl was first attempted with hydrogenation catalyzed by Pd/C. Unfortunately in these conditions the methanone was reduced to alcohol before the cleavage of ben-
zyl group. Although the alcohols were easily oxidized back to ketone with IBX or DDQ, another method was needed to avoid the extra step. Finally the removal of the benzyl protecting group without reducing the ketone was carried out using BF$_4$Et$_2$O and Me$_2$S (Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* 1980, *28*, 3662-3664). Later an even more efficient method for removal of the benzyl protecting group utilizing ionic liquid (Λ-1-butyldipyridinium bromide) and microwave irradiation was used (Chauhan, S.M.S.; Jain N. *J. Chem. Res.* 2004, 693-4). The aromatic alcohols were then coupled with isocyanates in a usual way (Scheme 1).

Scheme 2

![Scheme 2](image)

Scheme 2. Reagents and conditions for the preparation of compounds 1d and 9b: a) NaOH, BnBr, THF, reflux, 65%; b) SOCl$_2$, reflux, 98%; c) benzo[c]oxazole (X=O) or benzo[c]thiazole (X=S), n-BuLi, 1M ZnCl$_2$/Et$_2$O, Cul, THF, -75°C -> 0°C, 54-55%; d) BF$_3$Et$_2$O, Me$_2$S, CH$_2$Cl$_2$, rt, 84-91 % or 1/ν-1-BuPyrBr, MW, 30 sec, 90%
Oxazoline containing phenol 17a for the preparation of compounds 17b and 18 were prepared in a method described by Vorbrüggen et al. (*Tetrahedron* 1993, 49, 9353-72) (Scheme 3).

![Scheme 3](image)

**Scheme 3.** Reagents and conditions for the preparation of compound 17a: PPh₃, 2-aminoethanol, Et₃N, CCl₄, pyridine, acetonitrile, rt, 18 hrs, 29%.

2-Oxazole and 2-thiazole containing phenols for the preparation of carbamate derivatives 19c, 20-22, 51c were prepared from 3-methoxybenzamide or 3-methoxybenzothioamide and bromoacetaldehyde diethyl acetal under microwave conditions (Scheme 4, step a). The deprotection of phenol was carried out via method described by Chauhan and Jain (*J. Chem. Res.* 2004, 693-4) (Scheme 4, step b).

![Scheme 4](image)

**Scheme 4.** Reagents and conditions for preparation of compounds 19b, and 51b: X= O or S; a) 2-Bromoacetaldehyde diethyl acetal, THF or no solvent, MW-irradiation, 5 min, 45-90%; b) 1-Butyl-3-methylimidazolium bromide or /V-butylpyridinium bromide, MW-irradiation, 4x20 sec, 60-65%.

3-(2H-tetrazol-5-yl)phenol, methyl 3-hydroxybenzoate, 3-cyanophenol and methyl 4-hydroxybenzoate were used as starting materials in preparation of carbamates 23 and 26-28 in a usual way (Scheme 1).
In examples 24 and 25 3-(2H-tetrazol-5-yl)phenol was first converted to its cyclopentylcarbamate in a usual way (Scheme 5, step a). The proton of the tetrazole group was then substituted with either methyl or benzyl group (Scheme 5, step b).

Scheme 5. Reagents and conditions for the preparation of compounds 23-25: a) Et₃N, RNCO, toluene, reflux, 65%; b) MeI, Et₃N, acetone, 2 °C, 44% or BnBr, KI, Et₃N, acetone, 2 °C, 60%.

In examples 29a-35a oxazolines were prepared from aminoalcohols and 3-hydroxynitrile (Scheme 6) via a method described by Bolm et al. (Chem. Ber. 1991, 124, 1173-1180) and used as starting materials for the preparation of carbamate derivatives 29b-35b (Scheme 1).

Scheme 6. Reagents and conditions for the preparation of compounds 29a-35a: ZnCl₂, PhCl, reflux, 24 h, 70%.

The 3-(1,2,3-thiadiazol-4-yl)-phenol (36b) was prepared from the 3-hydroxyphenylketone by the Hurd-Mori reaction via the corresponding hydrazone as has been previously described in the literature (Molecules 2004, 9, 957) (Scheme 7). The carbamic acid esters of 3-(1,2,3-thiadiazol-4-yl)-phenol were obtained by treatment of heterocyclic phenol with suitable isocyanate (Scheme 1).
Scheme 7. Reagents and conditions for the preparation of compound 36b:

a) ethylcarbazate, p-TsOH, toluene, reflux, 69 %; b) SOCl₂, rt, 71 %.

1,2,4-oxadiazole containing phenols 45e and 46c-47c for the preparation of carbamate derivatives 45f and 46d-47d were prepared starting from 3-cyanophenol (Scheme 8).

First the phenol functionality was protected as MEM-ether and then the cyano group was converted to amidoxime. Amidoxime was converted to various acyl amidoximes following the method described by Unangst et al. (J. Med. Chem. 1992, 35, 3691-3698). The cyclization of acyl amidoximes to 3,5-disubstituted-1,2,4-oxadiazoles was performed in the presence of catalytic amount of TBAF (A. R. Gangloff et al. Tetrahedron Lett. 2001, 42, 1441-1443). Deprotection of phenolic hydroxyl was carried out by using ZnBr₂ (Unangst et al. J. Med. Chem. 1992, 35, 3691-3698). The 1,2,4-oxadiazole containing phenol 48b was prepared in a similar manner, but without the treatment with TBAF (Scheme 9). The resulting aromatic alcohols were then coupled with isocyanates in a usual way (Scheme 1).
Scheme 8. Reagents and conditions for the preparation of compounds 45e, 46c, and 47c:

a) Methoxyethoxymethyl chloride, triethyl amine, THF, reflux, 88%;
b) Hydroxylamine hydrochloride, triethyl amine, EtOH, rt, 77%;
c) Acetyl chloride/cyclopentylpropionyl chloride/trimethylacetyl chloride, triethylamine, CHCl₃, rt, 30-68%;
d) TBAF, THF, rt, 81-100%;
e) ZnBr₂, CH₂Cl₂, rt, 24-49%.

Scheme 9. Reagents and conditions for the preparation of compound 48b:
a) Ethyl chlorooxoxacetate, triethylamine, CHCl₃, rt, 20%;
b) ZnBr₂, CH₂Cl₂, rt, 68%.

3-Cyanophenol was oxidized to amide 49a via a method described by McKillop and Kemp (Tetrahedron, 1989, 47, 3299-3306). Scheme 10.
Scheme 10. Reagents and conditions for the preparation of phenol 49a: a) NaBO$_3$·4H$_2$O, H$_2$O, MeOH, 54%.

4-Oxazole and 4-imidazole containing phenols for the preparation of carbamate derivatives 50c and 52c were prepared from 2-bromo-1-(3-methoxyphenyl)-ethanone and formamide either by MW-irradiated reaction or by oil-bath heated reaction (Scheme 11 steps a and b). The deprotection of phenol was carried out either via a method described by Chauhan and Jain (*J. Chem. Res.* 2004, 693-4) or via treatment with BBr$_3$, (McOmie J. F. W.; and West, D. E. *Org. Synth.* 1973, *Coll. Vol. 5*, 412-414). Scheme 11.

Scheme 11. Reagents and conditions for the preparation of compounds 50b and 52b: a) Formamide, MW, 100 °C, 51%; b) Formamide, 165 °C, 85%; c) N-butylpyridinium bromide, MW, 100°C, 56%; d) BBr$_3$, CH$_2$Cl$_2$, -78 °C-rt, 59%.

2-Oxazolines 53b and 54a were prepared from 3-cyanophenol via imidate-intermediate 53a (Reider, P. J.; Conn, R. S. E.; Davis, P.; Grenda, V. J.; Zambito, A, J.; Grabowski, E. J. J. *J. Org. Chem.* 1987,52, 3326-3334) us-

Scheme 12. Reagents and conditions for the preparation of compounds 53b (R= CO₂Me, R’= H) and 54a (R= H, R’= CO₂Me): a) MeOH, HCl (gas), CH₂Cl₂, 20°C, 92%; b) Et₃N, CH₂Cl₂, reflux, 68%.

3-(N-hydroxycarbamimidoyl)phenyl cyclohexylcarbamate (56) was prepared from 3-cyanophenyl cyclohexylcarbamate (28) by converting the cyano group to amidoxime (Scheme 13).

Scheme 13. Reagents and conditions for the preparation of compound 56: a) Hydroxylamine hydrochloride, thethyl amine, EtOH, rt, 29%.

2-Hydroxyisonicotinic acid methyl ester 57a for the preparation of carbamate derivative 57b was prepared from 2-hydroxyisonicotinic acid (Scheme 14).
Scheme 14. Reagents and conditions for the preparation of phenol 57a: a) MeOH, cone. H₂SO₄, 82%.

The following examples further illustrate the invention described above.

**Examples**

*Methods employed in the characterization of examples*

Analytical thin-layer chromatography was carried out on Merck silica gel F₂₅₄ (60 A, 40-63 μm, 230-400 mesh) pre-coated aluminum sheets and detected under UV-light. Melting points (mp) were determined in open capillaries using a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance (¹H NMR and ¹³C NMR) spectra were recorded on a Bruker Avance DPX 400 (or Bruker Avance 500) spectrometer operating at 400 MHz (500.1 MHz) for ¹H and 100 MHz (125.8 MHz) for ¹³C. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual solvent (CDCl₃ 7.26 and 77.0 ppm; DMSO-c₆ 2.50 and 39.52 ppm). Infrared (IR) spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer, and values are reported as frequency (v) and expressed in cm⁻¹. Elemental analyses were recorded on a Perkin Elmer 2400 CHN or a ThermoQuest CE Instruments EA1110-CHNS-O elemental analyser. HRMS spectra were measured with a Jeol JMS-DX 303 and Micromass LCT or Waters Micromass LCT Premier (ESI / TOF) HRMS-spectrometer. ESI-MS spectra were acquired using A Finnigan LTQ quadrupole ion trap mass spectrometer (Thermo Electron Corporation, San Jose, CA, USA), equipped with an electrospray ion source.

**Example 1**

3-Benzylxybenzoic acid (1a). 3-Hydroxy-benzoic acid (22.0 g, 159 mmol, 100 mol-%) in THF (100 mL) was treated with 1 M aq. NaOH (200 mL, 400 mmol, 250 mol-%) during 30 min followed by dropwise addition of
BnBr (24 ml\_2, 202 mmol, 127 mol-%) in THF (100 ml\_) at 10°C. The mixture was refluxed for 48 h and then cooled to rt. The mixture was acidified with 1 M HCl (400 ml\_) and extracted with EA (3 x 150 ml\__). The combined organic phases were washed with water (150 ml\_) and brine (150 ml\_), dried over anhydrous Na\(_2\)SO\(_4\), filtered and evaporated to yield the crude product as a white solid which was recrystallized (AcOH) to yield 23.6 g (65%) of the title compound as a white solid: mp 137-139 °C (lit. 135.5-136 °C\(^3\)), Rf (5% MeOH in CH\(_2\)Cl\(_2\)) 0.22; \(^1\)H NMR (CDCl\(_3\)) 7.74-7.72 (m, 2 H), 7.46-7.32 (m, 6 H), 7.24-7.21 (m, 1 H), 5.13 (s, 2 H). CAS number: 69026-14-8.

3-BenzylOxy benzoyl chloride (1b). 3-BenzylOxy benzoic acid (1a, 550 mg, 2.4 mmol, 100 mol-%) was refluxed in SOCl\(_2\) (3 ml\_, 41 mmol, 1700 mol-%) for 3 h and evaporated to dryness. The crude product was twice diluted to benzene (20 ml\_) and evaporated to yield 580 mg (98%) of the title compound as a colourless oil: Rf (5% MeOH in CH\(_2\)Cl\(_2\)) 0.88; \(^1\)H NMR (CDCl\(_3\)) 7.63 (ddd, 1 H, \(J = 7.7, 1.6, 1.0\) Hz), 7.58 (dd, 1 H, \(J = 2.5, 1.7\) Hz), 7.35-7.23 (m, 6 H), 5.00 (s, 2 H) \(^{13}\)C NMR (CDCl\(_3\)) 168.1, 158.9, 136.0, 134.4, 129.9, 128.7, 128.3, 127.5, 124.2, 122.5, 116.5, 70.3. CAS number: 61535-46-4.

Benzo[c]floxazol-2-yl(3-benzylOxyphenyl)methanone (1c). To a mixture of benzo[c]oxazole (727 mg, 6.1 mmol, 100 mol-%) in THF (35 ml\_) was added n-BuLi (1.8 M in hex, 3.7 ml\_, 6.7 mmol, 110 mol%) at -75 °C dropwise during 10 min. After 30 min ZnCl\(_2\) (1.66 g, 12.2 mmol, 200 mol-%) in Et\(_2\)O (20 ml\_) was added. The mixture was warmed to 0 °C and after 45 min CuI (1.16 mg, 6.1 mmol, 100 mol-%) was added. Then after 10 min 3-benzyloxy benzoyl chloride (1b, 1.5 g, 6.1 mmol, 100 mol-%) in THF (10 ml\_) was added. The mixture was stirred at 0 °C for another 45 min and quenched by diluting with EtOAc (400 ml\_) and washing with 1:1 H\(_2\)O: 25% aq. ammonia (100 ml\_), H\(_2\)O (100 ml\_) and brine (100 ml\__). The organic phase was dried over anhydrous Na\(_2\)SO\(_4\), filtered and evaporated to yield the crude product as tan solid which was purified with flash chromatography (5% EtOAc in Hex) and recrystallized (EtOAc/Hex) to give 1.08 g (54%)
of the title compound as a yellow solid: mp 95-97 °C, Rf (20% EtOAc in Hex) 0.50; \(^1\)H NMR (CDCl\(_3\)) 8.22 (d, 1 H, J = 7.7 Hz), 8.13 (dd, 1 H, J = 2.4, 1.6 Hz), 7.93 (dd, 1 H, J = 7.9 Hz), 7.70 (d, 1 H, J = 8.2 Hz), 7.54 (td, 1 H, J = 7.8, 1.0 Hz), 7.49-7.44 (m, 4 H), 7.41-7.28 (m, 4 H), 5.17 (s, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) 180.1, 158.8, 157.1, 150.4, 140.7, 136.4, 136.2, 129.7, 128.6, 128.4, 127.6, 125.7, 124.1, 122.4, 121.7, 116.0, 111.8, 70.3; IR (KBr) 1648, 1604, 1577, 1443 cm\(^{-1}\); Anal. calcd for C\(_{21}\)H\(_{15}\)NO\(_3\): C, 76.58; H, 4.59; N, 4.25; Found C, 76.26; H, 4.24; N, 4.58.

**Benzo[c]floxazol-2-yl(3-hydroxyphenyl)methanone (1d).** 2-Benzoxazole-(3-benzylxoyphenyl)methanone (1c, 5.0 g, 15.2 mmol, 100 mol-%) was stirred in a solution of boron trifluoride diethyletherate (6.9 ml, 55 mmol, 360 mol-%) and dimethylsulfide (10 ml, 136 mmol, 900 mol-%) in dry CH\(_2\)Cl\(_2\) (100 ml) at rt for 72 h. The mixture was then quenched with H\(_2\)O (120 ml) and diluted with CH\(_2\)Cl\(_2\) (300 ml) and EtOAc (50 ml). The organic phase was washed with brine (2 x 100 ml), dried over anhydrous Na\(_2\)SO\(_4\), filtered and evaporated to yield a crude product as a red solid which was recrystallized (EtOAc/Hex) to yield 3.06 g (84%) of title compound as light yellow crystals; mp 125-128 °C, Rf (50% EtOAc/Hex) 0.61; \(^1\)H NMR (CDCl\(_3\)) 8.17 (ddd, 1 H, J = 7.8, 1.6, 1.0 Hz), 8.04 (dd, 1 H, J = 2.4, 1.6 Hz), 7.94 (ddd, 1 H, J = 8.0, 1.3, 0.7), 7.69 (dt, 1 H, J = 8.2, 0.9), 7.57-7.52 (m, 1 H), 7.48-7.41 (m, 2 H), 7.19 (ddd, 1 H, J = 8.1, 2.7, 0.9 Hz), 5.74 (s, 1 H); \(^{13}\)C NMR (CDCl\(_3\)) 180.2, 157.1, 156.0, 150.4, 140.6, 136.2, 130.0, 128.5, 125.8, 123.7, 122.3, 121.9, 117.2, 111.9; IR (KBr) 3463, 1651, 1593, 1525, 1450 cm\(^{-1}\); Elem. anal. calcd for Cl\(_4\)H\(_9\)NO\(_3\): C, 70.29; H, 3.79; N, 5.86; Found C, 70.24; H, 3.56; N, 5.76.

**3-(Benzo[d]oxazole-2-carbonyl)phenyl ethyl carbamate ester (1e).** 2-Benzoxazole-(3-hydroxy-phenyl)methanone (1d, 100 mg, 0.42 mmol, 100 mol-%) was dissolved in dry toluene (4 ml) followed by addition of TEA (60 \(\mu\)l, 0.42 mmol, 100 mol-%) and ethyl isocyanate (166 \(\mu\)l, 2.1 mmol, 500 mol-%). The mixture was stirred at rt for 12 h and monitored by TLC (5% Et\(_2\)O in CH\(_2\)Cl\(_2\)). After the reaction was complete the mixture was diluted
with EtOAc (8 ml_), filtered through a pad of silica gel and evaporated to
dryness. Recrystallization from EtOAc/Hex gave 121 mg (93%) of com-

pound 1e as a white cotton-like solid: mp 141-142 °C, Rf (5% Et₂O in

CH₂Cl₂) 0.70; ¹H NMR (CDCl₃) 8.46 (d, 1 H, J = 7.7 Hz), 8.32 (s, 1 H), 7.94
d, 1 H, J = 8.1 Hz), 7.70 (d, 1 H, J = 8.2 Hz), 7.57-7.45 (m, 4 H), 5.19 (br
s, 1H, NH), 3.33 (qui, 2 H, J = 6.8 Hz), 1.23 (t, 3 H, J = 7.2 Hz); ¹³C NMR
(CDCl₃) 179.4, 156.9, 154.0, 151.2, 150.4, 140.7, 136.0, 129.4, 128.5,
127.9, 127.8, 125.7, 123.9, 122.4, 111.8, 36.2, 15.0; IR (KBr) 3345, 2976,
1712, 1662, 1527 cm⁻¹; Anal. calcd for C₁₀H₈N₂O₄: C, 65.80; H, 4.55; N,
9.03; Found C, 65.69; H, 4.21; N, 8.98.

Example 2
3-(Benzo[d]oxazole-2-carbonyl)phenyl propyl carbamate ester (2). This
compound was synthesized and worked up as described for 1e using pro-
pyl isocyanate (86 µl, 0.90 mmol, 750 mol-%) as starting material. Recryst-
tallization from EtOAc/Hex gave 38 mg (97%) of compound 2 as a white
solid: mp 121-122 °C, Rf (50% EtOAc in Hex) 0.53; ¹H NMR (CDCl₃) 8.46
(d, 1 H, J = 7.5 Hz), 8.33 (s, 1 H), 7.96 (d, 1 H, J = 8.1 Hz), 7.72 (d, 1 H, J
= 8.1 Hz), 7.58-7.54 (m, 2 H), 7.51 - 7.46 (m, 2 H), 5.10 (s, 1 H, NH), 3.27 (q,
2 H, J = 6.6 Hz), 1.63 (sext, 2 H, J = 7.2 Hz), 0.99 (t, 3 H, J = 7.4 Hz); ¹³C
NMR (CDCl₃) 179.5, 157.0, 154.2, 151.3, 150.5, 140.8, 136.1, 129.5,
128.5, 128.0, 127.8, 125.8, 124.0, 122.5, 111.9, 43.1, 23.1, 11.2; IR (KBr)
3306, 2957, 1732, 1708, 1647, 1536 cm⁻¹; Anal. calcd for C₁₈H₁₄N₂O₄: C, 66.66;
H, 4.97; N, 8.64; Found C, 66.64, H, 4.76, N, 8.49.

Example 3
3-(Benzo[d]oxazole-2-carbonyl)phenyl butyl carbamate ester (3). This
compound was synthesized and worked up as described for 1e using butyl
isocyanate (240 µl, 2.1 mmol, 500 mol-%) as starting material. Recrystall-
ization from EtOAc/Hex yielded 140 mg (99%) of the title compound as a
white solid: mp 144-145 °C, Rf (5% Et₂O in CH₂Cl₂) 0.71 ; ¹H NMR (CDCl₃)
8.46 (d, 1 H, J = 7.7 Hz), 8.32 (s, 1 H), 7.95 (d, 1 H, J = 7.9 Hz), 7.71 (d, 1 H, J = 8.2 Hz), 7.58-7.46 (m, 4 H), 5.1 1 (br s, 1 H, NH), 3.30 (q, 2 H, J = 6.7 Hz), 1.58 (qui, 2 H, J = 7.3 Hz), 1.41 (sext, 2 H, J = 7.4 Hz), 0.96 (t, 3 H, J = 7.3 Hz); 13C NMR (CDCl3) 179.4, 156.9, 154.1, 151.2, 150.4, 140.7, 136.0, 129.4, 128.5, 127.9, 127.8, 125.7, 123.9, 122.4, 111.8, 41.0, 31.8, 19.9, 13.6; IR (KBr) 3356, 2953, 2951, 2854, 1663, 1529 cm⁻¹; Anal. calcd for C19H18N2O4; C, 67.44; H, 5.36; N, 8.28; Found C, 67.51; H, 5.15; N, 8.20.

Example 4

3-(Benzo[d]oxazole-2-carbonyl)phenyl cyclopentyl carbamate ester (4). This compound was synthesized and worked up as described for 1e using cyclopentyl isocyanate (240 μL, 2.1 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 142 mg (96%) of the title compound as a white solid: mp 156-157 0°C, Rf (5% Et2O in CH2Cl2) 0.70; 1H NMR (CDCl3) 8.46 (d, 1 H, J = 7.5 Hz), 8.32 (s, 1 H), 7.95 (d, 1 H, J = 7.9 Hz), 7.71 (d, 1 H, J = 8.2 Hz), 7.57-7.45 (m, 4 H), 5.1 1 (br d, 1 H, NH), 4.07 (sext, 1 H, J = 6.8 Hz), 2.1 0-2.00 (m, 2 H), 1.75-1.46 (m, 6 H); 13C NMR (CDCl3) 179.4, 156.9, 153.5, 151.2, 150.4, 140.7, 136.1, 129.4, 128.5, 127.9, 127.8, 125.7, 123.9, 122.4, 111.8, 53.1, 33.1, 23.5; IR (KBr) 3352, 2954, 1716, 1659, 1520 cm⁻¹; Anal. calcd for C20H18N2O4; C, 68.56; H, 5.18; N, 8.00; Found C, 68.54; H, 5.02; N, 7.90.

Example 5

3-(Benzo[d]oxazole-2-carbonyl)phenyl cyclohexyl carbamate ester (5).

This compound was synthesized and worked up as described for 1e but using cyclohexyl isocyanate (270 μL, 2.1 mmol, 500 mol-%) as a starting material. Recrystallization from EtOAc/Hex gave 122 mg (80%) of the title compound as a white solid: mp 172-173 0°C, Rf (20% EtOAc/Hex) 0.4; 1H NMR (CDCl3) 8.46 (d, 1 H, J = 7.7 Hz), 8.32 (t, 1 H, J = 1.9 Hz), 7.96 (d, 1 H, J = 7.9 Hz), 7.71 (d, 1 H, J = 8.2 Hz), 7.58-7.54 (m, 2 H), 7.51-7.46 (m, 2 H), 4.98 (d, 1 H, J = 7.5 Hz), 3.62-3.55 (m, 1 H), 2.05-2.03 (m, 2 H), 1.77-
Example 6
3-(Benzo[d]oxazole-2-carbonyl)phenyl benzyl carbamate ester (6). This compound was synthesized and worked up as described for 1e using benzyl isocyanate (260 µL, 2.1 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 156 mg (97%) of the title compound as a white solid: mp 165-166 °C, Rf (50% EtOAc in Hex) 0.52; 1H NMR (CDCl₃) 8.47 (d, 1 H, J = 7.5 Hz), 8.35 (s, 1 H), 7.95 (d, 1 H, J = 8.1 Hz), 7.71 (d, 1 H, J = 8.2 Hz), 7.58-7.46 (m, 4 H), 7.37-7.36 (m, 4 H), 7.33-7.31 (m, 1 H), 5.44 (s, 1 H), 4.48 (d, 2 H, J = 6.0 Hz); 13C NMR (CDCl₃) 179.4, 156.9, 154.2, 151.2, 150.5, 140.8, 137.8, 136.1, 129.5, 128.8, 128.5, 128.1, 127.83, 127.77, 125.8, 124.0, 122.5, 111.9, 45.4; IR (KBr) 3306, 3034, 2954, 1716, 1659, 1520 cm⁻¹; Anal. calc. for C₂₂H₁₈N₂O₄; C, 69.22; H, 5.53; N, 7.69; Found C, 68.78; H, 5.38; N, 7.62.

Example 7
3-(Benzo[d]oxazole-2-carbonyl)phenyl 4-methoxy-benzyl carbamate ester (7). This compound was synthesized and worked up as described for 1e using 4-methoxyphenyl isocyanate (180 µL, 1.2 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 64 mg (69%) of the title compound as a white solid: mp 155-157 °C, Rf (50% EtOAc in Hex) 0.44; 1H NMR (CDCl₃) 8.48 (d, 1 H, J = 7.5 Hz), 8.40 (s, 1 H), 7.94 (d, 1 H, J = 8.1 Hz), 7.70 (d, 1 H, J = 8.2 Hz), 7.59-7.52 (m, 3 H), 7.48-7.44 (m, 1 H), 7.35 (d, 2 H, J = 8.6), 7.08 (s, 1 H, NH), 6.86 (d, 2 H, J = 9.0 Hz), 3.77 (s, 3 H, -OCH₃); 13C NMR (CDCl₃) 179.3, 156.8, 156.4, 151.5, 150.8, 150.4, 140.7, 136.1, 130.1, 129.6, 128.5, 128.2, 127.7, 125.7, 124.1, 122.4, 120.8,
Example 8

3-(Benzo[d]oxazole-2-carbonyl)phenyl 3-methyl-benzyl carbamate ester (8). This compound was synthesized and worked up as described for 1e using 3-methyl-benzyl isocyanate (290 μL, 2.1 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 160 mg (97%) of the title compound as a white solid: mp 154-155 °C, Rf (5% Et₂O in CH₂Cl₂) 0.71; ¹H NMR (CDCl₃) 8.47 (d, 1 H, J = 7.7 Hz), 8.35 (s, 1 H), 7.95 (d, 1 H, J = 7.7 Hz), 7.70 (d, 1 H, J = 8.1 Hz), 7.58-7.45 (m, 4 H), 7.27-7.11 (m, 4 H), 5.45 (m, 1 H, NH), 4.43 (d, 2 H, J = 5.7 Hz), 2.36 (s, 3 H); ¹³C NMR (CDCl₃) 179.4, 156.9, 154.1, 151.2, 150.4, 140.7, 138.5, 137.7, 136.1, 129.5, 128.7, 128.5, 128.0, 127.7, 125.7, 124.7, 123.9, 122.4, 111.8, 45.4, 21.3; IR (KBr) 3297, 3042, 2946, 2870, 1644, 1588, 1491 cm⁻¹; Anal. calcd for C₂₃H₁₈N₂O₄; C, 71.49; H, 4.70; N, 7.25; found C, 71.41; H, 4.41; N, 7.14.

Example 9

Benzo[c/]thiazol-2-yl(3-benzylxoyphenyl)methanone (9a). This compound was synthesized and worked up as described for 1c but using benzo[c/]thiazole (2.6 mL, 23.9 mmol, 100 mol-%) as starting material instead of benzo[c/]oxazole. Purification with flash chromatography (8% EtOAc in Hex) and recrystallization (EtOAc/Hex) yielded 4.56 g (55%) of the title compound as a light yellow solid: mp 98-100 °C, Rf (20% EA in Hex) 0.47. ¹H NMR (CDCl₃) 8.22 (d, 2 H, J = 8.1 Hz), 8.16 (dd, 1 H, J = 2.6, 1.6 Hz), 8.01-7.99 (m, 1 H), 7.60-7.24 (m, 9 H), 5.17 (s, 2 H); ¹³C NMR (CDCl₃) 184.9, 167.1, 158.8, 153.9, 137.0, 136.6, 136.2, 129.6, 128.6, 128.1, 127.6, 126.9, 125.8, 124.4, 122.1, 121.4, 116.4, 113.4, 111.1, 70.3; IR (KBr) 1633, 1588, 1491 cm⁻¹; Anal. calcd for C₂₁H₁₅NO₂S; C, 73.02; H, 4.38; N, 4.06; Found C, 72.46; H, 4.25; N, 3.96.
**Benzo[c]flthiazol-2-yl(3-hydroxyphenyl)methanone (9b).** This compound was synthesized and worked up as described for 1d using benzo[c]/flthiazol-2-yl(3-hydroxy-phenyl)methanone (9a, 4.33 g, 12.5 mmol, 100 mol-%) as starting material. Purification with flash chromatography (25% EtOAc in Hex) and recrystallization from EtOAc/Hex gave 2.92 g (91%) of the title compound as a yellow solid: mp 146-147 °C; Rf (50% EtOAc in Hex) 0.50; \(^1\)H NMR (DMSO-D\(_2\)) 9.95 (s, 1 H), 8.27-8.22 (m, 2 H), 7.94 (app d, 1 H, J = 7.9 Hz), 7.85 (t, 1 H, J = 1.9 Hz), 7.67-7.60 (m, 2 H), 7.43 (t, 1 H, J = 8.0 Hz), 7.16 (ddd, 1 H, J = 8.1, 2.4, 0.9 Hz); \(^{13}\)C NMR (DMSO) 184.7, 166.8, 157.4, 153.3, 136.2, 135.6, 129.7, 127.9, 127.3, 125.3, 122.8, 121.9, 121.4, 117.0; IR (KBr) 3466, 1634, 1590, 1489, 1446 cm\(^{-1}\); Anal. calcd for C\(_{14}\)H\(_{11}\)NO\(_2\)S; C, 65.87; H, 3.55; N, 5.49; Found C, 66.01; H, 3.35; N, 5.32.

**3-(Benzo[d]thiazole-2-carbonyl)phenyl ethyl carbamate ester (9c).** This compound was synthesized and worked up as described for 1e using the compound 9b (100 mg, 0.39 mmol, 100 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 101 mg (79%) of the title compound as a white solid: mp 97-99 °C; Rf (5% Et\(_2\)O in CH\(_2\)Cl\(_2\)) 0.61; \(^1\)H NMR (CDCl\(_3\)) 8.46 (d, 1 H, J = 7.7 Hz), 8.32 (s, 1 H), 8.24 (app. dd, 1 H, J = 7.6, 1.2 Hz), 8.01-7.99 (m, 1 H), 7.60-7.46 (m, 4 H), 5.15 (m, 1 H, NH), 3.33 (qui, 2 H, J = 6.8 Hz), 1.22 (t, 3 H, J = 7.2 Hz); \(^{13}\)C NMR (CDCl\(_3\)) 184.2, 166.8, 154.0, 153.8, 151.1, 137.0, 136.0, 129.3, 128.2, 127.7, 127.4, 126.9, 125.8, 124.2, 122.1, 36.2, 15.1; IR (KBr) 3335, 2975, 1712, 1643, 1531 cm\(^{-1}\); Anal. calcd for C\(_{17}\)H\(_{14}\)N\(_2\)O\(_3\)S; C, 62.56; H, 4.32; N, 8.58; found C, 62.50; H, 4.40; N, 8.50.

**Example 10**

**3-(Benzo[d]thiazole-2-carbonyl)phenyl propyl carbamate ester (10).** This compound was synthesized and worked up as described for 9c (except that the mixture was stirred at 64 °C for 16 h) using propyl isocyanate (160 μL, 2.0 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 126 mg (95%) of the title compound as a white solid:
mp. 98-100 °C, Rf (CHCl₃) 0.50; ¹H NMR (CDCl₃) 8.46 (d, 1 H, J = 7.7 Hz), 8.32 (s, 1 H), 8.24 (dd, 1 H, J = 7.3, 1.3 Hz), 8.02-8.00 (m, 1 H), 7.60-7.46 (m, 4 H), 5.15 (s, 1 H, -NH), 3.26 (q, 2 H, J = 6.7 Hz), 1.62 (sext, 2 H, J = 7.3 Hz), 0.98 (t, 3 H, J = 7.3 Hz); ¹³C NMR (CDCl₃) 184.2, 166.8, 154.2, 153.9, 151.1, 137.0, 136.1, 129.3, 128.2, 127.7, 127.4, 126.9, 125.8, 124.2, 122.1, 43.0, 23.0, 11.2; IR (KBr) 3306, 2957, 1732, 1708, 1647, 1516 cm⁻¹; Anal. calcd for C₁₈H₁₆N₂O₃S; C, 63.51; H, 4.74; N, 8.23; found C, 63.61; H, 4.49; N, 8.14.

Example 11

3-(Benzo[d]thiazole-2-carbonyl)phenyl butyl carbamate ester (11). This compound was synthesized and worked up as described for 9c using butyl isocyanate (225 µL, 2.0 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 128 mg (90%) of the title compound as a white solid: mp 120-121 °C, Rf (5% Et₂O in CH₂Cl₂) 0.62; ¹H NMR (CDCl₃) 8.46 (d, 1 H, J = 7.7 Hz), 8.32 (s, 1 H), 8.24 (app. d, 1 H, J = 7.7 Hz), 8.00 (app. dd, 1 H, J = 7.7, 0.9 Hz), 7.60-7.46 (m, 4 H), 7.27-7.1 (m, 4 H), 5.12 (br s, 1 H, NH), 3.29 (q, 2 H, J = 6.7 Hz), 1.57 (qui, 2 H, J = 7.4 Hz), 1.41 (sext, 2 H, J = 7.6 Hz), 0.96 (t, 3 H, J = 7.3 Hz); ¹³C NMR (CDCl₃) 184.2, 166.8, 154.2, 153.9, 151.1, 137.0, 136.1, 129.3, 128.2, 127.7, 127.4, 126.9, 125.8, 124.2, 122.1, 41.0, 31.9, 19.9, 13.7; IR (KBr) 3327, 2961, 1715, 1646, 1536, 1489 cm⁻¹; Anal. calcd for C₁₉H₁₈N₂O₃S; C, 64.39; H, 5.12; N, 7.90; found C, 64.56; H, 4.91; N, 7.84.

Example 12

3-(Benzo[d]thiazole-2-carbonyl)phenyl cyclopentyl carbamate ester (12). This compound was synthesized and worked up as described for 9c using cyclopentyl isocyanate (225 µL, 2.0 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 120 mg (84%) of the title compound as a white solid: mp 121-123 °C, Rf (5% Et₂O in CH₂Cl₂) 0.60; ¹H NMR (CDCl₃) 8.45 (d, 1 H, J = 7.7 Hz), 8.32 (s, 1 H), 8.25-8.23 (m,
Example 13
3-(Benzo[d]thiazole-2-carbonyl)phenyl cyclohexyl carbamate ester (13). This compound was synthesized and worked up as described for 9c (except that mixture was refluxed for 17 hrs) using cyclohexyl isocyanate (278 µmol, 1.95 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 132 mg (89%) of the title compound as white solid: mp 151-152 °C, Rf (30% EtOAc/Hex) 0.50; ¹H NMR (CDCl₃) 8.45 (d, 1 H, J = 7.7 Hz), 8.32 (t, 1 H, J = 1.7 Hz), 8.24-8.22 (m, 1 H), 8.00-7.98 (m, 1 H), 7.59-7.46 (m, 4 H), 5.10 (d, 1 H, J = 7.7 Hz), 3.62-3.53 (m, 1 H), 2.04-2.00 (m, 2 H), 1.75-1.72 (m, 2 H), 1.64-1.60 (m, 1 H), 1.42-1.32 (m, 2 H), 1.28-1.14 (m, 3 H); ¹³C NMR (CDCl₃) 184.2, 166.8, 153.8, 153.2, 151.1, 137.0, 136.0, 129.2, 128.1, 127.6, 127.4, 126.9, 125.7, 124.1, 122.1, 50.2, 33.1, 25.4, 24.7; IR (KBr) 3351, 2935, 1707, 1642, 1523 cm⁻¹; Anal. calcd for C₂₁H₂₀N₂O₃S: C, 66.29; H, 5.30; N, 7.36; Found C, 66.21; H, 5.30; N, 7.24.

Example 14
3-(Benzo[d]thiazole-2-carbonyl)phenyl benzyl carbamate ester (14). This compound was synthesized and worked up as described for 9c (except that the mixture was stirred at 92 °C for 14 h) using benzyl isocyanate (240 µmol, 1.95 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 127 mg (84%) of the title compound as a white solid: mp 157-159 °C, Rf (5% Et₂O in CH₂Cl₂) 0.61; ¹H NMR (CDCl₃) 8.47 (d, 1 H,
$J = 7.7$ Hz), 8.35 (s, 1 H), 8.24 (d, 1 H, $J = 7.7$ Hz), 8.02-8.00 (m, 1 H), 7.60-7.48 (m, 4 H), 7.37-7.31 (m, 5 H), 5.45 (br s, 1 H, NH), 4.47 (d, 2 H, $J = 5.9$ Hz); $^{13}$C NMR (DMSO-d$_6$) 184.0, 166.5, 154.3, 153.2, 151.0, 139.1, 136.3, 135.6, 129.6, 128.3, 128.1, 127.6, 127.4, 127.1, 127.0, 125.4, 123.6, 122.9, 44.1; IR (KBr) 3351, 1710, 1649, 1519, 1491 cm$^{-1}$; Anal. calcd for $C_{22}H_{16}N_2O_4S$; C, 68.02; H, 4.15; N, 7.21; found C, 68.21; H, 3.88; N, 7.20.

**Example 15**

3-(Benzo[d]thiazole-2-carbonyl)phenyl 4-methoxy-benzyl carbamate ester (15). This compound was synthesized and worked up as described for 9c using 4-methoxy-benzyl isocyanate (280 µl, 2.0 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 62 mg (41%) of the title compound as white needles: mp 168-170 °C, Rf (5% Et$_2$O in CH$_2$Cl$_2$) 0.61; $^1$H NMR (CDCl$_3$) 8.49 (d, 1 H, $J = 7.7$ Hz), 8.41 (s, 1 H), 8.26-8.24 (m, 1 H), 8.02-8.00 (m, 1 H), 7.60-7.51 (m, 4 H), 7.37 (d, 2 H, $J = 8.8$ Hz), 6.95 (br s, 1 H, NH), 6.88 (d, 2 H, $J = 9.0$ Hz), 3.79 (s, 3 H); $^{13}$C NMR (CDCl$_3$) 184.1, 166.8, 153.9, 150.7, 137.1, 136.2, 130.2, 129.5, 128.6, 127.7, 127.3, 127.0, 125.8, 124.3, 122.2, 120.9, 120.8, 114.4, 55.5; IR (KBr) 3302, 1706, 1643, 1526, 1495 cm$^{-1}$; Anal. calcd for $C_{22}H_{16}N_2O_4S$; C, 65.33; H, 3.99; N, 6.93; found C, 65.1; H, 3.70; N, 6.73.

**Example 16**

3-(Benzo[d]thiazole-2-carbonyl)phenyl 3-methyl-benzyl carbamate ester (16). This compound was synthesized and worked up as described for 9c using 3-methyl-benzyl isocyanate (280 µl, 2.0 mmol, 500 mol-%) as starting material. Recrystallization from EtOAc/Hex yielded 135 mg (86%) of the title compound as a white solid: mp 131-132 °C, Rf (5% Et$_2$O in CH$_2$Cl$_2$) 0.59; $^1$H NMR (CDCl$_3$) 8.46 (d, 1 H, $J = 7.5$ Hz), 8.35 (s, 1 H), 8.25-8.22 (m, 1 H), 8.01-7.99 (m, 1 H), 7.60-7.48 (m, 4 H), 7.27-7.23 (m, 1 H); $^{13}$C NMR (CDCl$_3$) 184.2, 166.8, 154.2, 154.0, 153.8, 151.1, 138.5, 137.7,
137.0, 136.1, 129.3, 128.7, 128.5, 128.3, 127.7, 127.3, 126.9, 125.8, 124.7, 124.2, 122.1, 45.6, 21.3; IR (KBr) 3339, 3019, 1717, 1645, 1520, 1492 cm⁻¹; Anal. calcd for C₂₃H₁₈N₂O₃S; C, 68.64; H, 4.51; N, 6.96; found C, 68.45; H, 4.34; N, 6.92.

Example 17

3-(4,5-dihydrooxazol-2-yl)phenol (17a). 3-Hydroxy-benzoic acid (1.38 g, 10 mmol, 100 mol-%), 2-aminoethanol (4a, 610 µL, 10 mmol, 100 mol-%) and TEA (4.2 mL, 30 mmol, 300 mol-%) were stirred in pyridine (20 mL) and MeCN (30 mL) at 22 °C for 40 min. CCl₄ (6.15 g, 40 mmol, 400 mol-%) was added followed by dropwise admission of PPh₃ in pyridine-MeCN (1:1, 80 mL) during 2 hrs keeping the temperature of the mixture between 22-24 °C with water bath. The mixture was stirred for 18 hrs and mixture was concentrated with rotavapor to ca. 40 ml. The mixture was diluted with aq. ammonia (25%, 100 ml) and extracted with EtOAc (3×100 ml). Combined organic phases were washed with sat. aq. CuSO₄ (100 ml), water (100 ml) and brine (100 ml), dried with Na₂SO₄, filtered and evaporated. The crude product was a red solid which was purified with flash chromatography (0-4% MeOH in CH₂Cl₂) to yield 479 mg (29%) of the compound 17a as white solid: mp 188-189 °C, Rf (EtOAc) 0.5; ¹H NMR (DMSO-c/δ, 400 MHz) 9.70 (s, 1 H), 7.30-7.23 (m, 3 H), 6.91 (d, 1 H, J = 8.1 Hz), 4.36 (t, 2 H, J = 9.5 Hz), 3.92 (t, 2 H, J = 9.5 Hz); ¹³C NMR (DMSO-c/δ, 400 MHz) 163.0, 157.3, 129.7, 128.7, 118.5, 118.4, 114.3, 67.2, 54.4.

3-(4,5-Dihydrooxazol-2-yl)phenyl n-propylcarbamate (17b). This compound was synthesized and worked up as described for 1e using 17a (65 mg, 0.4 mmol, 100 mol-%) and n-propyl isocyanate (170 µL, 2.0 mmol, 500 mol-%) as starting materials. Recrystallization from EtOAc/Hex gave the title compound as white white crystals: mp 94-95 °C, Rf (EtOAc) 0.5; ¹H NMR (CDCl₃, 400 MHz) 7.78 (d, 1 H, J = 7.8 Hz), 7.70 (s, 1 H), 7.39 (t, 1 H, J = 8.0 Hz), 7.29-7.24 (m, 1 H), 5.05 (br s, 1H), 4.43 (app t, 2 H, J = 9.5 Hz), 4.06 (app t, 2 H, J = 9.5 Hz), 3.24 (q, 2 H, J = 6.7 Hz), 1.60 (sext, 2 H, 2.0 Hz).
\[ J = 7.3 \text{ Hz}, \ 0.97 \ (t, \ 3 \ H, \ J = 7.4 \text{ Hz}); \] 
\[ ^{13}\text{C} \text{ NMR (CDCl}_3, \ 400 \text{ MHz}) \ 163.9, \ 150.9, \ 129.1, \ 128.9, \ 124.9, \ 124.6, \ 121.4, \ 67.6, \ 54.8, \ 42.9, \ 23.0, \ 11.1; \] 
Anal. calcd for \( C_{13}H_{16}N_2O_3 \); C, 62.89; H, 6.50; N, 11.28; Found C, 62.77; H, 6.26; N, 11.15.

**Example 18**

3-(4,5-Dihydrooxazol-2-yl)phenyl cyclopentylcarbamate (18). This compound was synthesized and worked up as described for 17b using cyclopentyl isocyanate (50 \( \mu \text{L} \)), 0.5 mmol, 200 mol-% as starting material. Recrystallization from EA:Hex (4.6 \( \text{ml}_L \)) gave 48 mg (70%) of the compound as white crystals: mp 166-168 0\(^\circ\)C; Rf (10\% Et\(_2\text{O}\) in CH\(_2\text{Cl}_2\)) 0.40; \(^1\text{H}\) NMR (DMSO-c/e) 7.86 (d, 1H, \( J = 7.1 \text{ Hz} \)), 7.69 (d, 1H, \( J = 7.7 \text{ Hz} \)), 7.53 (s, 1H), 7.47 (t, 1H, \( J = 7.9 \text{ Hz} \)), 7.28 (dd, 1H, \( J = 1.5, \ 8.1 \text{ Hz} \)), 4.41 (t, 2H, \( J = 9.5 \text{ Hz} \)), 3.96 (t, 2H, \( J = 9.5 \text{ Hz} \)), 3.88-3.79 (m, 1H), 1.89-1.79 (m, 2H), 1.72-1.61 (m, 2H), 1.57-1.44 (m, 4H); \(^{13}\text{C} \text{ NMR (DMSO-c/e)} \) 162.3, 153.4, 151.0, 129.7, 128.6, 124.7, 124.1, 120.9, 67.5, 54.4, 52.4, 32.2, 23.3; Anal. calcd for \( C_{15}H_{18}N_2O_3 \); C, 66.68; H, 6.61; N, 10.21; Found C, 65.62; H, 6.91; N, 10.20.

**Example 19**

2-(3-Methoxy-phenyl)-oxazole (19a). 3-Methoxybenzamide (2.0 g, 13 mmol, 100 mol-%) and 2-bromoacetaldehyde diethyl acetal (5, 2.5 \( \text{ml}_L \)), 16 mmol, 120 mol-%) were added to a flame dried 10 ml round bottomed flask and irradiated with CEM microwave apparatus for 5 min (power 300 W for 30 sec, then 50 W, air cooling, \( T_{\text{max}} = 100 \text{ \(^\circ\)} \text{C} \)). The reaction mixture was dissolved to EtOAc (150 \( \text{ml}_L \)), MeOH (10 \( \text{ml}_L \)) and water (50 \( \text{ml}_L \)). The organic phase was washed with NaHCO\(_3\) (100 \( \text{ml}_L \)), water (50 \( \text{ml}_L \)) and brine (50 \( \text{ml}_L \)), dried over Na\(_2\text{SO}_4\), filtered and evaporated. The tan oil was Kugelrohr-distilled to yield 2.05 g of clear oil. The oil was diluted with hexane (5 \( \text{ml}_L \)) and put to freezer overnight which caused crystallization. The solid was filtrated, washed with cold hex (20 \( \text{ml}_L \)) and dried under reduced pres-
sure to yield 1.01 g (45%) of the title compound as a white crystals: mp 23
°C, Rf (EtOAc) 0.62; 1H NMR (CDCl₃) 7.69 (d, 1 H, J = 0.7 Hz), 7.65-7.62
(app. ddd, 1 H, J = 7.7, 1.4, 0.9), 7.59 (dd, 1 H, J = 1.4 Hz), 7.36 (t, 1 H, J =
7.5 Hz), 7.23 (d, 1 H, J = 0.7 Hz), 6.99, (ddd, 1 H, J = 8.3, 2.6, 0.9 Hz), 3.86
(s, 3 H), 13C NMR (CDCl₃) 161.8, 159.8, 138.5, 129.8, 128.6, 128.3, 118.7,
116.9, 110.9, 55.3; Anal. calc'd for C₁₀H₉NO₂, C, 68.56; H, 5.18; N, 8.00;
Found C, 68.43; H, 4.84; N, 7.86.

2-(3-Hydroxy-phenyl)-oxazole (19b). 2-(3-Methoxy-phenyl)-oxazole (19a,
900 mg, 5.14 mmol, 100 mol-%) and 1-butyl-3-methylimidazolium bromide
(2.20 g, 10 mmol, 200 mol-%) were irradiated with CEM microwave appara-
tus in an open vessel for 4 x 20 sec (power 300 W, air cooling, T_max 200
°C). The reaction mixture was dissolved to EtOAc (200 ml_) and water (50
ml_). The organic phase was washed with water (50 ml_) and brine (50 ml_),
dried over Na₂SO₄, filtered and evaporated. The crude product was purified
with flash chromatography (25% EtOAc in hex) to yield 500 mg (60%) of the
compound 19b as a white solid: mp 130-1 31 °C, Rf (40% EA in hex) 0.5; 1H
NMR (CDCl₃) 9.81 (s, 1 H), 8.19 (d, 1H, J = 0.8 Hz), 7.43-7.38 (m, 2 H),
7.36 (d, 1H, J = 0.8 Hz), 7.33 (t, 1H, J = 7.9 Hz), 6.91 (ddd, 1H, J = 1.1, 2.5,
8.1 Hz), 5.05 (br s, 1H, NH), 4.43 (app t, 2 H, J = 9.5 Hz), 4.06 (app t, 2 H,
J = 9.5 Hz), 3.24 (q, 2 H, J = 6.7 Hz), 1.60 (sext, 2 H, J = 7.3 Hz), 0.97 (t, 3
H, J = 7.4 Hz); 13C NMR (CDCl₃) 160.8, 157.8, 139.9, 130.3, 128.4, 128.1,
117.7, 116.6, 112.4; CAS 35582-09-3.

3-(Oxazol-2-yl)phenyl cyclopentylcarbamate (19c). This compound was
synthesized and worked up as described for 17b using compound 19b (64
mg, 0.40 mmol-%, 100 mol-%) and cyclopentyl isocyanate (150 µL, 1.6
mmol, 400 mol-%) as starting materials. Recrystallization from EtOAc:hex
(1:10 ml_) gave 103 mg (94%) of compound 19c as white crystals: mp. 120-
122 °C; Rf (10% Et₂O in CH₂Cl₂) 0.50; 1H NMR (DMSO-d₆) 8.25 (s, 1H),
7.90 (d, 1H, J = 7.1 Hz), 7.81 (d, 1H, J = 7.8 Hz), 7.66 (s, 1H), 7.54 (t, 1H, J
8.0 Hz), 7.41 (s, 1H), 7.27 (dd, 1H, J = 1.6, 8.1 Hz), 3.90-3.82 (m, 1H),
1.80-1.90 (m, 2H), 1.61-1.72 (m, 2H); 1H NMR (DMSO-
Example 20

3-(Oxazol-2-yl)phenyl cyclohexylcarbamate (20). This compound was synthesized and worked up as described for 19c using compound cyclohexyl isocyanate (190 µl, 1.5 mmol, 300 mol-%) as starting material. Recrystallization from EtOAc:hex gave 115 mg (80%) of compound 20 as white crystals: mp 142-143 °C; Rf (10% Et2O in CH2Cl2) 0.30; 1H NMR (CDCl3) 7.88 (d, 1 H, J = 7.8 Hz), 7.82-7.80 (m, 1 H), 7.70-7.69 (m, 1 H), 7.44 (t, 1 H, J = 8.0 Hz), 7.25-7.21 (m, 2 H), 5.06 (br d, 1 H, J = 7.5 Hz), 3.66-3.51 (m, 1 H) 2.08-1.97 (m, 2 H), 1.79-1.69 (m, 2 H), 1.66-1.58 (m, 1 H), 1.43-1.31 (m, 2 H), 1.29-1.13 (m, 3 H); 13C NMR (CDCl3) 161.2, 153.3, 151.4, 138.7, 129.7, 128.6, 128.5, 123.6, 123.0, 119.7, 50.2, 33.2, 25.4, 24.7; Anal. calcd for C18H16N2O3: C, 71.2; H, 6.34; N, 9.78; Found C, 66.72; H, 6.44; N, 9.74.

Example 21

3-(Oxazol-2-yl)phenyl 2-methyl-benzylcarbamate (21). This compound was synthesized and worked up as described for 20 using 2-methyl-benzyl isocyanate (165 µl, 1.1 mmol, 200 mol-%) as starting material. Recrystallization from EtOAc:hex gave compound 21 (154 mg, 89%) as white crystals: mp 120-121 °C; Rf, (5% Et2O in CH2Cl2) 0.5; 1H NMR (DMSO-c6) 8.35 (t, 1 H, J = 5.9 Hz), 8.24 (s, 1 H), 7.85-7.81 (m, 1 H), 7.70 (app. t, 1 H, J = 1.8 Hz), 7.56 (t, 1 H, J = 8.0 Hz), 7.41 (s, 1 H), 7.33-7.27 (m, 2 H), 7.23-7.17 (m, 3 H), 4.29 (d, 1 H, J = 5.9 Hz), 2.32 (s, 3 H); 13C NMR (DMSO-c6) 160.1, 154.2, 151.5, 140.4, 136.7, 135.5, 130.4, 130.0, 128.6, 128.0, 127.4, 127.0, 125.9, 123.9, 122.5, 119.0, 42.1, 18.6; Anal. calcd for C18H16N2O3: C, 70.1; H, 5.23; N, 9.09; Found C, 69.78; H, 5.14; N, 9.02.
Example 22

3-(Oxazol-2-yl)phenyl phenethylcarbamate (22). This compound was synthesized and worked up as described for 21 using phenethyl isocyanate (110 µl, 0.75 mmol, 200 mol-%) as starting material. Recrystallization from EtOAc:hex gave compound 22 as white crystals (83 mg, 73%): mp 112-1 13 °C; Rf (5% Et₂O in CH₂Cl₂) 0.5; ¹H NMR (DMSO-c/δ) 8.25 (app. d, 1 H, J = 0.6 Hz), 7.96 (t, 1 H, J = 5.6 Hz), 7.83-7.79 (m, 1 H), 7.64 (app. t, 1 H, J = 1.9 Hz), 7.54 (t, 1 H, J = 8.0 Hz), 7.41 (app. d, 1 H, J = 0.9 Hz), 7.35-7.20 (m, 6 H), 3.36-3.29 (m, 2 H), 2.82 (t, 2 H, J = 7.4 Hz); ¹³C NMR (DMSO-c/δ) 160.1, 154.0, 151.5, 140.4, 139.1, 130.3, 128.7, 128.6, 128.3, 128.0, 126.2, 123.8, 122.4, 119.0, 42.0, 35.2, Anal. calcd for C₁₈H₁₆N₂O₃: C, 70.12; H, 5.23; N, 9.09; Found C, 70.04; H, 5.09; N, 9.02.

Example 23

Cyclopentyl-carbamic acid 3-(2H-tetrazol-5-yl)-phenyl ester (23). 5-(3-Hydroxyphenyl)-tetrazole (98 mg, 0.6 mmol, 100 mol-%), cyclopentyl isocyanate (330 µl, 3.0 mmol, 500 mol-%) and TEA (170 µl, 1.2 mmol, 200 mol-%) were stirred in dry toluene (7 ml.) for 3 hrs at rt and refluxed for 6 hrs. The mixture was extracted with H₂O (3x20 ml.). The aqueous phase was acidified with 32% HCl (0.8 ml.) until white precipitate formed. Precipitate was filtered and recrystallized from MeOH:H₂O to give 48 mg (65%) of compound 23 as white crystals: mp 174-1 77 °C; Rf (8% MeOH, 2% AcOH in CHCl₃) 0.40; ¹H NMR (DMSO-c/δ) 7.94 (d, 1 H, J = 7.2 Hz), 7.89 (d, 1 H, J = 7.8 Hz), 7.77 (s, 1 H), 7.62 (t, 1 H, J = 8.0 Hz), 7.34 (dd, 1 H, J = 1.6, 8.1 Hz), 3.92-3.83 (m, 1 H), 1.91-1.80 (m, 2H), 1.73-1.63 (m, 2H), 1.59-1.45 (m, 4H); ¹³C NMR (DMSO-c/δ) 155.0, 153.4, 151.7, 130.6, 125.2, 124.7, 123.4, 120.3, 52.4, 32.2, 23.3; Anal. calcd for C₁₃H₁₆N₂O₂: C, 57.13; H, 5.53; N, 25.63; Found C, 56.90; H, 5.30; N, 25.23.
3-(2-Methyl-2H-tetrazol-5-yl)phenyl cyclopentylcarbamate (24). Compound 23 (123 mg, 0.45 mmol, 100 mol-%) in acetone (2.5 ml) was cooled to 2 °C (Tbath). Triethylamine (70 µL) was added followed by admission of MeI (160 mg, 1.1 mmol, 250 mol-%). After 2 hrs another portion of MeI (450 mg, 3.2 mmol, 700 mol-%) was added. The mixture was stirred for another 1 hrs at 2 °C and diluted with EtOAc (35 ml). The organic phase was washed with sat. NaHCO₃ (2x10 ml) and brine (10 ml), dried over Na₂SO₄, filtered and evaporated resulting 100 mg (74%) of 4:1 mixture of 2-methylated and 1-methylated tetrazoles. The isomers were separated by flash chromatography (0.5-1 % MeOH in CH₂Cl₂) and recrystallized (EtOAc:Hex) giving compound 24 as a white solid: mp 145-147 °C; Rf (3% MeOH in CH₂Cl₂) 0.7; ¹H NMR (CDCl₃) 7.97 (d, 1 H, J = 7.7 Hz), 7.91 (s, 1 H), 7.47 (t, 1 H, J = 7.9 Hz), 7.28-7.22 (m, 1 H), 5.05 (d, 1 H, J = 5.8 Hz), 4.39 (s, 3 H), 4.14-4.01 (m, 1 H), 2.1 0-1.98 (m, 2 H), 1.79-1.58 (m, 4 H), 1.56-1.46 (m, 2 H); ¹³C NMR (CDCl₃) 164.6, 153.7, 151.5, 129.8, 128.5, 123.6, 123.5, 120.1, 53.0, 39.5, 33.1, 23.5; Anal. calcd for C₁₄H₁₁N₅O₁₂; C, 58.52; H, 5.96; N, 24.37; Found C, 58.52; H, 5.85; N, 24.35.

Example 25

3-(2-Benzyl-2H-tetrazol-5-yl)phenyl cyclopentylcarbamate (25). Compound 23 (100 mg, 0.37 mmol, 100 mol-%) in acetone (2.5 ml) was cooled to 2 °C (Tbath). Triethylamine (60 µL) was added followed by admission of BnBr (50 µL, 0.41 mmol, 110 mol-%) and KI (30 mg, 0.19 mmol- 50 mol-%). After 90 min the mixture was diluted with EtOAc (40 ml). The organic phase was washed with sat. NaHCO₃ (2x10 mL) and brine (10 ml), dried over Na₂SO₄, filtered and evaporated resulting 105 mg (78%) of 9:1 mixture of 2-benzylated and 1-benzylated tetrazoles respectively. The isomers were separated by flash chromatography (CH₂Cl₂) and recrystallized (EtOAc:hex) giving compound 25 (81 mg, 60%) as a white solid: mp 129-130 °C; Rf (3% MeOH in CH₂Cl₂) 0.9; ¹H NMR (CDCl₃) 7.97 (d, 1 H, J = 7.2 Hz), 7.90 (s, 1 H), 7.48-7.34 (m, 6 H), 7.26-7.20 (m, 1 H), 5.79 (s, 2 H),
5.02 (br s, 1 H), 4.11-4.00 (m, 1 H), 2.08-1.96 (m, 2 H), 1.76-1.56 (m, 4 H),
1.54-1.46 (m, 2 H); 13C NMR (CDCl3) 164.8, 153.7, 151.4, 133.3, 129.8,
129.0, 128.9, 128.6, 128.3, 123.7, 123.6, 120.2, 56.8, 53.0, 33.1, 23.5;
Anal. calcd for C20H2N5O2: C, 66.10; H, 5.82; N, 19.27; Found C, 65.71; H,
5.85; N, 19.28.

Example 26

Methyl 3-(cyclopentylcarbamoyloxy)benzoate (26). This compound was
synthesized and worked up as described for 1e using methyl 3-
hydroxy benzoate (1.0 g, 6.6 mmol, 100 mol-%) and cyclopentyl isocyanate
(900 µL, 7.9 mmol, 120 mol-%) as starting materials. Purification by flash
chromatography (30% EtOAc in hex) and recrystallization (EtOAc:hex)
gave 26 (1.36 g, 79%) as colourless crystals: mp 112-114 °C; Rf (10% Et2O
in CH2Cl2) 0.5; 1H NMR (CDCl3) 7.85 (d, 1 H, J = 7.6 Hz), 7.78 (s, 1 H), 7.39
(t, 1 H, J = 7.9 Hz) 7.34-7.29 (m, 1 H), 5.53 (br d, 1 H, J = 7.0 Hz), 4.08-
3.97 (m, 1 H), 3.89 (s, 3 H), 2.01-1.91 (m, 2 H), 1.72-1.40 (m, 6 H); 13C
NMR (CDCl3) 166.2, 153.6, 150.9, 131.1, 128.9, 126.2, 126.0, 122.6, 52.8,
52.0, 32.7, 23.3; Anal. calcd for C14H11NO2: C, 63.87; H, 6.51; N, 5.32;
Found C, 63.96; H, 6.30; N, 5.39.

Example 27

Methyl 3-(cyclohexylcarbamoyloxy)benzoate (27). This compound was
synthesized and worked up as described for 1e using methyl 3-
hydroxy benzoate (230 mg, 1.5 mmol, 100 mol-%) and cyclohexyl isocy-
anate (330 µL, 2.6 mmol, 175 mol-%) as starting materials. Recrystallization
(EtOAc:hex) gave 27 (400 mg, quant.) as white crystals: mp 131-132
°C; Rf (10% Et2O in CH2Cl2) 0.5; 1H NMR (CDCl3) 7.87 (d, 1 H, J = 7.7
Hz), 7.80 (t, 1 H, J = 1.9 Hz), 7.42 (t, 1 H, J = 7.9 Hz), 7.36-7.31 (m, 1 H),
4.95 (d, 1 H, J = 7.0 Hz), 3.91 (s, 3 H), 3.64-3.51 (m, 1 H), 2.07-1.98 (m, 2
H), 1.80-1.70 (m, 2 H), 1.67-1.60 (m, 1 H), 1.45-1.32 (m, 2 H), 1.29-1.17
(m, 3 H); 13C NMR (CDCl3) 166.3, 153.3, 151.0, 131.3, 129.1, 126.3, 126.2,
Example 28

3-Cyanophenyl cyclohexylcarbamate (28). This compound was synthesized and worked up as described for 1e using 3-cyanophenol (1.05 g, 8.9 mmol, 100 mol-%) and cyclohexyl isocyanate (4.6 ml, 36 mmol, 400 mol-%) as reagents. Purification with flash chromatography (38 % EtOAc in hex) and recrystallization (EtOAc:hex) gave compound 28 (1.47 g, 68 %) as white needles: mp 117-120 °C; Rf 0.56 (50% EtOAc in hex); ¹H NMR (CDCl₃) 7.50-7.38 (m, 4 H), 4.98 (d, 1 H, J = 7.3), 3.61-3.51 (m, 1 H), 2.05-1.98 (m 2 H), 1.80-1.71 (m, 2 H), 1.68-1.60 (m, 1 H), 1.44-1.33 (m, 2 H), 1.29-1.15 (m, 3 H); ¹³C NMR (CDCl₃) 152.6, 151.2, 130.1, 128.8, 126.5, 125.3, 118.0, 113.2, 50.3, 33.1, 25.3, 24.7; Anal. calcd for C₁₄H₁₆N₂O₂: C, 68.83; H, 6.60; N, 11.47; Found C, 68.89; H, 6.55; N, 11.36.

Example 29

3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenol (29a). This compound was synthesized in two different methods:

Method 1: 3-cyanophenol (237 mg, 2.0 mmol, 100 mol-%), 2-amino-2-methylpropanol (450 µl, 4.0 mmol, 200 mol-%) and bismuth trifluoromethylsulfonate (64.5 mg, 0.1 mmol, 5 mol-%) were placed in a 10 ml CEM® microwave pressure tube irradiated for three times. The resulting mixture was diluted with EtOAc and purified with flash chromatography (40% EtOAc in hex).

Method 2: 3-cyanophenol (237 mg, 2.0 mmol, 100 mol-%), 2-amino-2-methylpropanol (450 µl, 4.0 mmol, 200 mol-%) and bismuth thfluoromethylsulfonate (64.5 mg, 0.1 mmol, 5 mol-%) were placed in a 5 ml flask and refluxed for 3 hrs. Crops from both reactions were combined and recrystallized (toluene) giving 29a (190 mg, 25% overall yield). Correct compound
was determined by NMR and melting point analysis: mp 159-161 °C; Rf 0.28 (65 % EtOAc in hex).

3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl cyclopentylcarbamate (29b). This compound was synthesized and worked up as described for 1e using 29a (100 mg, 0.5 mmol, 100 mol-%) cyclopentyl isocyanate (290 µL, 2.6 mmol, 500 mol-%) as starting materials. Purification with flash chromatography (10% EtOAc in CH₂Cl₂) and recrystallization (EtOAc:hex) gave 29b (73 mg, 48%) as white needles: mp 139-141 °C; Rf (10 % EtOAc in CH₂Cl₂) 0.27; ¹H NMR (DMSO-c/δ) 7.76 (d, 1 H, J = 7.7 Hz), 7.70 (s, 1 H), 7.38 (dd, J = 7.9 Hz), 7.23 (d, 2 H, J = 8.1 Hz), 4.98 (d, 1 H, J = 6.4 Hz), 4.10 (s, 2 H), 4.07-4.00 (m, 1 H), 2.06-1.98 (m, 2 H), 1.76-1.69 (m, 2 H), 1.66-1.60 (m, 2 H), 1.53-1.44 (m, 2 H), 1.37 (s, 6 H); ¹³C NMR (DMSO-c/δ) 151.3, 153.7, 150.9, 129.4, 129.1, 125.0, 124.5, 121.6, 79.1, 67.6, 53.0, 33.1, 28.4, 23.5; Anal. calcd for C₁₇H₂₂N₂O₃; C, 67.53; H, 7.33; N, 9.26; Found C, 67.35; H, 7.40; N, 9.38.

Example 30

(S)-3-(4-Methyl-4,5-dihydrooxazol-2-yl)phenol (30a). Zinc chloride (48 mg, 0.35 mmol, 10 mol-%) was melted in a 50 ml two-neck flask under high vacuum. 3-Cyanophenol (413 mg, 3.46 mmol, 100 mol-%) and chlorobenzene (10 ml) were added and heated up to reflux under argon atmosphere. (S)-2-Aminopropanol (510 µL, 6.5 mmol, 190 mol-%) was added and the mixture was refluxed for 22 hours. The mixture was cooled to rt and filtered through a pad of silica with EtOAc and purified with flash chromatography (33% EtOAc in hex) and recrystallized (EtOAc:Hex) giving 30a (317 mg, 52%) as white needles: mp 125-126 0°C; Rf (50 % EtOAc in hex) 0.31; [α]D²⁰ 3.82 (C= 0.5, CDCl₃); ¹H NMR (CDCl₃) 9.45 (bs, 1 H), 7.45 (dd, 1 H, J = 2.3, 1.6 Hz), 7.30 (td, 1 H, J = 7.7, 1.3 Hz), 7.18 (t, 1 H, J = 7.9 Hz), 6.95 (ddd, 1 H, J = 8.1, 2.5, 1.0 Hz), 4.53 (dd, 1 H, J = 9.4, 8.0 Hz), 4.45-4.36 (m, 1 H), 3.96 (t, 1 H, J = 7.9 Hz), 1.33 (d, 3 H, J = 6.6 Hz); ¹³C NMR (CDCl₃) 164.6,
156.9, 129.6, 128.0, 119.8, 119.5, 115.1, 74.2, 61.2, 21.1; Anal. calcd for C_{10}H_{11}NO_2: C, 67.78; H, 6.26; N, 7.90; Found C, 67.88; H, 5.85; N, 7.72.

**Example 31**

(S)-3-(4-methyl-4,5-dihydrooxazol-2-yl)phenyl cyclopentylcarbamate

This compound was synthesized and worked up as described for 30b using 30a (100 mg, 0.56 mmol, 100 mol-%) and cyclopentyl isocyanate (300 µl, 2.7 mmol, 470 mol-%) as starting materials. Purification with flash chromatography (50% EtOAc in hex) and recrystallization (EtOAc:hex) gave 30b (83 mg, 51%) as white crystals: mp 139-142 °C; Rf (15% EtOAc in CH₂Cl₂) 0.33; [α]_D^{20} -53.8 (c= 0.5, CHCl₃); ^1H NMR (CDCl₃) 7.77 (d, 1 H, J = 7.7 Hz), 7.70 (s, 1 H), 7.38 (t, 1 H, J = 8.0 Hz), 7.24 (d, 1 H, J = 8.1 Hz), 5.04 (d, 1 H, J = 6.6 Hz), 4.51 (dd, 1 H, J = 9.3, 8.1 Hz), 4.41-4.32 (m, 1 H), 4.09-4.00 (m, 1 H), 3.94 (t, 1 H, J = 7.9 Hz), 2.96-2.97 (m, 2 H), 1.75-1.56 (m, 4 H), 1.53-1.44 (m, 2 H), 1.35 (d, 3 H, J = 6.6 Hz); ^13C NMR (CDCl₃) 162.7, 160.1, 153.7, 151.0, 129.1, 125.0, 124.6, 121.6, 74.1, 62.0, 53.0 (rotam. 52.1), 33.1 (rotam. 33.6), 23.5, 21.4; Anal. calcd for C_{16}H_{20}N_{2}O_{3}: C, 66.65; H, 6.99; N, 9.72; Found C, 66.68; H, 7.15; N, 9.82.

(S)-3-(4-Methyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate

This compound was synthesized and worked up as described for 30b using 30a (85 mg, 0.48 mmol, 100 mol-%) and cyclohexyl isocyanate (120 µl, 0.94 mmol, 200 mol-%) as starting materials. Purification with flash chromatography (50% EtOAc in hex) and recrystallization (EtOAc:hex) gave 31 (94 mg, 65%) as white crystals: mp 133-135 °C; Rf (50% EtOAc in hex) 0.40; [α]_D^{20} -48.9 (c= 0.5, CHCl₃); ^1H NMR (CDCl₃) 7.77 (d, 1 H, J = 7.7 Hz), 7.70 (s, 1 H), 7.38 (t, 1 H, J = 7.9 Hz), 7.26-7.23 (m, 1 H), 4.92 (d, 1 H, J = 7.3 Hz), 4.51 (dd, 1 H, J = 9.2, 8.2 Hz), 4.42-4.32 (m, 1 H), 3.94 (t, 1 H, J = 7.9 Hz), 3.61-3.51 (m, 1 H), 2.05-1.97 (m, 2 H), 1.78-1.70 (m, 2 H), 1.66-1.59 (m, 1 H), 1.43-1.32 (m, 2 H), 1.35 (d, 3 H, J = 6.6 Hz), 1.28-1.15 (m, 3 H); ^13C NMR (CDCl₃) 162.8, 153.4, 151.0, 129.1 (2C), 125.0, 124.6,
Example 32

(R)-3-(4-methyl-4,5-dihydrooxazol-2-yl)phenol (32a). This compound was synthesized and worked up as described for 30a using (R)-2-amino-1-propanol (440 μL, 5.6 mmol, 200 mol-%) as starting material. Purification with flash chromatography (40% EtOAc in hex) and recrystallization (EtOAc:hex) gave 32a (283 mg, 57%) as white needles: mp 126-127 °C; Rf (50% EtOAc in hex) 0.19; [α]D²⁰ -45.6 (c= 0.5, CHCl₃); ¹H NMR (CDCl₃) 9.46 (bs, 1 H), 7.44 (dd, 1 H, J = 2.4, 1.6 Hz), 7.29 (td, 1 H, J = 7.7, 1.3 Hz), 7.18 (t, 1 H, J = 7.9 Hz), 6.95 (ddd, 1 H, J = 8.1, 2.6, 1.0 Hz), 4.53 (dd, 1 H, J = 9.5, 8.1 Hz), 4.45-4.36 (m, 1 H), 3.96 (t, 1 H, J = 7.9 Hz), 1.33 (d, 3 H, J = 6.6 Hz); ¹³C NMR (CDCl₃) 164.5, 156.9, 129.6, 127.9, 119.8, 119.5, 115.0, 74.2, 61.1, 21.1; Anal. calcd for C₁₀H₁₁NO₂: C, 76.78; H, 6.26; N, 7.90; Found C, 76.89; H, 6.10; N, 7.90.

(R)-3-(4-Methyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (32b). This compound was synthesized and worked up as described for 31 using 32a (100 mg, 0.56 mmol, 100 mol-%) and cyclohexyl isocyanate (150 μL, 1.2 mmol, 210 mol-%) as starting materials. Purification with flash chromatography (50% EtOAc in hex) and recrystallization (EtOAc:hex) gave 32b (46 mg, 27%) as white crystals: mp 133-134 °C; Rf (50% EtOAc in hex) 0.24; [α]D²⁰ 44.6 (c= 0.5, CDCl₃); ¹H NMR (CDCl₃) 7.77 (d, 1 H, J = 7.7 Hz), 7.70 (m, 1 H), 7.38 (t, 1 H, J = 7.9 Hz), 7.24 (dd, 1 H, J = 8.1, 1.4 Hz), 4.94 (d, 1 H, J = 7.4 Hz), 4.51 (dd, 1 H, J = 9.3, 8.1 Hz), 4.42-4.32 (m, 1 H), 3.94 (t, 1 H, J = 7.9 Hz), 3.60-3.50 (m, 1 H), 2.07-1.96 (m, 2 H), 1.78-1.70 (m, 2 H), 1.66-1.57 (m, 1 H), 1.43-1.32 (m, 2 H), 1.35 (d, 3 H, J = 6.6 Hz), 1.27-1.15 (m, 3 H); ¹³C NMR (CDCl₃) 162.8, 153.4, 151.0, 129.1 (2C), 124.9, 124.6, 121.6, 74.1, 62.0, 50.1, 33.2, 25.4, 24.7, 21.4; Anal. calcd for C₁₇H₂₂N₂O₃: C, 67.53; H, 7.33, N, 9.26; Found C, 67.63; H, 7.33; N, 9.17.
Example 33

(S)-3-(4-Benzyl-4,5-dihydrooxazol-2-yl)phenol (33a). This compound was synthesized and worked up as described for 30a using (S)-2-amino-3-phenyl-1-propanol (970 mg, 6.41 mmol, 190 mol-%) as starting material. Purification with flash chromatography (40 % EtOAc in hex) and recrystallization (EtOAc:hex) gave 33a (446 mg, 52%) as a white waxy solid: mp 109-111 °C; Rf (10 % Et2O in CH2Cl2) 0.14; [a]D20 38.5 (c= 0.5, CHCl3); 1H NMR (CDCl3) 7.92 (s, 1 H), 7.50 (dd, 1 H, J = 2.4, 1.5 Hz), 7.39 (td, 1 H, J = 7.7, 1.2 Hz), 7.30-7.18 (m, 6 H), 6.98 (ddd, 1 H, J = 8.1, 2.6, 1.0 Hz), 4.65-4.57 (m, 1 H), 4.35 (t, 1 H, J = 9.0 Hz), 4.17 (dd, 1 H, J = 8.6, 7.2 Hz), 3.23 (dd, 1 H, J = 13.7, 4.9 Hz), 2.75 (dd, 1 H, J = 13.7, 9.0 Hz); 13C NMR (CDCl3) 164.8, 156.4, 137.6, 129.7, 129.3, 128.6, 128.3, 126.6, 120.2, 119.4, 115.2, 72.0, 67.2, 41.5; Anal. calcd for C16H15NO2: C, 75.87; H, 5.97; N, 5.53; Found C, 75.79; H, 5.74; N, 5.50.

(S)-3-(4-Benzyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (33b). This compound was synthesized and worked up as described for 31 using 33a (143 mg, 0.57 mmol, 100 mol-%) as starting material. Purification with flash chromatography (30% EtOAc in hex) and recrystallization (EtOAc:hex) gave 33b (120 mg, 56%) as white crystals: mp 152-155 °C; Rf 0.46 (10% Et2O in CH2Cl2); [a]D20 5.8 (c= 0.5, CHCl3); 1H NMR (CDCl3) 7.78 (d, 1 H, J = 7.8), 7.70 (t, 1 H, J = 1.8 Hz), 7.39 (t, 1 H, J = 8.0 Hz), 7.33-7.21 (m, 6 H), 4.93 (d, 1 H, J = 7.6 Hz), 4.62-4.54 (m, 1 H), 4.34 (t, 1 H, J = 8.9 Hz), 4.13 (dd, 1 H, J = 8.3, 7.5 Hz), 3.61-3.51 (m, 1 H), 3.23 (dd, 1 H, J = 13.7, 5.1 Hz), 2.72 (dd, 1 H, J = 13.7, 8.9 Hz), 2.05-1.97 (m, 2 H), 1.78-1.70 (m, 2 H), 1.66-1.61 (m, 1 H), 1.43-1.32 (m, 2 H), 1.28-1.14 (m, 3 H); 13C NMR (CDCl3) 163.3, 153.3, 151.0, 137.9, 129.2, 129.2, 129.0, 128.6, 126.5, 125.0, 124.7, 121.6, 71.9, 67.9, 50.2, 41.8, 33.2, 25.4, 24.7; Anal. calcd for C23H28N2O3: C, 72.99; H, 6.92; N, 7.40; Found C, 73.17; H, 6.70; N, 7.37.

Example 34
(S)-3-(4-(1H-Indol-3-yl)methyl)-4,5-dihydrooxazol-2-yl)phenol (34a). This compound was synthesized and worked up as described for 30a using (R)-2-amino-3-phenyl-1-propanol (768 mg, 5.08 mmol, 200 mol-%) as starting material. Purification with flash chromatography (33% EtOAc in hex) and recrystallization (EtOAc:hex) gave 34a (267 mg, 41%) as a white waxy solid: mp 108-111 0°C; Rf 0.21 (15% Et₂O in CH₂Cl₂); [α]D²⁰ -40.0 (c= 0.5, CHCl₃); 1H NMR (CDCl₃) 8.50 (bs, 1H), 7.50 (dd, 1H, J = 2.3, 1.5 Hz), 7.36 (td, 1H, J = 7.7, 1.1 Hz), 7.29-7.18 (m, 6H), 6.97 (ddd, 1H, J = 8.2, 2.5, 0.9 Hz), 4.66-4.57 (m, 1H), 4.34 (t, 1H, J = 9.0 Hz), 4.17 (dd, 1H, J = 8.5, 7.3 Hz), 3.24 (dd, 1H, J = 13.7, 4.8 Hz), 2.75 (dd, 1H, J = 13.7, 9.2 Hz); 13C NMR (CDCl₃) 165.0, 156.6, 137.5, 129.7, 129.3, 128.6, 128.2, 126.6, 126.1, 119.5, 115.2, 72.0, 67.0, 41.4; Anal. calcd for C₃₆H₃₅NO₂: C, 75.87; H, 5.97; N, 5.53; Found C, 75.96; H, 5.71; N, 5.25.

(R)-3-(4-Benzyl-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (34b). This compound was synthesized and worked up as described for 31 using 34a (178 mg, 0.70 mmol, 100 mol-%) as starting material. Purification with flash chromatography (10% Et₂O in CH₂Cl₂) and recrystallization (EtOAc:hex) gave 34b (152 mg, 57%) as white crystals: mp 153-155 0°C; Rf 0.38 (13% Et₂O in CH₂Cl₂); [α]D²⁰ -7.4 (c= 0.5, CHCl₃); 1H NMR (CDCl₃) 7.78 (d, 1H, J = 7.7 Hz), 7.7 (m, 1H), 7.39 (t, 1H, J = 8.0 Hz), 7.33-7.20 (m, 6H), 4.93 (d, 1H, J = 8.0 Hz), 4.62-4.53 (m, 1H), 4.33 (t, 1H, J = 8.9 Hz), 4.13 (dd, 1H, J = 8.3, 7.5 Hz), 3.62-3.50 (m, 1H), 3.23 (dd, 1H, J = 13.7, 5.1 Hz), 2.71 (dd, 1H, J = 13.7, 8.9 Hz), 2.05-1.97 (m, 2H), 1.77-1.70 (m, 2H), 1.66-1.58 (m, 1H), 1.43-1.32 (m, 2H), 1.28-1.14 (m, 3H); 13C NMR (CDCl₃) 163.3, 153.3, 151.0, 137.9, 129.2, 129.2, 129.0, 128.5, 126.5, 125.0, 124.7, 12.1, 71.9, 67.9, 50.1, 41.8, 33.2, 25.4, 24.7; Anal. calcd for C₃₆H₃₅NO₂: C, 72.99; H, 6.92; N, 7.40; Found C, 73.09; H, 7.09; N, 7.44.

Example 35

(S)-3-(4-((1H-Indol-3-yl)methyl)-4,5-dihydrooxazol-2-yl)phenol (35a). This compound was synthesized and worked up as described for 30a using
(S)-tryptophanol (326 mg, 1.71 mmol, 120 mol-%) as starting material. Recrystallization (EtOAc:hex) gave 35a (140 mg, 35%) as a gray powder: mp 183-186 °C; Rf (50% EtOAc in hex) 0.20; [α]₀²₀ 58.7 (c = 0.3, MeOH); ¹H NMR (DMSO-d/e) 10.85 (bs, 1 H), 9.68 (s, 1 H), 7.59 (d, 1 H, J = 7.9 Hz), 7.33 (d, 1 H, J = 8.0 Hz), 7.31 -7.19 (m, 4 H), 7.06 (td, 1 H, J = 7.5, 1.1 Hz), 6.98 (td, 1 H, J = 7.4, 1.0 Hz), 6.93-6.89 (m, 1 H), 4.64-4.55 (m, 1 H), 4.38 (dd, 1 H, J = 9.4, 8.4 Hz), 4.07 (t, 1 H, J = 7.9 Hz), 3.13 (dd, 1 H, J = 14.8, 4.9 Hz), 2.82 (dd, 1 H, J = 14.6, 8.1 Hz); ¹³C NMR (DMSO-d/e) 162.1, 157.3, 136.1, 129.6, 128.8, 127.5, 123.4, 120.9, 118.5, 118.5, 118.4, 118.3, 114.4, 111.3, 110.4, 71.7, 66.6, 31.0; Anal. calcd for C₁₈H₁₆N₂O₂: C, 73.95; H, 5.52; N, 9.58; Found C, 73.60; H, 5.43; N, 9.39.

(S)-3-(4-((1H-indol-3-yl)methyl)-4,5-dihydrooxazol-2-yl)phenyl cyclohexylcarbamate (35b). This compound was synthesized and worked up as described for 31 using 35a (crude, 70 mg, 0.24 mmol, 100 mol-%) as starting material. Flash chromatography (10% Et₂O in CH₂Cl₂) and recrystallization (EtOAc: hex) gave 35b (35 mg, 35%) as white crystals: mp 149-151 °C; Rf 0.23 (10% Et₂O in CH₂Cl₂); [α]₀²₀ 21.9 (c = 0.5, CDCl₃); ¹H NMR (CDCl₃) 8.11 (bs, 1 H), 7.79 (d, 1 H, J = 7.8 Hz), 7.72 (s, 1 H), 7.66 (d, 1 H, J = 7.8 Hz), 7.41-7.33 (m, 2 H), 7.20 (td, 1 H, J = 7.5, 1.1 Hz), 7.13 (td, 1 H, J = 7.4, 1.0 Hz), 7.28-7.24 (m, 1 H), 7.04 (d, 1 H, J = 2.2 Hz), 4.94 (d, 1 H, J = 7.8 Hz), 4.75-4.67 (m, 1 H), 4.33 (t, 1 H, J = 8.9 Hz), 4.15 (t, 1 H, J = 7.9 Hz), 3.62-3.51 (m, 1 H), 3.36 (dd, 1 H, J = 14.5, 4.6 Hz), 2.88 (dd, 1 H, J = 14.6, 8.9 Hz), 2.05-1.97 (m, 2 H), 1.78-1.70 (m, 2 H), 1.67-1.58 (m, 1 H), 1.43-1.32 (m, 2 H), 1.28-1.14 (m, 3 H); ¹³C NMR (CDCl₃) 163.2, 153.4, 151.0, 136.2, 129.2 (2C), 127.7, 125.0, 124.6, 122.4, 122.1, 121.6, 119.5, 118.8, 112.0, 111.1, 72.3, 67.0, 50.2, 33.2, 31.3, 25.4, 24.7; Anal. calcd for C₂₅H₂₇N₃O₃: C, 71.92; H, 6.52; N, 10.06; Found C, 71.58; H, 6.32; N, 10.05.

Example 36

(£)-ethyl 2-(1-(3-hydroxyphenyl)ethylidene)hydrazinecarboxylate (36a). A mixture of 3’-hydroxyacetophenone (4.09 g, 30 mmol, 1 equiv.), ethyl
carbazate (3.28 g, 31.5 mmol, 1.05 equiv.) and p-TsOH (280 mg, 1.5 mmol, 0.05 equiv.) in dry toluene (100 ml) was refluxed overnight under Dean-Stark conditions. Evaporation of solvent under reduced pressure gave crude product, which was washed with diethyl ether to remove excess reactants giving 4.63 g (69%) of the title compound as pale brown solid. \(^1\)H NMR (DMSO-de, 500.1 MHz) 10.08 (bs, 1H), 7.26-7.14 (m, 3H), 6.80 (ddd, \(J = 7.9, 2.4, 0.9\) Hz), 4.20 (q, \(J = 7.1\) Hz, 2H), 2.19 (s, 3H), 1.29 (t, \(J = 7.1\) Hz, 3H) ppm; \(^{13}\)C NMR (DMSO-\(d_6\), 125.1 MHz) 158.1, 155.1, 140.6, 130.1, 126.4, 118.0, 116.9, 113.5, 61.4, 15.5, 14.8 ppm; MS (ES\(^{+}\)) calcd. for C\(_{11}\)H\(_8\)N\(_2\)O\(_3\) 222.25; found: [M + H\(^{+}\)] 223.25.

### 3-(1,2,3-Thiadiazol-4-yl)phenol (36b)

Hydrazone 36a (3.5 g, 15.7 mmol, 1 equiv.) was stirred overnight with an excess amount of thionyl chloride (35 ml, 30 equiv.) at room temperature. The remaining thionyl chloride was evaporated under reduced pressure. The reaction crude was filtered through a plug of silica (PE/EtOAc 1:1) and then recrystallized from CHCl\(_3\) giving 2.0 g (71%) of product as pale yellow solid. \(^1\)H NMR (DMSO-\(d_6\), 500.1 MHz) 9.76 (bs, 1H), 9.59 (s, 1H), 7.60-7.57 (m, 2H), 7.38 (dd, \(J = 7.9, 7.9\) Hz, 1H) ppm; \(^{13}\)C NMR (DMSO-\(d_6\), 125.1 MHz): 162.9, 158.9, 134.0, 132.8, 131.3, 118.9, 117.3, 114.8 ppm; Anal. calcd for C\(_8\)H\(_6\)N\(_2\)O\(_3\): C, 53.92; H, 3.39; N, 15.72; found: C, 53.45; H, 3.42; N, 15.41; MS (ES\(^{+}\)) calcd. for C\(_8\)H\(_6\)N\(_2\)O\(_3\)S 178.21; found: [M + H\(^{+}\)] 179.28.

### 3-(1,2,3-Thiadiazol-4-yl)phenyl cyclohexyl carbamate (36c)

To a mixture of 3-(1,2,3-thiadiazol-4-yl)phenol (36b, 178.21 mg, 1 mmol) in dry toluene (3 ml) was added cyclohexyl isocyanate (140 \(\mu\)l, 1.1 mmol, 1.1 equiv.). The reaction mixture was gently refluxed overnight and monitored by TLC. After refluxing the reactants 5 h, a further amount of isocyanate (0.5 equiv.) was added. The reaction mixture was cooled and solvent evaporated. Purification by recrystallization (EtOAc/Hex 1:2) gave the product as pale crystals (200 mg, 66%). Mp. 137.6-138.8 °C; \(^1\)H NMR (CDCl\(_3\), 500.1 MHz) 8.65 (s, 1H), 7.89 (d, \(J = 7.9\) Hz, 1H), 7.83 (s, 1H), 7.49 (pt, \(J = 8.1\) Hz, 7.9 Hz, 1H), 7.22 (d, \(J = 8.1\) Hz, 1H), 4.97 (d, \(J = 7.3\) Hz, 1H), 3.62-3.55 (m, 1H), 2.48-2.38 (m, 1H), 1.29-1.19 (m, 1H).
2.05-2.02 (m, 2H), 1.75 (dt, J = 13.5, 3.9 Hz, 2H), 1.66-1.17 (m, 6H) ppm; 13C NMR (CDCl₃, 125.1 MHz) 162.0, 153.4, 151.7, 132.0, 130.5, 130.0, 124.1, 122.6, 120.7, 50.2, 33.2, 25.4, 24.7 ppm; Anal. calcd for C₁₅H₁₇N₃O₂S: C, 59.39; H, 5.65; N, 13.85; found: C, 59.18; H, 5.73; N, 13.53; MS (ES⁺) calcd. for C₁₅H₁₇N₃O₂S 303.39, found: [M + H]⁺ 304.18.

Example 37

3-(1,2,3-Thiadiazol-4-yl)phenyl cyclopentylcarbamate (37). This compound was prepared according to the method described above for 36c. Purification by recrystallization (EtOAc/Hex 1:2) gave the product as white crystals (210 mg, 73%). Mp. 141.2-142.2 0°C; ¹H NMR (CDCl₃, 500.1 MHz) 8.65 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.83 (s, 1H), 7.49 (pt, J = 8.1, 7.9 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 5.04 (d, J = 6.2 Hz, 1H), 4.08 (m, 1H), 2.01-1.76 (m, 2H), 1.68-1.63 (m, 2H), 1.55-1.48 (m, 2H) ppm; ¹³C NMR (CDCl₃, 125.1 MHz) 162.0, 153.7, 151.7, 131.9, 130.5, 130.0, 124.1, 122.7, 120.7, 53.0, 33.1, 23.5 ppm; Anal. calcd for C₁₄H₁₅N₃O₂S: C, 58.11; H, 5.23; N, 14.52; found: C, 57.76; H, 5.27; N, 14.24; MS (ES⁺) calcd. for C₁₄H₁₅N₃O₂S 289.36, found: [M + H]⁺ 290.42.

Example 38

3-(1,2,3-Thiadiazol-4-yl)phenyl butyricarbamate (38). This compound was prepared according to the method described above for 36c. Purification by recrystallization (EtOAc/Hex 1:2) gave the product as pale brown crystals (244 mg, 81%). Mp. 101.6-102.9 0°C; ¹H NMR (CDCl₃, 500.1 MHz) 8.65 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.83 (s, 1H), 7.49 (pt, J = 8.1, 7.9 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 5.07 (s, 1H), 3.32-3.28 (m, 2H), 1.61-1.55 (m, 2H), 1.45-1.38 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H) ppm; ¹³C NMR (CDCl₃, 125.1 MHz) 162.0, 154.3, 151.6, 131.9, 130.6, 130.0, 124.1, 122.6, 120.6, 41.0, 31.8, 19.8, 13.7 ppm; Anal. calcd for C₁₃H₁₅N₃O₂S: C, 56.30; H, 5.45; N, 15.15; found: C, 55.95; H, 5.46; N, 15.14.
Example 39

3-(1,2,3-Thiadiazol-4-yl)phenyl benzylcarbamate (39). This compound was prepared according to the method described above for 36c. Purification by flash chromatography (EtOAc/PE 1:4) gave the product as white solid (263 mg, 84%). Mp. 109.0-109.6 °C; ^1H NMR (CDCl₃, 500.1 MHz) 8.66 (s, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.86 (s, 1H), 7.51 (pt, J = 8.0 Hz, 1H), 7.40-7.32 (m, 6H), 5.40 (s, 1H), 4.49 (d, J = 6.0 Hz, 2H) ppm; ^13C NMR (CDCl₃, 125.1 MHz) 161.9, 154.4, 151.6, 137.8, 132.0, 130.6, 130.0, 128.7, 127.69, 127.65, 124.2, 122.6, 120.6, 45.3 ppm; Anal. calcd for C₁₆H₁₃N₂O₂S: C, 61.72; H, 4.21; N, 13.50; found: C, 61.58; H, 4.32; N, 12.95; MS (ES⁺) calcd for C₁₆H₁₃N₂O₂S 311.36, found: [M + H]⁺ 312.33.

Example 40

3-(1,2,3-Thiadiazol-4-yl)phenyl phenylcarbamate (40). This compound was prepared according to the method described above for 36c. Purification by flash chromatography (EtOAc/PE 1:4) and recrystallization (EtOAc/Hex 1:3) gave the product as white crystals (130 mg, 44%). Mp. 155.4-156.0 °C; ^1H NMR (CDCl₃, 500.1 MHz) 8.66 (s, 1H), 7.94-7.90 (m, 2H), 7.53 (pt, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.35 (pt, J = 7.4 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 7.07 (s, 1H) ppm; ^13C NMR (CDCl₃, 125 MHz); Anal. calcd for C₁₅H₁₁N₂O₂S: C, 60.59; H, 3.73; N, 14.13. Found: C, 61.65; H, 3.95; N, 13.76.

Example 41

3-(1,2,3-Thiadiazol-4-yl)phenyl isopropylcarbamate (41). To a mixture of 3-(1,2,3-thiadiazol-4-yl)phenol (36b, 89.1 mg, 0.5 mmol) and triethyl amine (0.42 µL, 0.06 equiv.) in toluene (2 mL) was added isopropyl isocyanate (54 µL, 1.1 mmol, 1.1 equiv.). The reaction mixture was stirred at 80 °C until phenol could not be detected on TLC. The reaction mixture was cooled and solvent evaporated. Purification by flash chromatography (EtOAc/PE 1:1) and recrystallization (EtOAc/Hex 1:2) gave the product as white crys-
tals (87.6 mg, 67 %). Mp. 130.4-131.4 °C; 1H NMR (CDCl₃, 500.1 MHz) 8.65 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 7.48 (pt, J = 8.1, 7.9 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 4.96 (d, J = 5.7 Hz, 1H), 3.90 (m, 1H), 1.25 (d, J = 6.6 Hz, 6H) ppm; 13C NMR (CDCl₃, 125.1 MHz) 162.1, 153.4, 151.7, 132.0, 130.5, 130.0, 124.1, 122.7, 120.7, 43.5, 22.9 ppm; Anal. calcd for C₁₂H₁₃N₃O₂S: C, 54.56; H, 4.96; N, 15.82; MS (ES⁺) calcd for C₁₂H₁₃N₃O₂S 263.32, found: [M + H]+ 264.26.

Example 42

3-(1,2,3-Thiadiazol-4-yl)phenyl dodecylcarbamate (42). This compound was prepared according to the method described above for 41, but in 0.28 mmol scale. Purification by flash chromatography (EtOAc/PE 1:3) and recrystallization (EtOAc/Hex 1:2) gave the product as white crystals (98.8 mg, 90 %). Mp. 106.4-107.4 °C; 1H NMR (CDCl₃, 500.1 MHz) 8.65 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H), 7.50 (pt, J = 8.1, 7.8 Hz , 1H), 7.23 (d, J = 8.1 Hz, 1H), 5.06 (s, 1H), 3.29 (dt, J = 6.7, 6.7 Hz , 2H), 1.62-1.59 (m, 2H), 1.37-1.27 (m, 20H), 0.88 (t, J = 6.7 Hz , 3H) ppm; 13C NMR (CDCl₃, 125.1 MHz) 162.1, 154.3, 151.7, 132.0, 130.4, 130.1, 124.2, 122.7, 120.7, 41.4, 31.9, 29.8, 29.62, 29.58, 29.5, 29.3, 29.3, 26.8, 22.7, 14.1 ppm; Anal. calcd for C₂₁H₃₁N₃O₂S: C, 64.75; H, 8.02; N, 10.79; found: C, 64.67; H, 8.26; N, 10.75; MS (ES⁺) calcd for C₂₁H₃₁N₃O₂S 389.56, found: [M + H]+ 390.28.

Example 43

3-(1,2,3-Thiadiazol-4-yl)phenyl hexylcarbamate (43). This compound was prepared according to the method described above for 41, but in 1.0 mmol scale. Purification by flash chromatography (EtOAc/PE 1:2) gave the product as white solid (284 mg, 93 %). Mp. 100.8-101.3 °C; 1H NMR (CDCl₃, 500.1 MHz) 8.65 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.83 (s, 1H), 7.49 (pt, J = 8.0 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 5.07 (s, 1H), 3.31-3.27 (m, 2H), 1.62-1.30 (m, 8H), 0.91 (t, J = 6.7 Hz, 3H) ppm; 13C NMR (CDCl₃, 125.1 MHz) 162.1, 154.3, 151.7, 132.0, 130.4, 130.1, 124.2, 122.7, 120.7,
4.1.4, 3.1.4, 29.8, 26.4, 22.5, 14.0 ppm. Anal. calcd for C_{15}H_{19}N_{3}O_{2}S: C, 8.02; H, 8.02; N, 10.79. Found: C, 64.67; H, 8.26; N, 10.75.

Example 44

3-(1,2,3-Thiadiazol-4-yl)phenyl (4-phenyl-butyl)carbamate (44). This compound was prepared according to the method described above for 41, but in 1.0 mmol scale. Purification by flash chromatography (EtOAc/PE 1:1) gave the product as white solid (294 mg, 83%). M.p. 112.2-113.2 °C; {^1}H NMR (CDCl_{3}, 500.1 MHz) 8.64 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.82 (s, 1H), 7.49 (pt, J = 8.0 Hz, 1H), 7.31 -7.28 (m, 2H), 7.23-7.19 (m, 4H), 5.1 (s, 1H), 3.32 (dt, J = 6.6, 6.6 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 1.76-1.61 (m, 4H) ppm. {^{13}}C NMR (CDCl_{3}, 125.1 MHz) 162.0, 154.3, 151.7, 142.0, 132.0, 130.4, 128.38, 128.37, 125.9, 124.2, 122.6, 120.7, 41.1, 35.4, 29.4, 28.5 ppm. Anal. calcd for C_{19}H_{19}N_{3}O_{2}S: C, 58.99; H, 6.27; N, 13.76; found: C, 58.84; H, 6.27; N, 13.87.

Example 45

3-(2-Methoxyethoxymethoxy)-benzonitrile (45a). To an ice cold mixture of 3-cyanophenol (1.79 g, 15 mmol, 1 equiv.) and triethyl amine (2.7 ml, 19.5 mmol, 1.3 equiv.) in dry THF (60 ml) was added dropwise methoxyethoxymethyl chloride (2.7 ml, 24.0 mmol, 1.6 equiv.) under argon atmosphere. The mixture was allowed to cool to room temperature and then refluxed overnight. The mixture was poured to ethyl acetate, washed with water and brine and dried (Na_{2}SO_{4}). Evaporation of solvent under reduced pressure gave 2.74 g (88%) of the product as white solid. {^1}H NMR (CDCl_{3}, 500.1 MHz) 7.39-7.34 (m, 2H), 7.30-7.27 (m, 2H), 5.28 (s, 2H), 3.83-3.81 (m, 2H), 3.56-3.54 (m, 2H), 3.37 (s, 3H) ppm.

N-Hydroxy-3-(2-methoxy-ethoxymethoxy)-benzamidine (45b). A mixture of MEM-protected 3-cyanophenol 45a (2.74 g, 13.0 mmol, 1 equiv.), hydroxylamine hydrochloride (1.36 g, 19.5 mmol, 1.5 equiv.) and triethyl amine (2.7 ml, 19.5 mmol, 1.5 equiv.) in EtOH was stirred overnight at room tem-
perature. The solvent was evaporated under reduced pressure and the re-
action crude was dissolved in EtOAc/CH$_2$Cl$_2$ mixture. The organic phase
was washed with brine and dried over anhydrous Na$_2$SO$_4$. Evaporation of
solvent gave the crude product, which was purified by flash chromatogra-
phy (PE/EtOAc 1:1) giving 2.4 g (77%) of the pure product as viscous liq-
uid. $^1$H NMR (DMSO-de, 500.1 MHz) 9.67 (s, 1H), 7.37-7.30 (m, 3H), 7.06
(d, $J = 7.5$ Hz, 2H), 5.81 (s, 2H), 5.30 (s, 2H), 3.77-3.75 (m, 2H), 3.52-3.49
(m, 2H), 3.00 (s, 3H) ppm.

**N-Acetoxy-3-(2-methoxy-ethoxymethoxy)-benzamidine (45c).** To an ice
cold solution of 45b (673 mg, 2.8 mmol, 1 equiv.) and triethyl amine (0.5
ml, 3.6 mmol, 1.3 equiv.) in CHCl$_3$ was added dropwise acetyl chloride (0.2
ml, 2.8 mmol, 1 equiv.). The solution was stirred at room temperature for 1
h and then washed with brine, dried (Na$_2$SO$_4$) and solvent evaporated. Pu-
rification by flash chromatography (PE/EtOAc 1:2) gave 0.42 g (54%) of the
title compound. $^1$H NMR (CDCl$_3$, 500.1 MHz) 7.37-7.31 (m, 3H), 7.18-7.15
(m, 1H), 5.28 (s, 2H), 5.24 (bs, 2H), 3.83-3.81 (m, 2H), 3.56-3.54 (m, 2H)
3.36 (s, 3H), 2.25 (s, 3H) ppm.

**3-[3-(2-Methoxyethoxymethoxy)-phenyl]-5-methyl-1,2,4-oxadiazole
(45d).** Acetylated amidoxime 45c (420 mg, 1.5 mmol, 1 equiv.) was dis-
solved in dry THF (5 ml) and solution of TBAF (47.3 mg, 0.15 mmol, 0.1
equiv.) in THF was added dropwise under argon atmosphere. The reaction
was stirred at rt for 3 hours and then poured into ethyl acetate and washed
with water and brine. The organic layer was dried (Na$_2$SO$_4$) and evaporated
giving 396 mg (100%) of the title compound as yellowish liquid. The prod-
uct was used as such for the preparation of 45e. $^1$H NMR (CDCl$_3$, 500.1
MHz) 7.73 (s, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.39 (pt, $J = 7.9$ Hz, 1H), 7.19
(d, $J = 8.3$ Hz, 1H), 5.33 (s, 2H), 3.86-3.84 (m, 2H), 3.58-3.56 (m, 2H), 3.37
(s, 3H), 2.65 (s, 3H) ppm.

**3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenol (45e).** The compound 45d (396
mg, 1.5 mmol, 1 equiv.) in CH$_2$Cl$_2$ (6 ml) was treated with anhydrous ZnBr$_2$
(1.69 g, 7.5 mmol, 5 equiv.), and the mixture was stirred overnight at room
temperature. The solvent was decanted and the solid washed with 1:1 mixture EtOAc/CH$_2$C1$_2$. The combined organic phases were washed with sat. NaHCO$_3$, brine and water, and dried with anhydrous Na$_2$SO$_4$. Evaporation of solvent gave the crude product, which was purified by recrystallization giving 130.2 mg (49%) of the title compound. $^1$H NMR (CDCl$_3$, 500.1 MHz) 7.63 (d, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.35 (pt, J = 8.0 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 2.66 (s, 3H) ppm.

**3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl cyclohexylcarbamate (45f).** To a mixture of 3-(5-methyl-1,2,4-oxadiazol-3-yl)phenol (45e, 44.0 mg, 0.25 mmol, 1 equiv.) and thethyl amine (catalytic amount, 1 small drop) in dry toluene (2 ml) was added cyclohexyl isocyanate (60 µl, 0.5 mmol, 2 equiv.). The reaction mixture was gently refluxed for 2.5 hours. The reaction mixture was cooled and solvent evaporated. Purification by flash chromatography (EtOAc/Pet 1:2) gave the product as pale crystals (67.0 mg, 89%). Mp. 169.2-170.0 °C; $^1$H NMR (CDCl$_3$, 500.1 MHz) 7.89 (d, J = 7.6 Hz, 1H), 7.83 (s, 1H), 7.45 (pt, J = 7.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 4.99 (s, 1H), 3.57 (m, 1H), 2.64 (s, 3H), 2.02-2.00 (m, 2H), 1.75-1.73 (m, 2H), 1.63-1.61 (m, 1H), 1.42-1.16 (m, 5H); $^{13}$C NMR (CDCl$_3$, 125.1 MHz) 176.6, 167.8, 153.3, 151.4, 129.7, 128.0, 124.5, 124.0, 120.7, 50.2, 33.2, 25.4, 24.7, 12.3 ppm; Anal. calcd for C$_6$H$_{19}$N$_3$O$_3$: C, 63.77; H, 4.36; N, 13.94; found: C, 63.21; H, 6.49; N, 13.53.

**Example 46**

**N-Cyclopentylpropionyloxy-3-(2-methoxy-ethoxymethoxy)-benzamidine (46a).** To an ice cold solution of 45b (563 mg, 2.3 mmol, 1 equiv.) and triethyl amine (0.4 ml, 3.0 mmol, 1.3 equiv.) in CHCl$_3$ (20 ml) was added dropwise cyclopentylpropionyl chloride (0.4 ml, 2.3 mmol, 1 equiv.). The solution was stirred at room temperature for 1 h and then washed with brine, dried (Na$_2$SO$_4$) and solvent evaporated. Purification by flash chromatography (PE/EtOAc 1:2) gave 247 mg (30%) of the title compound. $^1$H NMR (CDCl$_3$, 500.1 MHz) 7.37-7.31 (m, 3H), 7.18-7.15 (m, 1H),
5.30 (s, 2H), 5.13 (bs, 2H), 3.83-3.81 (m, 2H), 3.57-3.55 (m, 2H) 3.37 (s, 3H), 2.52 (t, J = 7.7 Hz, 2H), 1.88-1.50 ... (m, 1H), 2.95 (t, J = 7.4 Hz, 2H), 1.84-1.15 (m, 21 H) ppm; 13C NMR (CDCl3, 125.1 MHz) 180.2, 167.7, 153.3,

3-[3-(2-Methoxyethoxymethoxy)-phenyl]-5-(2-cyclopentyl-ethyl)-1,2,4-oxadiazole (46b). Acetylated amidoxime 46a (247 mg, 0.7 mmol, 1 equiv.) was dissolved in dry THF (2 ml) and solution of TBAF (22 mg, 0.7 mmol, 1 equiv.) in THF was added dropwise under argon atmosphere. The reaction was stirred overnight at room temperature and then poured into ethyl acetate and washed with water and brine. The organic layer was dried (Na2SO4) and evaporated giving 191 mg (86%) of the title compound as viscous liquid. 1H NMR (CDCl3, 500.1 MHz) 7.74-7.70 (m, 2H), 7.38 (pt, J = 8.1 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 5.33 (s, 2H), 3.85-3.83 (m, 2H), 3.58-3.56 (m, 2H), 3.37 (s, 3H), 2.95 (t, J = 7.6 Hz, 2H), 1.86-1.15 (m, 11H) ppm.

S-^-^-cyclopentyl-ethylJ-i^^-oxadiazol-S-yOphenol (46c). The compound 46b (191 mg, 0.6 mmol, 1 equiv.) in CH2Cl2 (2 ml) was treated with anhydrous ZnBr2 (631 mg, 2.8 mmol, 5 equiv.), and the mixture was stirred overnight at room temperature. The solvent was decanted and the solid washed with 1:1 mixture EtOAc/CH2Cl2. The combined organic phases were washed with sat. NaHCO3, brine and water, and dried with anhydrous Na2SO4. Evaporation of solvent gave 72.2 mg (47%) of the title compound.

1H NMR (CDCl3, 500.1 MHz) 7.66 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.35 (pt, J = 8.0 Hz, 1H), 7.0 (d, J = 8.2 Hz, 1H), 2.96 (t, J = 7.7 Hz, 2H), 1.90-1.15 (m, 11H) ppm; 13C NMR (CDCl3, 125.1 MHz) 180.3, 168.0, 156.0, 130.3, 128.3, 120.0, 118.2, 114.1, 39.6, 32.9, 32.3, 26.0, 25.1 ppm.

3-(5-(2-cyclopentyl-ethyl)-1,2,4-oxadiazol-3-yl)phenyl cyclohexylcarbamate (46d). This compound was prepared according to the method described above for 45f. Purification by flash chromatography (EtOAc/PE 1:1) and recrystallization (EtOAc/Hex 1:3) gave the product as white crystals (44.2 mg, 46 %). Mp. 125.2-1 25.9 0C; 1H NMR (CDCl3, 500.1 MHz) 7.90 (d, J = 7.7 Hz, 1H), 7.84 (s, 1H), 7.45 (pt, J = 8.0 Hz, 1H), 7.28 (d, J = 9.3 Hz, 1H), 4.94 (d, J = 7.4 Hz, 1H), 3.60-3.54 (m, 1H), 2.95 (t, J = 7.4 Hz, 2H), 1.84-1.15 (m, 21 H) ppm; 13C NMR (CDCl3, 125.1 MHz) 180.2, 167.7, 153.3,
Example 47

N-trimethylacetoxyl-3-(2-methoxy-ethoxymethoxy)-benzamidine (47a).

To an ice cold solution of 45b (721 mg, 3.0 mmol, 1 equiv.) and thethyl amine (0.5 ml, 3.9 mmol, 1.3 equiv.) in CHCl₃ (30 ml) was added dropwise trimethyacetyl chloride (0.4 ml, 3.0 mmol, 1 equiv.). The solution was stirred at room temperature for 2.5 h and then washed with brine, dried (Na₂SO₄) and solvent evaporated. Purification by flash chromatography (PE/EtOAc 1:2) gave 666 mg (68%) of the title compound. ¹H NMR (CDCl₃, 500.1 MHz) 7.37-7.36 (m, 2H), 7.32 (pt, J = 8.1 Hz, 1H), 7.17-7.15 (m, 1H), 5.28 (s, 2H), 5.05 (bs, 2H), 3.82-3.80 (m, 2H), 3.56-3.54 (m, 2H), 3.13 (s, 3H), 1.33 (s, 9H) ppm.

3-[3-(2-Methoxyethoxymethoxy)-phenyl]-5-tert-butyl-1,2,4-oxadiazole (47b). Acetylated amidoxime 47a (666 mg, 2.1 mmol, 1 equiv.) was dissolved in dry THF (6 ml) and solution of TBAF (66 mg, 0.21 mmol, 0.1 equiv.) in THF was added dropwise under argon atmosphere. The reaction was stirred at room temperature for 3 hours and then poured into ethyl acetate and washed with water and brine. The organic layer was dried (Na₂SO₄) and evaporated giving 525 mg (81%) of the title compound as viscous liquid. ¹H NMR (CDCl₃, 500.1 MHz) 7.75-7.72 (m, 2H), 7.38 (pt, J = 8.0 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 5.33 (s, 2H), 3.85-3.84 (m, 2H), 3.58-3.56 (m, 2H), 3.38 (s, 3H), 1.49 (s, 9H) ppm.

3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)phenol (47c). The compound 47b (525 mg, 1.7 mmol, 1 equiv.) in CH₂Cl₂ (1.5 ml) was treated with anhydrous ZnBr₂ (1.91 g, 8.5 mmol, 5 equiv.), and the mixture was stirred overnight at room temperature. The solvent was decanted and the solid washed with 1:1 mixture EtOAc/CH₂Cl₂. The combined organic phases were washed with sat. NaHCO₃, brine and water, and dried with anhydrous
Na₂SO₄. Evaporation of solvent gave and the purification by flash chromatography (Hex/EtOAc 1:1) gave 86.0 mg (24%) of the title compound. ¹H NMR (CDCl₃, 500.1 MHz) 7.74 (d, J = 7.7 Hz, 1H), 7.64 (s, 1H), 7.42 (pt, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 1.57 (s, 9H) ppm.

3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)phenyl cyclohexylcarbamate (47d).

This compound was prepared according to the method described above for 45f. Purification by flash chromatography (EtOAc/Hex 1:2) and recrystallization (EtOAc/Hex 1:2) gave the product as white crystals (28.0 mg, 20%). ¹H NMR (CDCl₃, 500.1 MHz) 7.92 (d, J = 7.7 Hz, 1H), 7.85 (s, 1H), 7.45 (pt, J = 7.9 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 4.92 (s, 1H), 3.61-3.54 (m, 1H), 2.04-2.02 (m, 2H), 1.76-1.61 (m, 3H), 1.49 (s, 9H), 1.40-1.35 (m, 2H), 1.27-1.19 (m, 3H) ppm. ¹³C NMR (CDCl₃, 125.1 MHz) 186.3, 167.6, 153.3, 151.4, 129.6, 128.4, 124.3, 124.1, 120.8, 50.2, 33.6, 33.2, 28.4, 25.4, 24.7 ppm.

Example 48

3-[3-(2-Methoxyethoxymethoxy)-phenyl]-1,2,4-oxadiazole-5-carboxylic acid ethyl ester (48a). To an ice cold solution of 45b (721 mg, 3.0 mmol, 1 equiv.) and triethyl amine (0.5 ml, 3.9 mmol, 1.3 equiv.) in CHCl₃ (30 ml) was added dropwise ethyl chlorooxoacetate (0.3 ml, 3.0 mmol, 1 equiv.). The solution was stirred overnight at room temperature and then washed with brine, dried (Na₂SO₄) and solvent evaporated. Purification by flash chromatography (PE/EtOAc 1:2) gave 193 mg (20%) of the title compound. ¹H NMR (CDCl₃, 500.1 MHz) 7.81-7.79 (m, 2H), 7.42 (pt, J = 8.0 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 5.33 (s, 2H), 4.57 (q, J =7.2 Hz, 2H), 3.86-3.84 (m, 2H), 3.58-3.56 (m, 2H), 3.38 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H) ppm.

3-(3-Hydroxy-phenyl)-1,2,4-oxadiazole-5-carboxylic acid ethyl ester (48b). The above prepared compound 48a (193 mg, 0.6 mmol, 1 equiv.) in CH₂Cl₂ (3 ml) was treated with anhydrous ZnBr₂ (673 mg, 3.0 mmol, 5 equiv.), and the mixture was stirred overnight at room temperature. The solvent was decanted and the solid washed with 1:1 mixture EtOAc/CH₂Cl₂.
The combined organic phases were washed with sat. NaHCO₃, brine and water, and dried with anhydrous Na₂SO₄. Evaporation of solvent and the purification by flash chromatography (Hex/EtOAc 1:1) gave 95.0 mg (68%) of the title compound. ¹H NMR (CDCl₃, 500.1 MHz) 7.74 (d, J = 7.7 Hz, 1H), 7.62 (s, 1H), 7.38 (pt, J = 8.0 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 5.03 (bs, 1H), 4.57 (q, J = 7.2 Hz, 2H), 1.49 (t, J =7.2 Hz, 3H) ppm.

3-(3-Cyclohexylcarbamoyloxy-phenyl)-1,2,4-oxadiazole-5-carboxylic ethyl ester (48c). This compound was prepared according to the method described above for 45f. Purification by flash chromatography (EtOAc/Hex 1:2) gave the product as white solid (61.0 mg, 68%). ¹H NMR (CDCl₃, 500.1 MHz) 7.99 (d, J = 7.7 Hz, 1H), 7.93 (s, 1H), 7.49 (pt, J = 8.0 Hz, 1H), 7.33 (d, J =8.1 Hz, 1H), 4.94 (d, J = 7.4 Hz, 1H), 4.57 (q, J = 7.1 Hz, 2H), 3.60-3.55 (m, 1H), 2.04-2.02 (m, 2H), 1.77-1.74 (m, 2H), 1.65-1.64 (m, 1H), 1.49 (t, J = 7.1 Hz, 3H), 1.43-1.18 (m, 5H) ppm; ¹³C NMR (CDCl₃, 125.1 MHz) 168.9, 166.6, 154.1, 153.2, 151.5, 129.9, 126.8, 125.3, 124.3, 121.1, 64.0, 50.2, 33.2, 25.4, 24.7, 14.2, 14.0 ppm.

Example 49

3-Hydroxybenzamide (49a). 3-Cyanophenol (295 mg, 2.48 mmol, 100 mol-%) and NaBO₃·4 H₂O (1.146 mg, 7.45 mmol, 300 mol-%) in H₂O (8 ml) were heated to 50 °C and MeOH (14 ml) was added until mixture was clear. The mixture was stirred at 50 °C for 70 hours and excess MeOH was evaporated and the pH of remaining mixture was adjusted to 5 with cone. HCl (aq). Mixture was extracted with CH₂Cl₂ (12 ml) and with EtOAc (5x1.5 ml). Organic phases were combined, washed with brine (25 ml) and dried over Na₂SO₄. Filtering and evaporation of solvents gave 49a as spectroscopically pure white solid (183 mg, 54%): mp 165-168 °C; Rf (50% EtOAc in hex) 0.10.
3-Carbamoylphenyl cyclohexylcarbamate (49b). This compound was synthesized and worked up as described for 1e using compound 49a (140 mg, 1.0 mmol, 100 mol-%) and cyclohexyl isocyanate (0.28 mL, 2.2 mmol, 220 mol-%) as starting materials and DMF (4 mL) as solvent. Purification by flash chromatography (10% MeOH in CH₂Cl₂) and recrystallization (EtOAc) gave 49b (40 mg, 15%) as white crystals; mp 169-179 °C; Rf (15% MeOH in CH₂Cl₂) 0.36; 1H NMR (DMSO-d₆) 8.01 (s, 1H), 7.78 (d, 1H, J = 7.9 Hz), 7.71 (d, 1H, J = 7.8 Hz), 7.58 (s, 1H), 7.44 (m, 2H), 7.26-7.24 (m, 1H), 3.36-3.28 (m, 1H), 1.86-1.80 (m, 2H), 1.74-1.68 (m, 2H), 1.59-1.53 (m, 1H), 1.30-1.20 (m, 4H), 1.17-1.08 (m, 1H); 13C NMR (DMSO-d₆) 167.8, 154.2, 151.9, 136.3, 130.0, 125.6, 124.8, 121.7, 50.7, 33.4, 26.0, 25.4; Anal. calcd for C₁₄H₁₈N₂O₃; C, 64.10; H, 6.92; N, 10.68; Found C, 64.32; H, 6.97; N, 10.47

Example 50

4-(3-Methoxy-phenyl)-oxazole (50a). 2-Bromo-1-(3-methoxyphenyl)-ethanone (230 mg, 1.0 mmol, 100 mol-%) and formamide (0.4 mL, 10 mmol, 1000 mol-%) were placed in a 10 mL microwave tube and irradiated (300W) until the temperature reached 100 °C (took 30 sec) and kept at that temperature for 30 sec. The irradiation was repeated and the mixture was partitioned between EtOAc (30 mL) and water (30 mL). The organic phase was dried over Na₂SO₄, filtered and evaporated. Purification by flash chromatography (10% EtOAc in hex) and recrystallization (Hex/CH₂Cl₂) gave 50a (90 mg, 51%) as light yellow crystals; mp. 81-82 °C; Rf (EtOAc) 0.6; 1H NMR (CDCl₃) 7.93-7.92 (m, 2H), 7.34-7.32 (m, 1H), 7.32-7.30 (m, 2H), 6.90-6.85 (m, 1H), 3.85 (s, 3H); 13C NMR (CDCl₃) 160.0, 151.2, 140.3, 133.9, 132.0, 129.8, 117.9, 114.1, 110.8, 55.2; Anal. calcd for C₁₀H₉NO₂; C, 68.56; H, 5.18; N, 8.00; Found C, 68.04; H, 5.10; N, 7.74; HRMS (ESI) [M+Na+] calcd for C₁₀H₉NO₂ 198.0531; Found 198.0524.

4-(3-Hydroxyphenyl)oxazole (50b). Compound 50a (200 mg, 1.1 mmol, 100 mol-%) and butylpyridinium bromide (490 mg, 2.2 mmol, 200 mol-%)
were placed in a 10 mL microwave tube and irradiated (300W) until the
temperature reached 100 °C (took 30 sec.) and kept at that temperature for
30 sec. Another portion of ionic liquid (430 mg, 2.0 mmol, 180 mol-%) was
added and irradiation was repeated for five times. The mixture was diluted
with CH₂Cl₂ (10 ml) and purified with flash chromatography (CH₂Cl₂). Re-
crystallization (Hex/CH₂Cl₂/MeOH) gave light yellow crystals (100 mg,
56%); mp. 123-124 °C; Rf (10% MeOH in CH₂Cl₂) 0.5; ¹H NMR (DMSO-CD₃) 9.53 (s, 1H), 8.56 (d, 1H, J = 0.9 Hz), 8.43 (d, 1H, J = 0.9 Hz), 7.23-7.20
(m, 3H), 6.76-6.70 (m, 1H); ¹³C NMR (DMSO-CD₃) 157.7, 152.5, 139.3,
135.0, 131.9, 129.8, 116.1, 115.0, 112.0; Anal. calcd for C₉H₇NO₂: C, 67.07; H, 4.38; N, 8.69; Found C, 66.89; H, 4.30; N, 8.32.

3-(Oxazol-4-yl)phenyl cyclohexylcarbamate (50c).

This compound was synthesized and worked up as described for 1e using
compound 50b (100 mg, 0.62 mmol, 100 mol-%) and cyclohexyl isocyanate
(115 mg, 0.93 mmol, 150 mol-%) as starting materials. Purification by flash
chromatography (1% MeOH in CH₂Cl₂) and recrystallization (EtOAc/hex)
gave 50c (160 mg, 90%) as white crystals; mp 139.5-140.5 °C; Rf (10% MeOH in CH₂Cl₂) 0.4; ¹H NMR (CDCl₃) 7.93 (d, 2H, J = 6.9 Hz), 7.58 (d,
1H, J = 7.8 Hz), 7.53 (s, 1H), 7.39 (t, 1H, J = 7.9 Hz), 7.10 (dd, 1H, J = 8.1,
1.6 Hz), 4.95 (br d, 1H, J = 6.8 Hz), 3.64-3.52 (m, 1H), 2.08-1.97 (m, 1H),
1.80-1.70 (m, 2H), 1.67-1.58 (m, 1H), 1.44-1.32 (m, 2H), 1.30-1.14 (m, 3H);
¹³C NMR (CDCl₃) 153.5, 151.5, 151.2, 139.8, 134.0, 132.0, 129.6, 122.3,
121.4, 118.9, 50.1, 33.2, 25.4, 24.7; Anal. calcd for C₉H₇NO₂: C, 67.12; H,
6.34; N, 9.78; Found C, 67.05; H, 6.61; N, 9.71.

Example 51

2-(3-Methoxy-phenyl)-thiazole (51a). To a mixture of 3-methoxy ben-
zothioamide (420 mg, 2.5 mmol, 100 mol-%) in THF (2.5 mL) was added 2-
bromoacetaldehyde diethyl acetal (0.5 mL, 3.3 mmol, 132 mol-%) and the
mixture placed in an CEM 10 mL glass tube. The mixture was irradiated
with CEM microwave apparatus for 30 min (power 300 W, T_max = 115 °C).
The mixture was purified by flash chromatography (1% EtOAc in toluene) giving 51a (200 mg, 42%) as an oil: Rf (10% EtOAc in toluene) 0.5; 1H NMR (CDCl₃) 7.85 (d, 1H, J = 3.3 Hz), 7.55 (dd, 1H, J = 2.4, 1.7 Hz) 7.51 (ddd, 1H, J = 7.7, 1.5, 1.0 Hz) 7.33 (t, 1H, J = 8.1 Hz), 7.30 (d, 1H, J = 3.3 Hz), 6.96 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz), 3.86 (s, 3H); 13C NMR (CDCl₃) 168.2, 159.9, 143.5, 134.7, 129.9, 119.1, 118.8, 116.2, 111.0, 55.3.

2-(3-Hydroxy-phenyl)-thiazole (51b). Compound 51a (170 mg, 0.9 mmol, 100 mol-%) and 1-butyl-3-methylimidazolium bromide (700 mg, 3.2 mmol, 350 mol-%) were irradiated with CEM microwave apparatus in an open vessel for 2x30 sec (power 300 W, air cooling, T_max 100 °C). The reaction mixture was partitioned between EtOAc (30 ml) and water (30 ml). The organic phase was dried over Na₂SO₄, filtered and evaporated. Resulting crude product was purified by flash chromatography (25% EtOAc in hex) and recrystallized (EtOAc/hex) giving 51b (70 mg, 44%) as a white solid: mp 141.1-143 °C, Rf (35% EtOAc in hex) 0.5; 1H NMR (CDCl₃) 7.87 (d, 1H, J = 3.2 Hz), 7.52 (ddd, 1H, J = 2.5, 1.6, 0.4 Hz), 7.49 (ddd, 1H, J = 7.7, 1.6, 1.0 Hz), 7.34 (d, 1H, J = 3.3 Hz), 7.31 (ddd, 1H, J = 8.1, 7.7, 0.4 Hz), 6.92 (ddd, 1H, J = 8.1, 1.6, 1.0 Hz), 5.68 (br s).

3-(Thiazol-2-yl)phenyl cyclohexylcarbamate (51c). This compound was synthesized and worked up as described for 1e using compound 51b (30 mg, 0.23 mmol, 100 mol-%) and cyclohexyl isocyanate (43 mg, 0.35 mmol, 150 mol-%) as starting materials. Purification by flash chromatography (1-2% MeOH in CH₂Cl₂) and recrystallization (EtOAc/hex) gave 51c (35 mg, 50%) as white crystals; mp 147 °C; Rf (EtOAc) 0.8; 1H NMR (CDCl₃) 7.86 (d, 1H, J = 3.2 Hz), 7.81-7.74 (m, 2H), 7.42 (t, 1H, J = 7.9 Hz) 7.34 (d, 1H, J = 3.2 Hz), 7.21 (dd, 1H, J = 8.1, 1.6 Hz) 4.98, (br d, 1H, J = 7.3 Hz), 3.67-3.52 (m, 1H), 2.10-1.98 (m, 2H), 1.80-1.70 (m, 2H), 1.68-1.58 (m, 2H), 1.45-1.32 (m 2H), 1.30-1.14 (M, 3H); 13C NMR (CDCl₃) 167.4, 153.3, 151.6, 143.7, 134.8, 129.8, 123.3, 123.2, 119.8, 119.1, 50.2, 33.2, 25.4, 24.7, Anal. calcd for C₁₆H₁₈N₂O₂S: C, 63.55; H, 6.00; N, 9.26; Found C, 63.38; H, 5.78; 9.14.
Example 52

4-(3-Methoxyphenyl)-1H-imidazole (52a). 2-Bromo-1-(3-methoxyphenyl)-
ethanone (530 mg, 2.3 mmol, 100 mol-%) and formamide (2 ml, 50 mmol,
2200 mol-%) were placed in a 10 ml flask and heated up until the tempera-
ture (T_o) reached 165 °C (took 90 min.) The mixture was cooled to rt and
partitioned between EtOAc (30 ml) and water (50 ml). The aqueous layer
was collected and made basic (pH 12) with NaOH (35%) and extracted with
EtOAc (2x50 ml). The organic phase was dried (Na_2SO_4), filtered and
evaporated to dryness. Recrystallization (MeOH/H_2O, 40:1) of crude prod-
uct gave 52a (340 mg, 85%) as light yellow crystals: mp. 121-122 °C; Rf
(EtOAc) 0.1; ^1H NMR (CDCl_3) 11.16 (br s, 1 H), 7.68 (d, 1 H, J = 1.0 Hz),
7.34 (d, 1 H, J = 1.0 Hz), 7.31 - 7.23 (m, 3 H), 6.80 - 6.76 (m, 1 H), 3.74 (s, 3
H); ^13C NMR (CDCl_3) 159.9, 138.4, 135.7, 134.3, 129.8, 117.4, 115.9,
112.7, 110.2, 55.1; Anal. calcd for C_{10}H_{10}N_2O: C, 68.95; H, 5.79; N, 16.08;
Found C, 68.83; H, 5.43; 16.32.

4-(3-Hydroxyphenyl)-1H-imidazole (52b). Compound 52a (650 mg, 3.73
mmol, 100 mol-%) was dissolved to dry CH_2Cl_2 (37 ml) and cooled to -78
°C. BBr_3 (1 M in CH_2Cl_2, 6.5 ml, 175 mol-%) was added dropwise during 15
min. The mixture was stirred at -78 °C for 25 min and another portion of
BBr_3 (1 M in CH_2Cl_2, 4.7 ml, 125 mol-%) was added. The mixture was al-
lowed to warm to rt and stirred overnight. The mixture was diluted with wa-
ter (150 ml) and the organic phase was separated. The aqueous phase was
neutralized with 35% NaOH (pH adjusted to 6) and extracted with
EOAc (80+70+2x50 ml). The combined organic phases were dried
(Na_2SO_4), filtered and evaporated resulting in 52b (350 mg, 59%) as solid:
Rf (20% MeOH in CH_2Cl_2) 0.1; ^1H NMR (CDCl_3) 9.35 (br s, 1 H), 7.81 (br s,
1 H), 7.53 (br s, 1 H), 7.19 - 7.11 (m, 3 H), 6.62 (dt, 1 H, J = 7.1 , 2.1 Hz).

S\(^\text{I}\)CyclohexylcarbamoylJ-IH-imidazolo^ylJphenyl cyclohexylcar-
bamate (52c). This compound was synthesized and worked up as de-
scribed for 1e using compound 52b (140 mg, 0.87 mmol, 100 mol-%) and
cyclohexyl isocyanate (120 mg, 0.87 mmol, 100 mol-%) as starting materials. Purification by flash chromatography (25-70% EtOAc in hex) and recrystallization (EtOAc/hex) gave 52c (154 mg, 43%) as a white solid; mp 158-165 °C; Rf (EtOAc) 0.55; 1H NMR (CDCl₃) 8.06 (d, 1H, J = 1.2 Hz), 7.54-7.44 (m, 3H), 7.28 (t, 1H, J = 7.8 Hz), 6.97 (dd, 1H, J = 8.0, 1.6 Hz), 6.22 (d, 1H, J = 7.6 Hz), 5.12 (d, 1H, J = 8.1 Hz), 3.82-3.71 (m, 1H), 3.63-3.51 (m, 1H), 2.10-1.95 (m, 4H), 1.82-1.71 (m, 4H), 1.71-1.59 (m, 2H), 1.45-1.31 (m, 4H), 1.31-1.14 (m, 6H); 13C NMR (CDCl₃) 154.0, 151.2, 148.0, 141.9, 136.2, 134.5, 129.4, 122.0, 120.6, 118.4, 111.4, 50.4, 50.3, 33.2, 32.9, 25.4, 25.3, 24.9, 24.7; Anal. calcd for C₂₃H₃₀N₄O₃: C, 67.29; H, 7.37; N, 13.65; Found C, 67.30; H, 7.37; 13.63.

Example 53
Methyl 3-hydroxybenzimidate hydrochloride (53a). To a mixture of 3-cyanophenol (1840 mg, 15.5 mmol, 100 mol-%) in dry CH₂Cl₂ (36 ml) was added dry MeOH (3.2 ml, 79 mmol, 510 mol-%) and the mixture was bubbled with HCl gas in an ice bath. The mixture was stirred at 2 °C for 3 days and solvents were evaporated. Filtering and washing with dry Et₂O gave 53a as a white powder (2.67 g, 92%): 1H NMR (DMSO-d₆) 11.68 (bs, 1H), 10.34 (s, 1H), 7.57-7.53 (m, 1H), 7.46-7.41 (m, 2H), 7.24-7.21 (m, 1H), 4.27 (s, 3H).

(S)-Methyl 2-(3-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxylate (53b). (S)-Serine methylester hydrochloride (127 mg, 0.82 mmol, 100 mol-%) was suspended in dry CH₂Cl₂ and Et₃N was added (180 µl, 1.28 mmol, 160 mol-%) followed by 53a (153 mg, 0.82, 100 mol-%) and the mixture was refluxed overnight. Solvent was evaporated and remaining solid partitioned between H₂O (10 ml) and EtOAc (15 ml). Organic phase was washed with H₂O (10 ml). Aqueous phases were combined and back-washed with EtOAc (2x15 ml). Organic phases were combined, washed with brine (20 ml), dried over Na₂SO₄, filtered and evaporated. Purification by flash chromatography (twice, 70% EtOAc:hex, then 5% MeOH:CH₂Cl₂)
gave compound 53b as an oil (122 mg, 68%); Rf (60% EtOAc:hex) 0.28; [α]D20 64.5 (c = 1.8, CDCl3); 1H NMR (CDCl3) 8.16 (s, 1H), 7.43-7.42 (m, 1H), 7.40 (d, 1H, J = 7.8 Hz), 7.20 (t, 1H, J = 7.9 Hz), 6.97 (ddd, 1H, J = 8.2, 2.5, 0.9 Hz), 4.96 (dd, 1H, J = 10.7, 7.9 Hz), 4.69 (dd, 1H, J = 8.7, 7.9), 4.59 (dd, 1H, J = 10.7, 8.8 Hz), 3.71 (s, 3H); 13C NMR (CDCl3) 171.4, 170.0, 156.5, 129.6, 127.3, 120.4, 119.8, 115.4, 69.6, 67.8, 52.7; HRMS (ESI): calcd for [M+H+] C11H11NO4: 222.0766, found 222.0759.

(S)-Methyl 2-(3-(cyclohexylcarbamoyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate (53c). This compound was synthesized and worked up as described for 1e using 53b (120 mg, 0.54 mmol, 100 mol-%) and cyclohexyl isocyanate (200 µL, 1.57 mmol, 290 mol-%) as starting materials. Purification by flash chromatography (70% EtOAc:hex) and recrystallization (EtOAc:hex) gave compound 53c as white crystals (141 mg, 75%); mp; Rf (17% Et2O:CH2Cl2) 0.33; [α]D20 72.5 (c = 0.5, CHCl3); 1H NMR (CDCl3) 7.81 (d, 1H, J = 7.8 Hz), 7.75 (s, 1H), 7.39 (t, 1H, J = 7.9 Hz), 7.29-7.26 (m, 1H), 4.94 (dd, 2H, J = 10.5, 8.0); 4.69 (t, 1H, J = 7.8), 4.59 (dd, 1H, J = 10.6, 8.8), 3.82 (s, 3H), 3.59-3.52 (m, 1H), 2.04-1.97 (m, 2H), 1.78-1.70 (m, 2H), 1.67-1.59 (m, 1H), 1.43-1.32 (m, 2H), 1.27-1.16 (m, 3H); 13C NMR (CDCl3) 121.9, 69.6, 68.6, 52.7, 50.1, 33.2, 25.4, 24.7; Anal. calcd for C18H22N2O5: C, 62.42; H, 6.40; N, 8.09; Found C, 62.45; H, 6.12; N, 8.02.

Example 54

(R)-Methyl 2-(3-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxylate (54a). This compound was synthesized and worked up as described for 53b using (R)-serine methylester hydrochloride (125 mg, 0.80 mmol, 100 mol-%) and 53a (150 mg, 0.80 mmol, 100 mol-%) as starting materials. Purification by flash chromatography gave compound 54a as an oil (121 mg, 68%); Rf (70% EtOAc:hex) 0.33; [α]D20 -57.4 (c = 1, CDCl3); 1H NMR (CDCl3) 8.57 (s, 1H), 7.42 (dd, 1H, J = 2.4, 1.6 Hz), 7.38 (app. ddd, 1H), 7.18 (t, 1H, J = 7.9), 6.96 (ddd, 1H, J = 8.2, 2.5, 0.9), 4.96 (dd, 1H, J =
10.7, 7.8), **4.69** (dd, 1H, J = 8.7, 7.9 Hz), 4.58 (dd, 1H, J = 10.7, 8.8), 3.69 (s, 3H); **13**C NMR (CDCl$_3$) 171.3, 167.1, 156.6, 129.6, 127.2, 120.3, 119.8, 115.4, 69.6, 67.7, 52.7; HRMS (ESI): calcd for [M+H$^+$] C$_{11}$H$_{11}$NO$_4$; 222.0766, found 222.0766

**5 (R)-Methyl 2-(3-(cyclohexylcarbamoyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate (54b).** This compound was synthesized and worked up as described for 1e using 54a (120 mg, 0.54 mmol, 100 mol-%) and cyclohexyl isocyanate (200 µL, 1.57 mmol, 290 mol-%) as starting materials. Purification by flash chromatography (70% EtOAc:hex) and recrystallization (EtOAc:hex) gave compound 54b as white crystals (136 mg, 73%); mp: Rp (17% Et$_2$O:CH$_2$Cl$_2$) 0.33; [$\alpha$]$^D_{d0}$ -68.3 (c = 0.5, CHCl$_3$); **1H NMR** (CDCl$_3$) 7.81 (d, 1H, J = 7.8 Hz), 7.75 (s, 1H), 7.39 (t, 1H, J = 8.0 Hz), 7.29-7.26 (m, 1H), 4.95 (dd, 2H, J = 10.5, 8.0 Hz), 4.69 (t, 1H, J = 8.3 Hz), 4.59 (dd, 1H, J = 10.5, 8.8 Hz), 3.82 (s, 3H), 3.60-3.51 (m, 1H), 2.04-1.97 (m, 2H), 1.78-1.70 (m, 2H), 1.67-1.59 (m, 1H), 1.43-1.32 (m, 2H), 1.27-1.16 (m, 3H); **13**C NMR (CDCl$_3$) **13**C-NMR (CDCl$_3$) 171.4, 165.6, 153.3, 151.0, 129.2, 128.1, 125.3, 125.2, 121.9, 69.6, 68.6, 52.7, 50.1, 33.2, 25.4, 24.7; Anal. calcd for C$_{18}$H$_{22}$N$_2$O$_5$: C, 62.42; H, 6.40; N, 8.09; Found C, 62.47; H, 6.15; N, 8.03.

**Example 55**

**Dimethyl 4-(cyclohexylcarbamoyloxy)phthalate (55).** This compound was synthesized and worked up as described for 1e using dimethyl 4-hydroxyphthalate (120 mg, 0.54 mmol, 100 mol-%) and cyclohexyl isocyanate (200 µL, 1.57 mmol, 290 mol-%) as starting materials. Purification by recrystallization (EtOAc:hex) gave compound 55 as white crystals (190 mg, 80%); mp 112-125 0C; Rp (EtOAc) 0.5; **1H NMR** (CDCl$_3$) 7.75 (d, 1H, J = 8.5 Hz), 7.46 (d, 1H, J = 2.1 Hz) 7.32 (dd, 1H, J = 8.5, 2.1 Hz), 5.05 (d, 1H, J = 7.4 Hz) 3.90 (s, 3H), 3.89 (s, 3H), 3.62-3.49 (m, 1H), 2.06-1.95 (m, 2H), 1.80-1.70 (m, 2H), 1.67-1.59 (m, 1H), 1.44-1.30 (m, 2H), 1.28-1.16 (m, 3H); **13**C NMR (CDCl$_3$) 167.5, 167.1, 153.2, 152.4, 133.9, 130.5, 127.8,
123.7, 121.8, 52.7, 52.6, 50.3, 33.1, 25.3, 24.7; Anal. calcd for C_{17}H_{21}NO_{6}: C, 60.89; H, 6.31; N, 4.18; Found C, 60.98; H, 6.38; N, 4.27.

Example 56

3-(/V-hydroxycarbamimidoyl)phenyl cyclohexylcarbamate (56). 3-Cyanophenyl cyclohexylcarbamate (28, 0.95 g, 3.9 mmol, 1 equiv.), hydroxylamine hydrochloride (0.41 g, 5.9 mmol, 1.5 equiv.) and triethyl amine (0.8 ml_, 5.9 mmol, 1.5 equiv.) in EtOH (20 ml_) was added cyclohexyl isocyanate (0.13 ml_, 1.0 mmol, 2 equiv.). The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the reaction crude was dissolved in EtOAc/CH\textsubscript{2}Cl\textsubscript{2} mixture. The organic phase was washed with brine and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. Evaporation of solvent gave the crude product, which was purified by recrystallization (EtOAc/Hex 1:1) giving 314 mg (29%) of the title compound as white crystals. Mp. 154.5-154.8 0C; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500.1 MHz) 9.71 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.41-7.38 (m, 2H), 7.13 (d, J = 7.9 Hz, 1H), 5.86 (s, 1H), 1.88-1.86 (m, 2H), 1.76-1.74 (m, 2H), 1.61-1.59 (m, 1H), 1.35-1.14 (m, 5H) ppm; Anal. calcd for C\textsubscript{14}H\textsubscript{19}N\textsubscript{3}O\textsubscript{3}: C, 60.63; H, 6.91; N, 15.15; found: C, 60.68; H, 6.95; N, 15.14.

Example 57

2-Hydroxyisonicotinic acid methyl ester (57a). A mixture of 2-hydroxyisonicotinic acid (0.28 g, 2.0 mmol, 1 equiv.) and a catalytic amount of concentrated H\textsubscript{2}SO\textsubscript{4} (1 drop) in methanol (8 ml_) was refluxed overnight. Evaporation of solvent gave crude product, which was purified by flash chromatography (EtOAc/MeOH 1:1) giving 0.25 g (82%) of the product as white solid. \textsuperscript{1}H NMR (CH\textsubscript{3}Cl, 500.1 MHz) 13.00 (bs, 1H), 7.44 (d, J = 6.7 Hz, 1H), 7.21 (s, 1H), 6.79 (d, J = 6.7 Hz, 1H), 3.93 (s, 3H) ppm.

2-Cyclohexylcarbamoyloxy-isonicotinic acid methyl ester (57b). To a mixture of 2-hydroxyisonicotinic acid methyl ester (57a, 76.6 mg, 0.5 mmol) and triethyl amine (0.42 \mu_, 0.06 equiv.) in toluene (2 ml_) was added cyclohexyl isocyanate (0.13 ml_, 1.0 mmol, 2 equiv.). The reaction mixture
was stirred overnight at 80 °C. The reaction mixture was cooled and solvent evaporated. Acid free ethyl acetate was added to the crude product and the solvent decanted. Evaporation of solvent gave 56.0 mg (20 %) of the product as white solid. $^1$H NMR (CDCl$_3$, 500.1 MHz) 10.43 (d, $J = 6.3$ Hz, 1H), 8.50 (d, $J = 7.7$ Hz, 1H), 7.22 (d, $J = 1.4$ Hz, 1H), 6.79 (dd, $J = 7.7$, 1.4 Hz, 1H), 3.88-3.81 (m, 1H), 2.00-1.25 (m, 10H) ppm.

**Animals and preparation of rat brain homogenate for FAAH assay.**

Eight-week-old male Wistar rats were used in these studies. All animal experiments were approved by the local ethics committee. The animals lived in a 12-h light/12-h dark cycle (lights on at 0700 h) with water and food available *ad libitum*. The rats were decapitated, whole brains minus cerebellum were dissected and homogenized in one volume (v/w) of ice-cold 0.1 M potassium phosphate buffer (pH 7.4) with a Potter-Elvehjem homogenizer (Heidolph). The homogenate was centrifuged at 10,000 g for 20 min at 4 °C and the resulting supernatant was used as a source of FAAH activity. The protein concentration of the supernatant (7.2 mg/ml) was determined by the method of Bradford with BSA as a standard. $^{34}$ Aliquots of the supernatant were stored at -80 °C until use.

**Animals and preparation of rat cerebellar membranes for MGL assay.**

Four-week-old male Wistar rats were used in these studies. All animal experiments were approved by the local ethics committee. The animals lived in a 12-h light/12-h dark cycle (lights on at 0700 h), with water and food available *ad libitum*. The rats were decapitated, eight hours after lights on (1500 h), whole brains were removed, dipped in isopentane on dry ice and stored at -80 °C. Membranes were prepared as previously described. $^{35}$ Briefly, cerebella (minus brain stem) from eight animals were weighed and homogenized in nine volumes of ice-cold 0.32 M sucrose with a glass Teflon homogenizer. The crude homogenate was centrifuged at low speed
(1000 x g for 10 min at 4°C) and the pellet was discharged. The supernatant was centrifuged at high speed (100,000 x g for 10 min at 4°C). The pellet was resuspended in ice-cold deionized water and washed twice, repeating the high-speed centrifugation. Finally, membranes were resuspended in 50 mM Tris-HCl, pH 7.4 with 1 mM EDTA and aliquoted for storage at -80°C. The protein concentration of the final preparation, measured by the Bradford method, was 11 mg ml⁻¹.

**In vitro assay for FAAH activity.** The endpoint enzymatic assay was developed to quantify FAAH activity with tritium labelled arachidonoylethanolamide [ethanolamine 1⁻³H]. The assay buffer was 0.1 M potassium phosphate (pH 7.4) used and test compounds were dissolved in DMSO (the final DMSO concentration was max 5% v/v). The incubations were performed in the presence of 0.5% (w/v) BSA (essentially fatty acid free). Test compounds were preincubated with rat brain homogenate protein (18 µg) for 10 min at 37°C (60 µl). At the 10 min time point, arachidonoylethanolamide was added so that its final concentration was 2 µM (containing 50 x 10⁻³ µCi of 60 Ci/mmol [³H]AEA) and the final incubation volume was 100 µl. The incubations proceeded for 10 min at 37°C. Ethyl acetate (400 µl) was added at the 20 min time point to stop the enzymatic reaction. Additionally, 100 µl of unlabelled ethanolamine (1 mM) was added as a ‘carrier’ for radioactive ethanolamine. Samples were centrifuged at 16,000 g for 4 min at RT, and aliquots (100 µl) from aqueous phase containing [ethanolamine 1⁻³H] were measured for radioactivity by liquid scintillation counting (Wallac 1450 MicroBeta; Wallac Oy, Finland).

**In vitro assay for MGL activity.** The assay for MGL has been described previously. Briefly, experiments were carried out with preincubations (80 µl, 30 min at 25°C) containing 10 µg membrane protein, 44 mM Tris-HCl (pH 7.4), 0.9 mM EDTA, 0.5% (wt/vol) BSA and 1.25% (vol/vol) DMSO as a solvent for inhibitors. The preincubated membranes were kept at 0°C just
prior to the experiments. The incubations (90 min at 25°C) were initiated by adding 40 µl of preincubated membrane cocktail, in a final volume of 400 µl. The final volume contained 5 µg membrane protein, 54 mM Tris-HCl (pH 7.4), 1.1 mM EDTA, 100 mM NaCl, 5 mM MgCl₂, 0.5% (wt/vol) BSA and 50 µM of L-7250. At time-points of 0 and 90 min, 100 µl-samples were removed from the incubation, acetonitrile (200 µl) was added to stop the enzymatic reaction and the pH of the samples was simultaneously decreased to 3.0 with phosphoric acid (added to acetonitrile) to stabilize compound 1 against acyl migration to 1(3)-AG. Samples were centrifuged at 23,700 g for 4 min at RT prior to HPLC analysis of the supernatant.

**HPLC method.** The analytical HPLC was performed as previously described. Briefly, the analytical HPLC system consisted of a Merck Hitachi (Hitachi Ltd., Tokyo, Japan) L-7100 pump, D-7000 interface module, L-7455 diode-array UV detector (190 - 800 nm, set at 211 nm) and L-7250 programmable autosampler. The separations were accomplished on a Zorbax SB-C18 endcapped reversed-phase precolumn (4.6 x 12.5 mm, 5 µm) and column (4.6 x 150 mm, 5 µm) (Agilent, U.S.A). The injection volume was 50 µl. A mobile phase mixture of 28% phosphate buffer (30 mM, pH 3.0) in acetonitrile was used at a flow rate of 2.0 ml min⁻¹. Retention times were 5.8 min for 1, 6.3 min for 1(3)-AG and 10.2 min for arachidonic acid. The relative concentrations of 1, 1(3)-AG and arachidonic acid were determined by the corresponding peak areas. This was justified by the equivalence of response factors for the studied compounds, and was supported by the observation that the sum of the peak areas was constant throughout the experiments.

**Data analyses.** The results from the enzyme inhibition experiments are presented as mean ± 95% confidence intervals of at least three independent experiments performed in duplicate. Data analyses for the dose-
response curves were calculated as non-linear regressions using Graph-Pad Prism 4.0 for Windows.

The structures of compounds and their inhibition potencies for FAAH and MGL-like enzyme activity are presented in the Table 1.

**Table 1.** IC$_{50}$ values for the inhibition of FAAH and MGL-like enzymes activity by compounds tested.

<table>
<thead>
<tr>
<th>Example</th>
<th>R</th>
<th>R$'$</th>
<th>IC$_{50}$ (95% CI)$^a$</th>
<th>FAAH</th>
<th>MGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound 1" /></td>
<td>C$_2$H$_5$</td>
<td>379 (303-474) nM</td>
<td>75$^b$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Compound 2" /></td>
<td>n-C$_3$H$_7$</td>
<td>109 (90-132) nM</td>
<td>57$^b$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Compound 3" /></td>
<td>n-C$_4$H$_9$</td>
<td>54 (46-64) nM</td>
<td>59$^b$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Compound 4" /></td>
<td><img src="image5" alt="Cyclopentane" /></td>
<td>28 (23-34) nM</td>
<td>54$^b$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image6" alt="Compound 5" /></td>
<td><img src="image7" alt="Cyclohexane" /></td>
<td>47 (36-62) nM</td>
<td>83$^b$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image8" alt="Compound 6" /></td>
<td><img src="image7" alt="Cyclohexane" /></td>
<td>152 (122-189) nM</td>
<td>57$^b$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Solvent</td>
<td>IC₅₀ (Units)</td>
<td>% inhibition</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>nd³</td>
<td>nd³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>C₂H₅</td>
<td>32 (26-40) nM</td>
<td>16 (14-18) µM</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>n-C₃H₇</td>
<td>238 (177-321) nM</td>
<td>80%³</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>n-C₄H₉</td>
<td>143 (113-180) nM</td>
<td>70%³</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>n-C₄H₉</td>
<td>103 (81-131) nM</td>
<td>76%³</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>C₆H₁₂</td>
<td>47 (38-57) nM</td>
<td>71%³</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td>C₆H₁₂</td>
<td>56 (41-77) nM</td>
<td>79%³</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
<td>C₆H₁₂</td>
<td>121 (105-140) nM</td>
<td>75%³</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="image9.png" alt="Chemical Structure" /></td>
<td>nd³</td>
<td>nd³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td><img src="image10.png" alt="Chemical Structure" /></td>
<td>n-C₃H₇</td>
<td>38 (33-43) nM</td>
<td>23 (20-27) µM³</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td><img src="image11.png" alt="Chemical Structure" /></td>
<td>n-C₃H₇</td>
<td>33 (28-38) nM</td>
<td>68 %³</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>12.5 (11.1-14.1) nM</td>
<td>90 %</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>5.2 (4.6-5.9) nM</td>
<td>89 %</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>0.74 (0.59-0.92) nM</td>
<td>74 %</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>6.6 (5.0-8.7) nM</td>
<td>91 %</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>11.9 (9.5-15.0) nM</td>
<td>94 %</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>21 (18-24) nM</td>
<td>93 %</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td><img src="image13" alt="Chemical Structure" /></td>
<td><img src="image14" alt="Chemical Structure" /></td>
<td>2.5 (2.0-3.1) nM</td>
<td>67 %</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td><img src="image15" alt="Chemical Structure" /></td>
<td><img src="image16" alt="Chemical Structure" /></td>
<td>39 (33-45) nM</td>
<td>83 %</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td><img src="image17" alt="Chemical Structure" /></td>
<td><img src="image18" alt="Chemical Structure" /></td>
<td>16.5 (12.7-21.3) nM</td>
<td>91 %</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td><img src="image19" alt="Chemical Structure" /></td>
<td><img src="image20" alt="Chemical Structure" /></td>
<td>3.9 (3.3-4.7) nM</td>
<td>66 %</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td><img src="image21" alt="Chemical Structure" /></td>
<td><img src="image22" alt="Chemical Structure" /></td>
<td>49 (42-58) nM</td>
<td>35 µM</td>
<td></td>
</tr>
<tr>
<td><strong>29</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>65 (53-81) nM</td>
<td>72 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>30</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>109 (91-131) nM</td>
<td>72 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>31</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>51 (45-58) nM</td>
<td>72 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>32</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>16 (14-18) nM</td>
<td>84 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>33</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>2100 (1700-2700) nM</td>
<td>83 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>34</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>590 (506-689) nM</td>
<td>86 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>35</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>1900 (1600-2400) µM</td>
<td>75 %(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>36</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>1.1 (0.8-1.3) nM</td>
<td>89 %(^i)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>37</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>4.1 (3.4-4.9) nM</td>
<td>91 %(^i)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>38</strong></td>
<td><img src="image" alt="Structure" /></td>
<td>6.9 (5.4-8.8) nM</td>
<td>86 %(^i)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td></td>
<td></td>
<td>5.9 (4.9-7.1) nM</td>
<td>94 %</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td>nd</td>
<td>99 %</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td></td>
<td>i-C₃H₇</td>
<td>33 (22-51) nM</td>
<td>92 %</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td>n-C₁₂H₂₅</td>
<td>0.24 (0.19-0.30) nM</td>
<td>49 %</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td></td>
<td>n-C₆H₁₃</td>
<td>2.0 (1.8-2.2) nM</td>
<td>62 %</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td></td>
<td></td>
<td>2.6 (2.2-3.1) nM</td>
<td>86 %</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
<td></td>
<td>0 %</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structure 1</td>
<td>Structure 2</td>
<td>Activity 1</td>
<td>Activity 2</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image2.png" alt="Structure" /></td>
<td>31.72 %(^h)</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td><img src="image3.png" alt="Structure" /></td>
<td><img src="image4.png" alt="Structure" /></td>
<td>57.66 %(^h)</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td><img src="image5.png" alt="Structure" /></td>
<td><img src="image6.png" alt="Structure" /></td>
<td>12.53 %(^h)</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td><img src="image7.png" alt="Structure" /></td>
<td><img src="image8.png" alt="Structure" /></td>
<td>62 (54-72) nM</td>
<td>82 %</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td><img src="image9.png" alt="Structure" /></td>
<td><img src="image10.png" alt="Structure" /></td>
<td>11 (10-13) nM</td>
<td>86 %(^b)</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td><img src="image11.png" alt="Structure" /></td>
<td><img src="image12.png" alt="Structure" /></td>
<td>5.7 (5.0-6.6) nM</td>
<td>78 %(^b)</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td><img src="image13.png" alt="Structure" /></td>
<td><img src="image14.png" alt="Structure" /></td>
<td>43 (37-48) nM</td>
<td>87 %(^b)</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td><img src="image15.png" alt="Structure" /></td>
<td><img src="image16.png" alt="Structure" /></td>
<td>9 nM(^i)</td>
<td>nd</td>
<td></td>
</tr>
</tbody>
</table>
Values represent the mean of three independent experiments (n=3) performed in duplicate (95% confidence intervals (95% CI) are given in parentheses).

Remaining enzyme activity (%) at 100 µM compound concentration (n=2).

Not stable in used assay conditions.

Remaining enzyme activity at 1 mM was -22%.

Remaining enzyme activity (%) at 10 µM compound concentration (n=2).

Remaining enzyme activity (%) at 1 µM compound concentration (n=2).

Values represent the mean of two independent experiments (n=2) performed in duplicate (95% confidence intervals (95% CI) are given in parentheses).

Remaining enzyme activity (%) at 100 nM compound concentration (n=1).

Remaining enzyme activity (%) at 1 µM compound concentration (n=1).

Represents the value of one experiment (n=1) performed in duplicate (95% confidence intervals (95% CI) are given in parentheses).

<table>
<thead>
<tr>
<th></th>
<th>Structure</th>
<th>Remaining Activity</th>
<th>Effect</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td><img src="image1" alt="Structure" /></td>
<td>90 nM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td><img src="image2" alt="Structure" /></td>
<td>23 (19-27) nM</td>
<td>11.7 (9.3-14.9) µM</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td><img src="image3" alt="Structure" /></td>
<td>55.38 %&lt;sup&gt;h&lt;/sup&gt;</td>
<td>nd</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Values represent the mean of three independent experiments (n=3) performed in duplicate (95% confidence intervals (95% CI) are given in parentheses).

<sup>b</sup>Remaining enzyme activity (%) at 100 µM compound concentration (n=2).

<sup>c</sup>Not stable in used assay conditions.

<sup>d</sup>Remaining enzyme activity at 1 mM was -22%.

<sup>e</sup>Remaining enzyme activity (%) at 10 µM compound concentration (n=2).

<sup>f</sup>Remaining enzyme activity (%) at 1 µM compound concentration (n=2).

<sup>g</sup>Values represent the mean of two independent experiments (n=2) performed in duplicate (95% confidence intervals (95% CI) are given in parentheses).

<sup>h</sup>Remaining enzyme activity (%) at 100 nM compound concentration (n=1).

<sup>i</sup>Remaining enzyme activity (%) at 1 µM compound concentration (n=1).

<sup>j</sup>Represents the value of one experiment (n=1) performed in duplicate (95% confidence intervals (95% CI) are given in parentheses).
Table 2. IC$_{50}$ values for the inhibition of FAAH and MGL-like enzymes activity by pyridinylcarbamates tested.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Example</th>
<th>R</th>
<th>R'</th>
<th>IC$_{50}$ (95% CI) $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td><img src="image" alt="Chemical structure" /></td>
<td><img src="image" alt="Chemical structure" /></td>
<td>FAAH</td>
</tr>
</tbody>
</table>

$^a$ IC$_{50}$ values are in μM.
Claims

1. A compound of the formula I

\[
\begin{align*}
\text{Z} & \quad \text{R} & \quad \text{R'} \\
\text{-} & \quad \text{-} & \quad \text{-}
\end{align*}
\]

wherein \( Z \) is \( \text{CH} \) or \( \text{N} \),

\( R' \) is selected from the group consisting of \( \text{H} \), substituted or unsubstituted alkyl of 1 to 24 carbon atoms, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, and

\( R \) is a cyano, carboxyl, (C1-4 alkoxy)carbonyl, mono-C1-4 aliphatic aminocarbonyl, di-C1-4 aliphatic aminocarbonyl, N-hydroxycarbamimidoal, N-alkoxycarbamimidoal, acyloxycarbamimidoal, a heterocyclic moiety or heterocyclic carbonyl moiety, wherein the heterocyclic moiety is selected from the group represented by the following structures:

\[
\begin{align*}
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\text{R}_{2} & \quad \text{R}_{1} & \quad \text{R}_{3} & \quad \text{X} \\
\end{align*}
\]
wherein \( X \) is \( O, S, NH \) or \( NCH_3 \), and
\( R_1, R_2, R_3, R_4 \) are individually \( \text{H, halogen, alkyl, cycloalkyl, alylene, acyl, aroyl, aryl, phenoxy, alkoxy, alkoxyalkyl, alklythio, hydroxy, hydroxyalkyl, carboxy, alkoxy carbonyl, acyloxy, acylamino, acyloxyalkyl, acylaminoalkyl, hydroxyacetyl, sulfonate, alkylsulfonyle, arylsulfonyle, nitro, cyano, amino-NR}_5R_6, \( \text{aminoalkyl -(CH}_2)_n-NR}_5R_6, \) aminoacyl \(-\text{CO-(CH}_2)_n-NR}_5R_6, \) carbamoyl \(-\text{CO-NR}_5R_6, \) carbamoyloxy \(-\text{O-CO-NR}_5R_6, \) sulfonamido \(-\text{SO}_2NR}_5R_6, \) wherein \( n \) represents an integer from 1 to 4 and wherein \( R_5 \) and \( R_6 \) are selected from \( \text{H, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyalkyl} \) and wherein optionally \( R_5 \) and \( R_6 \) together with the N atom to which they are attached form a 5-7 membered cyclic ring, and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein \( Z \) is \( \text{CH} \).

3. A compound according to claim 1 wherein \( R' \) is selected from the group consisting of \( \text{H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted benzyl} \).

4. A compound according to claim 1 wherein \( R \) is selected from the group consisting of the following structures

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{O} & \quad \text{R}  \\
\text{R} & \quad \text{S} & \quad \text{N} & \quad \text{R}  \\
\text{R} & \quad \text{N} & \quad \text{N} & \quad \text{R}  \\
\text{R} & \quad \text{N} & \quad \text{H} & \quad \text{R}  \\
\text{R} & \quad \text{N} & \quad \text{S} & \quad \text{R}  \\
\text{R} & \quad \text{N} & \quad \text{R}  
\end{align*}
\]

wherein \( R_1, R_2, R_3 \) and \( R_4 \) are individually hydrogen, alkyl, aryl, acyl, alkoxy carbonyl, aminoacyl, or dialkylaminoacyl.
5. A compound according to claim 1 wherein

\( Z \) is \( \text{CH} \) or \( \text{N} \),

\( R' \) is selected from the group consisting of \( \text{H} \), substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted benzyll,

\( R \) is selected from the group consisting of the following structures

\[
\begin{align*}
\text{R1} & \quad \text{R2} & \quad \text{R3} & \quad \text{R4} \\
\text{N} & \quad \text{O} & \quad \text{N} & \quad \text{O} \\
\text{R1} & \quad \text{H} & \quad \text{R2} & \quad \text{R3} \\
\text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{O} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\end{align*}
\]

wherein \( R_1 \), \( R_2 \), \( R_3 \) and \( R_4 \) are individually hydrogen, alkyl, aryl, acyl, alkoxycarbonyl, aminoacyl, or dialkylaminoacyl.

6. A compound according to claim 1 wherein

\( R' \) is a substituted or unsubstituted alkyl (preferably an unsubstituted alkyl of 5 to 12 carbon atoms), cycloalkyl (preferably cyclopentyl or cyclohexyl), or a substituted or unsubstituted benzyll,

\( R \) is methoxycarbonyl, oxazolyl, tetrazolyl, thiadiazolyl, benzoxazolecarbonyl or benzothiazolecarbonyl.

7. A compound selected from the group consisting of:

- \( 3-(\text{Oxazol-2-yl})\text{phenyl cyclopentylcarbamate} \);
- \( 3-(\text{Oxazol-2-yl})\text{phenyl cyclohexylcarbamate} \);
- \( 3-(2\text{-Methyl-2H-tetrazol-5-yl})\text{phenyl cyclopentylcarbamate} \);
- \( \text{Methyl 3-(cyclohexylcarbamoyloxy)benzoate} \);
- \( 3-(1,2,3\text{-Thiadiazol-4-yl})\text{phenyl cyclohexylcarbamate} \);
- \( 3-(1,2,3\text{-Thiadiazol-4-yl})\text{phenyl cyclopentylcarbamate} \);
3-(1,2,3-Thiadiazol-4-yl)phenyl benzylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl dodecylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl hexylcarbamate;
3-(1,2,3-Thiadiazol-4-yl)phenyl (4-phenyl-butyl)carbamate; and
3-(Thiazol-2-yl)phenyl cyclohexylcarbamate.

8. A compound according to any one of claims 1 to 7 for use as a pharmaceutical.

9. A process for preparing the compounds of claim 1, wherein a heterocycle phenol having the formula

\[
\text{R} \begin{array}{c} \text{O} \\ \text{H} \end{array}
\]

wherein R and Z have the meanings given in claim 1, is reacted with an isocyanate having the formula R'NCO, where R' has the meaning given in claim 1.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier.

11. Use of a compound according to any one of claims 1 to 7 for the manufacture of a medicament for the treatment of disease states, disorders and conditions mediated by fatty acid amide hydrolase and/or monoglyceride lipase activity.

12. The use according to claim 11 for the manufacture of a medicament for the treatment of pain, inflammation, anxiety, epilepsy, depression, appetite disorders, glaucoma and insomnia.
13. A method of inhibiting fatty acid amide hydrolase in a mammal, said method comprising administering an effective amount of a compound of the formula I according to claim 1 to a subject in need of inhibition of FAAH.

14. A method of inhibiting monoglyceride lipase in a mammal, said method comprising administering an effective amount of a compound of the formula I according to claim 1 to a subject in need of inhibition of MGL.

15. A method of treating pain, inflammation, anxiety, epilepsy, depression, appetite disorders, glaucoma, insomnia or other disease states, disorders and conditions mediated by fatty acid amide hydrolase activity in a mammal, said method comprising administering an effective amount of a compound of the formula I according to claim 1 to a subject in need of such treatment.

16. The method according to claim 15, wherein the compound is administered orally.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

See extra sheet

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)

IPC 8: C07C, C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

FI, SE, NO, DK

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO Internal, WPI, Biosis, Medline, STN/Registry, CAplus

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  * A* document defining the general state of the art which is not considered to be of particular relevance
  * E* earlier application or patent but published on or after the international filing date
  * L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  * O* document referring to an oral disclosure, use, exhibition or other means
  * P* document published prior to the international filing date but later than the priority date claimed
  * T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  * X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  * Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  * &* document member of the same patent family

**Date of the actual completion of the international search**


**Date of mailing of the international search report**

29 July 2008 (29.07.2008)

**Name and mailing address of the ISA/FI**

National Board of Patents and Registration of Finland

P.O. Box 1160, FI-00101 HELSINKI, Finland

Facsimile No. +358 9 6939 5328

**Authorized officer**

Leena Tikkanen

**Telephone No.** +358 9 6939 500

Form PCT/ISA/210 (second sheet) (April 2007)
### DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>Boger, Dale L. et al., Exceptionally potent inhibitors of fatty acid amide hydrolase: The enzyme responsible for degradation of endogenous oleamide and anandamide. PNAS 2000, Vol. 97, No. 10, pages 5044-5049</td>
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**Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: **13-16**
   because they relate to subject matter not required to be searched by this Authority, namely:
   methods for treatment of the human or animal body by therapy (Rule 39.1(iv))

2. **□** Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **□** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **□** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **□** As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. **□** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  

4. **□** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

**Remark on Protest**

- **□** The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- **□** The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **□** No protest accompanied the payment of additional search fees.
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### Classification of Subject Matter

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