(54) Title: TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

(57) Abstract: There are disclosed compounds of Formula (1). Pharmaceutical compositions containing the compounds are also provided. Methods of treatment of Duchenne muscular dystrophy, Becker muscular dystrophy and cachexia using the compounds and compositions are also provided.
TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

RELATED APPLICATION

Priority is claimed herein to British application GB0715939.5, filed August 15, 2007, entitled "TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY." The disclosure of the above-referenced application is incorporated by reference herein in its entirety.

FIELD

Provided is a method of treatment of Duchenne muscular dystrophy.

BACKGROUND

Duchenne muscular dystrophy (DMD) is a common, genetic neuromuscular disease associated with the progressive deterioration of muscle function, first described over 150 years ago by the French neurologist, Duchenne de Boulogne, after whom the disease is named. DMD has been characterized as an X-linked recessive disorder that affects 1 in 3,500 males caused by mutations in the dystrophin gene. The gene is the largest in the human genome, encompassing 2.6 million base pairs of DNA and containing 79 exons. Approximately 60% of dystrophin mutations are large insertion or deletions that lead to frameshift errors downstream, whereas approximately 40% are point mutations or small frameshift rearrangements. The vast majority of DMD patients lack the dystrophin protein. Becker muscular dystrophy is a much milder form of DMD caused by reduction in the amount, or alteration in the size, of the dystrophin protein. The high incidence of DMD (1 in 10,000 sperm or eggs) means that genetic screening will never eliminate the disease, so an effective therapy is highly desirable.

A number of natural and engineered animal models of DMD exist, and provide a mainstay for preclinical studies (Allamand, V. & Campbell, K. P. Animal models for muscular dystrophy: valuable tools for the development of therapies. *Hum. Mol. Genet.* 9, 2459-2467 (2000). Although the mouse, cat and dog models all have mutations in the *DMD* gene and exhibit a biochemical dystrophinopathy similar to that seen in humans, they show surprising and considerable variation in terms of their phenotype. Like humans, the canine (Golden retriever muscular dystrophy and German short-haired pointer) models have a severe phenotype; these dogs typically die of cardiac failure. Dogs offer the best phenocopy for human disease, and are considered a high benchmark for preclinical studies. Unfortunately, breeding these animals is expensive and difficult, and the clinical time course can be variable among litters.
The \textit{mdx} mouse is the most widely used model due to availability, short gestation time, time to mature and relatively low cost (Bulfield, G., Siller, W. G., Wight, P. A. & Moore, K. J. X chromosome-linked muscular dystrophy (\textit{mdx}) in the mouse. \textit{Proc. Natl Acad. Sci. USA} 81, 1189-1192 (1984)).

Since the discovery of the DMD gene about 20 years ago, varying degrees of success in the treatment of DMD have been achieved in preclinical animal studies, some of which are being followed up in humans. Present therapeutic strategies can be broadly divided into three groups: first, gene therapy approaches; second, cell therapy; and last, pharmacological therapy. Gene- and cell-based therapies offer the fundamental advantage of obviating the need to separately correct secondary defects/ pathology (for example, contractures), especially if initiated early in the course of the disease. Unfortunately, these approaches face a number of technical hurdles. Immunological responses against viral vectors, myoblasts and newly synthesized dystrophin have been reported, in addition to toxicity, lack of stable expression and difficulty in delivery.

Pharmacological approaches for the treatment of muscular dystrophy differ from gene- and cell-based approaches in not being designed to deliver either the missing gene and/or protein. In general, the pharmacological strategies use drugs/molecules in an attempt to improve the phenotype by means such as decreasing inflammation, improving calcium homeostasis and increasing muscle progenitor proliferation or commitment. These strategies offer the advantage that they are easy to deliver systemically and can circumvent many of the immunological and/or toxicity issues that are related to vectors and cell-based therapies. Although investigations with corticosteroids and sodium cromoglycate, to reduce inflammation, dantrolene to maintain calcium homeostasis and clenbuterol to increase muscle strength, have produced promising results none of these potential therapies has yet been shown to be effective in treating DMD.

An alternative pharmacological approach is upregulation therapy. Upregulation therapy is based on increasing the expression of alternative genes to replace a defective gene and is particularly beneficial when an immune response is mounted against a previously absent protein. Upregulation of utrophin, an autosomal paralogue of dystrophin has been proposed as a potential therapy for DMD (Perkins & Davies, Neuromuscul Disord, S1: S78-S89 (2002), Khurana & Davies, Nat Rev Drug Discov 2:379-390 (2003)). When utrophin is overexpressed in transgenic \textit{mdx} mice it localizes to the sarcolemma of muscle cells and restores the components of the dystrophin-associated protein complex (DAPC), which
prevents the dystrophic development and in turn leads to functional improvement of skeletal muscle. Adenoviral delivery of utrophin in the dog has been shown to prevent pathology. Commencement of increased utrophin expression shortly after birth in the mouse model can be effective and no toxicity is observed when utrophin is ubiquitously expressed, which is promising for the translation of this therapy to humans. Upregulation of endogenous utrophin to sufficient levels to decrease pathology might be achieved by the delivery of small diffusible compounds.

DESCRIPTION

Provided are compounds which upregulate endogenous utrophin in predictive screens and, thus, may be useful in the treatment of DMD.

In one embodiment, provided is a compound of Formula (1)

![Formula Image]

wherein

R₉ represents a C₅-10 carbocycle which is partially or fully aromatic containing 0-4 hetero atoms and optionally substituted by 1-4 halogen, C₁-C₆ alkyl, OC₁-C₆ alkyl or NR₉₀(C=Q)-M-Z-R₉₃ wherein R₉₀ represents H or C₁-₆ alkyl, Q represents O, S, or NR₉₁ wherein R₉₁ represents H or C₁-₆ alkyl, M represents C₁-₃ alkyl optionally substituted with halogen, C₁-₆ alkyl, or C₁-₆ alkoxy, Z represents O, S or NR₉₂ wherein R₉₂ represents H or C₁-₆ alkyl and R₉₃ represents a C₅-₁₀ carbocycle which is partially or fully aromatic containing 0-4 hetero atoms and optionally substituted by 1-4 halogen, C₁-C₆ alkyl or OC₁-C₆ alkyl; three of A₁, A₂, A₃ and A₄ represent CH, and one of A₁, A₂, A₃ and A₄ represents CRₙ wherein Rₙ represents:

an alkyl group selected from C₂-C₃ alkyl, n-butyl and sec-butyl, optionally substituted with hydroxyl, halogen, carboxylic acid, piperidin-1-yl, N-morpholino, -NMe₂ or alkoxy (such as C₁-₆alkoxy);

hydroxyl, halogen, CO₂(C₁-₆alkyl), or -O(C₁-₆alkyl) or C₁ alkyl substituted with hydroxyl, halogen, carboxylic acid, piperidin-1-yl, N-morpholino, -NMe₂ or alkoxy (such as C₁-₆alkoxy);
hydroxyl, halogen, CO\(_2\)(C\(_1\)-C\(_6\)alkyl), or -O(C\(_1\)-C\(_6\)alkyl);
-N-(S)-2-amino-3-hydroxypropionamide;
-N-(S)-2-(methylamino)propionamide;
-N-(S)-2-aminopropionamide;
-N-(S)-2-methylaminoacetamide;
-(S=O)R\(_2\), wherein R\(_2\) represents C\(_1\)-C\(_6\)alkyl;
-SOnR\(_2\), wherein n = 0, 1 or 2 and R\(_2\) represents CH\(_3\), CH\(_2\)CD\(_3\) or C\(_3\)-alkyl, optionally substituted with OH or ethyl substituted with hydroxyl;
-SO\(_2\)NR\(_5\)R\(_5\), wherein R\(_2\) and R\(_5\) represent H or C\(_1\)-C\(_4\)alkyl;
-CO\(_2\)R\(_2\), wherein R\(_2\) represents C\(_1\)-C\(_6\)alkyl;
-NR\(_5\)SO\(_n\)R\(_2\), wherein n = 0, 1 or 2 and R\(_2\) represents CH\(_3\), CH\(_2\)CD\(_3\) or C\(_3\)-alkyl, optionally substituted with one or more hydroxy, halogen, alkoxy (such as C\(_1\)-alkoxy) or amine;
-K-SOnR\(_2\), wherein K represents C\(_1\)-C\(_3\) alkyl optionally substituted with C\(_1\)-C\(_6\) alkyl, n=0-2 and R\(_2\) represents C\(_1\)-C\(_{10}\) alkyl optionally substituted with one or more hydroxy, halogen, alkoxy (such as C\(_1\)-alkoxy) or amine;
an N-linked mono- or bicyclic ring substituted by one or more oxo, hydroxyl, halogen, C\(_1\)-C\(_6\) alkyl, alkoxy (such as C\(_1\)-alkoxy) or aryl (such as C\(_5\)-aryl) substituent; or
NR\(_{15}\)C(=W)R\(_{17}\) wherein
W represents NH, S or O;
R\(_{17}\) represents C\(_2\)-alkyl, n-propyl, or C\(_4\)-C\(_{10}\)alkyl; C\(_1\)-C\(_{10}\) alkyl substituted with one or more halogen, hydroxyl, alkoxy (such as C\(_1\)-alkoxy) or amine; a mono or disaccharide unit attached at the anomeric position via a C\(_1\)-C\(_4\)alkyl group which is optionally substituted with one or more C\(_1\)-alkyl group; CH\(_2\)aryl, wherein aryl represents an aromatic hydrocarbon (such as a 5 to 10 membered aromatic hydrocarbon) or a 5 to 10 membered aromatic heterocyle containing 1 to 4 hetero atoms selected from an oxygen atom, a sulphur atom and a nitrogen atom as a ring constituent besides carbon; -CH\(_2\)OCH\(_3\), -CH\(_2\)OCH\(_2\)CH\(_2\)OCH\(_3\), CH\(_2\)piperidin-1-yl or CH\(_2\)-N-morpholinoyl;
R\(_{15}\) represents H, C\(_1\)-alkyl or together with R\(_{17}\) represents -CH\(_2\)CH\(_2\)-, -CH\(_2\)CH\(_2\)-, or -CH\(_2\)CH\(_2\)CH\(_2\)-;
X is O or N; and
Y is O or N.
Compounds of formula I may exist in tautomeric, enantiomeric and diastereomeric forms, all of which are included within the scope of this disclosure.

Certain compounds of formula I are novel. Also provided are those compounds of formula I which are novel, together with processes for their preparation, compositions containing them, as well as their use as pharmaceuticals.

Some of the compounds falling within the scope of formula I are known, as such, but not as pharmaceuticals. Also provided are compounds known in the art as such, but not previously described for use as pharmaceuticals, as pharmaceuticals.

The instant disclosure will now be described with reference to the accompanying drawings in detail:

Figure 1 shows a luciferase reporter assay (murine H2K cells).

Figure 2 shows a dose dependent luciferase induction.

Figure 3 shows an example of TA muscle sections stained with antibody specific for mouse utrophin.

Figure 4 shows that mice exposed to CPD-A (V2 and V3) showed increased levels of utrophin expression compared to control.


Some general methods of synthesis are as follows.

Benzoxazoles of formula I or pharmaceutically acceptable salts thereof may be prepared from compounds of formula II.
Scheme 1

Reaction conditions:

i. \( R^3CO_2H \) (or \( R^9COCl \)), PPA, heat; or \( R^9COCl \), dioxane, microwave, then NaOH

ii. \( R^9COCl \), pyridine, rt (= room temperature)

iii. TsOH, xylene

iv. \( R^9CO_2H \), HATU, pyridine, DMF

v. PPA, heat

vi. HATU, DMF, \(^1Pr_2NEt\), alkylNH₂, rt

Formation of the benzoxazole I can be carried out in a variety of ways, as illustrated above.

For example, reaction of the compound of formula II with an acyl derivative, such as the acid or the acid chloride, and heating in an appropriate solvent and an appropriate temperature in the presence of an acid catalyst, for example polyphosphoric acid. This is illustrated above as step (i).

The reaction may be carried out in an aprotic solvent, in one embodiment a polar, aprotic solvent, for example tetrahydrofuran, and a temperature of from -10°C to +150°C. Generally the reaction may be carried on at the reflux temperature of the solvent at normal pressure.

Alternatively, the compound of formula II may first be reacted with an excess of an acyl derivative \( R^9COX \) (where X is for example Cl), such that acylation takes place on both oxygen and nitrogen. This can be brought about by, for example, reaction in pyridine at
room temperature (step ii). Ring closure to form the compound of formula II can then occur in a subsequent ring closure step in which, for example, the doubly acylated product is heated in xylenes in the presence of an acid catalyst such as a sulfonic acid (step iii).

Another illustrative example of formation of a compound of formula I is shown by steps iv and v. First the amine is coupled to an acid using a peptide coupling reagent. Available coupling reagents are well known to those skilled in the art, and include HBTU, TBTU and HATU. Amide formation in the presence of an appropriate coupling reagent occurs, for example, in DMF in the presence of a nucleophilic catalyst such as pyridine.

When R¹ = CO₂H, this acid may be coupled with an amine as shown by step (vi). Suitable coupling conditions include use of HATU in DMF in the presence of 1Pr₂NEt, R¹NH₂ at room temperature.

Compounds in which the six membered ring is substituted with an amide derivative are of particular interest. These may be produced from an intermediate amide derivative III.

Scheme 2

Reaction conditions:
i. As for (i); Scheme 1

ii. R¹COCl, pyridine (or NEt₃, DCM); or R⁹CO₂H, HATU, pyridine, DMF

iii. As for (i); Scheme 1
iv. SnCl\textsubscript{2}, EtOH, heat; or Pd/C, H\textsubscript{2}, IMS; or Fe, NH\textsubscript{4}Cl, IMS / water, heat

v. R\textsuperscript{2}NCO, DCM, rt

vi. NaBH\textsubscript{(OAc)}\textsubscript{3}, R\textsuperscript{10}CHO, DCE, rt

vii. R\textsuperscript{14}SO\textsubscript{2}Cl, pyridine, DCM, rt

Intermediate amine III may be synthesised either by using the method outlined in scheme 1, step (i) wherein R\textsuperscript{1} = NH\textsubscript{2}, or alternatively, in a two step process as defined by steps (iii) and (iv) of scheme 2. Nitro substituted benzoxazole derivative V is produced from nitro substituted phenyl derivative IV, also in a method analogous to that illustrated by scheme 1, step 1, and then the nitro-benzoxazole derivative V is reduced in a subsequent step to give intermediate amine III. The skilled person is well aware of suitable methods to reduce a nitro group to give an amine. Selective methods for reducing NO\textsubscript{2} to NH\textsubscript{2} include Sn/HCl, or H\textsubscript{2}/Pd/C in a suitable solvent, e.g. ethanol at a temperature of from 0\textdegree{} to 80\textdegree{}C or heating in the presence of iron, NH\textsubscript{4}Cl in industrial methylated spirits / water.

Intermediate amine III can then be coupled or derivatised as required (see scheme 2a for example).

![Scheme 2a](image)

Amide derivatives of formula VI can be produced by coupling amine III with an acyl derivative. This can be achieved by, for example, reaction of an appropriate acid chloride in either pyridine, or in CH\textsubscript{2}Cl\textsubscript{2} (step ii).

Sulfonamide derivatives VII can be produced by reaction of amine III with an appropriate sulfonyl chloride in, for example, CH\textsubscript{2}Cl\textsubscript{2} in the presence of pyridine at room temperature.

Amine derivatives VIII can be produced by use of an appropriate reductive amination strategy. Methods of reductive amination are well known in the art. They include, for example, reaction of the amine with an appropriate aldehyde and sodium triacetoxyborohydride in 1,2-dichloroethane.
Urea derivatives of formula IX can be produced, for example, by reaction of amine III with the appropriate isocyanate, for example, at room temperature in CH$_2$Cl$_2$.

Benzothiazoles of formula X or pharmaceutically acceptable salts thereof may be prepared from compounds of formula XI.

\[
\text{Scheme 3}
\]

**Reaction conditions:**

i. $R^9$COCl, pyridine, rt

ii. Na$_2$S, S$_8$, IMS, heat

iii. Fe, NH$_4$Cl, IMS, heat

iv. $R^{17}$COCl, pyridine (or NEt$_3$, DCM); or $R^{17}$CO$_2$H, HATU, pyridine, DMF

The compounds of formula XI can be converted to the corresponding amide by, for example, reaction with the appropriate acid chloride in pyridine (step (i)), or by using an appropriate peptide coupling reagent. Such methods are well known to the person skilled in the art as discussed hereinabove.

The amide can then be converted to the nitro-benzothiazole of formula XII in a one-pot procedure involving reaction with Na$_2$S, S$_8$ at elevated temperature in industrial methylated spirit. Nitro derivative XII can be reduced as discussed previously and the resulting primary amine manipulated in an analogous manner to the primary amine in scheme 2 steps (ii), (v), (vi) and (vii).
Benzimidazoles of formula XII can be produced according to scheme 4. Reaction of a diaminophenyl derivative of formula XIII with an acyl derivative, such as an acid or an acid chloride in an appropriate solvent and at an appropriate temperature in the presence of an acid catalyst, for example polyphosphoric acid, produces a benzimidazole derivative of formula XII. This is illustrated above as step (i). The nitro group may then be reduced and manipulated to produce other functionality as discussed hereinabove.

Alternatively, benzimidazoles may be produced by reacting a di-nitro compound of formula XIV, wherein X represents a leaving group, in one embodiment a halogen such as chlorine or fluorine, with an amine, for example, in DMSO at elevated temperature in the presence of a base. Subsequent selective reduction of one nitro group using sodium dithionite in THF/water can then take place to give a diamine of formula XV. Ring closure to form a benzimidazoles, and manipulation of the nitro group can then proceed as illustrated and discussed previously.
Scheme 5

Reaction conditions:

i.  Na₂S hydrate, MeOH, NH₄Cl, water; or Na₂S₂O₄ / EtOH; or SnCl₂, EtOH

ii.  As for (i), Scheme 1; or R⁹COCl, pyridine; then PPA, heat

iii.  SnCl₂, EtOH, heat

iv.  R¹B(OH)₂, Pd(PPh₃)₄, K₂CO₃, dioxane / water, microwave

v.  R¹¹COCl, pyridine, rt

vi.  EtOC(S)SK, pyridine, heat

vii.  SOCl₂; or POCl₃

viii.  R³B(OH)₂, Pd(PPh₃)₄, K₂CO₃, solvent

ix.  PPA, R⁵CO₂H heat

Benzoxazoles of formula XVI can be made by methods analogous to those discussed previously. For example the method illustrated above (ix) involves heating a compound of formula XVII in an appropriate solvent in the presence of acid catalyst and an appropriate acyl derivative eg a carboxylic acid.

Benzoxazoles of formula XVIII and XIX can be synthesised from the appropriate nitro compound of formula XX. Reduction of the nitro compound XX gives the
corresponding amino alcohol XXI (for example using Sn / HCl, or any of the other appropriate methods well known to the person skilled in the art). Benzoxazole formation via reaction of the amino alcohol with an appropriate acyl derivative can then be achieved using any of the methods disclosed hereinabove.

For oxazoles of formula XXIII in which $X = \text{Br}$, a Suzuki coupling reaction can then be used to give further derivatives. An example of appropriate conditions are $R'B(OH)_2$, $\text{Pd(PPh}_3\text{)}_4$, $\text{K}_2\text{CO}_3$, dioxane / water, $\mu$wave, in which a benzoxazole of formula XIX results. The person skilled in the art is familiar with Suzuki coupling reactions and could easily manipulate the conditions to produce a wide variety of compounds.

For oxazoles produced by step (ii) in which $X = \text{NO}_2$, the nitro group can be reduced to the corresponding amine, using any of the methods well known to the person skilled in the art discussed hereinabove. The amine may then be manipulated using, for example, any of the methods discussed in scheme 2 above, to give, for example, a compound of formula XVIII.

Alternatively, benzoxazoles of formula XVIII can be made, also from a compound of formula XX, via thiocarbamate XXII, which is produced by heating a compound of formula XX with $\text{EtOC(S)SK}$ in pyridine. The compound of formula XXII can be converted to the chloride of formula XXIII for example by use of well known reagents such as $\text{SOCl}_2$ or $\text{POCl}_3$. A Suzuki coupling using, for example, conditions illustrated by step viii above gives a benzoxazole of formula XVIII.

In the above processes it may be necessary for any functional groups, e.g. hydroxy or amino groups, present in the starting materials to be protected, thus it may be necessary to remove one or more protective groups to generate the compound of formula I.

Suitable protecting groups and methods for their removal are, for example, those described in "Protective Groups in Organic Synthesis" by T. Greene and P.G.M. Wutts, John Wiley and Sons Inc., 1991. Hydroxy groups may, for example, be protected by arylmethyl groups such as phenylmethyl, diphenylmethyl or triphenylmethyl; acyl groups such as acetyl, trichloroacetyl or trifluoroacetyl; or as tetrahydropyranyl derivatives. Suitable amino protecting groups include arylmethyl groups such as benzyl, (R,S)-$\alpha$-phenylethyl, diphenylmethyl or triphenylmethyl, and acyl groups such as acetyl, trichloroacetyl or trifluoroacetyl. Conventional methods of deprotection may be used including hydrogenolysis, acid or base hydrolysis, or photolysis. Arylmethyl groups may, for example, be removed by
hydrogenolysis in the presence of a metal catalyst e.g. palladium on charcoal. Tetrahydropyranyl groups may be cleaved by hydrolysis under acidic conditions. Acyl groups may be removed by hydrolysis with a base such as sodium hydroxide or potassium carbonate, or a group such as trichloroacetyl may be removed by reduction with, for example, zinc and acetic acid.

The compounds of formula I, and salts thereof, may be isolated from their reaction mixtures using conventional techniques.

Salts of the compounds of formula I may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or derivative thereof, with one or more equivalents of the appropriate base or acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. ethanol, tetrahydrofuran or diethyl ether, which may be removed in vacuo, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

Pharmaceutically acceptable salts of the compounds of formula I include alkali metal salts, e.g. sodium and potassium salts; alkaline earth metal salts, e.g. calcium and magnesium salts; salts of the Group III elements, e.g. aluminium salts; and ammonium salts. Salts with suitable organic bases, for example, salts with hydroxylamine; lower alkylamines, e.g. methylamine or ethylamine; with substituted lower alkylamines, e.g. hydroxy substituted alkylamines; or with monocyclic nitrogen heterocyclic compounds, e.g. piperidine or morpholine; and salts with amino acids, e.g. with arginine, lysine etc, or an N-alkyl derivative thereof; or with an aminosugar, e.g. N-methyl-D-glucamine or glucosamine. In one embodiment, non-toxic physiologically acceptable salts are provided, although other salts are also useful, e.g. in isolating or purifying the product.

Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various optical isomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation.

Substituents that alkyl may represent include methyl, ethyl, butyl, eg sec butyl.

Halogen may represent F, Cl, Br and I, especially Cl.
References to particular elements should be construed to include all isotopes of the particular element.

In one group of compounds that may be mentioned A₁, A₂ and A₄ represent CH, and A₃ represents CR₁.

In one group of compounds R₉ represents 2-naphthyl.

In another group of compounds that can be mentioned R₉ represents 2-naphthyl optionally substituted with halogen or phenyl optionally substituted with halogen; A₁, A₂ and A₄ represent CH, and A₃ represents CR₁ wherein R₁ represents:

NR₁₅C(=W)R₁₇ wherein

W represents NH, S or O;
R₁₇ represents C₂-alkyl, n-propyl, or C₄-C₁₀alkyl; C₁-C₁₀alkyl substituted with one or more halogen, hydroxyl, alkoxy (such as C₁-C₆alkoxy) or amine; a mono or disaccharide unit attached at the anomeric position via a C₁-C₄alkyl group which is optionally substituted with one or more C₁-C₆ alkyl group; CH₂aryl, wherein aryl represents an aromatic hydrocarbon (such as a 5 to 10 membered aromatic hydrocarbon) or a 5 to 10 membered aromatic heterocycle containing 1 to 4 hetero atoms selected from an oxygen atom, a sulphur atom and a nitrogen atom as a ring constituent besides carbon; CH₂OCH₃, CH₂OCH₂CH₂OCH₃, CH₂piperidin-1-yl or CH₂-N-morpholino; and
R₁₅ represents H, C₁-C₆ alkyl or together with R₁₇ represents –CH₂CH₂–, –CH₂ CH₂–, or –CH₂CH₂CH₂–.

In one group of compounds that may be mentioned R₉ represents a C₅-C₁₀ carbocycle which is partially or fully aromatic containing 0-4 hetero atoms substituted by NR₉₀(C=Q)-M-Z-R₉₃ wherein R₉₀ represents H or C₁-C₆ alkyl, Q represents O, S, or NR₉₁ wherein R₉₁ represents H or C₁-C₆ alkyl, M represents C₁-C₃ alkyl optionally substituted with halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, Z represents O, S or NR₉₂ wherein R₉₂ represents H or C₁-C₆ alkyl and R₉₃ represents a C₅-C₁₀ carbocycle which is partially or fully aromatic containing 0-4 hetero atoms and optionally substituted by 1-4 halogen, C₁-C₆ alkyl, OC₁-C₆ alkyl.

In another group of compounds that can be mentioned R₉ represents a 5-10 membered heterocyclic ring containing one or more SOₙ units, wherein n=0-2 and may be the same or different for each SOₙ unit.
In one group of compounds that may be mentioned, R₁ represents a N-linked mono- or bicyclic ring which is a lactam.

In another group of compounds R₁ represents -K-SO₂-R₂₈, wherein K represents C₁-C₃ alkyl optionally substituted with C₁-C₆ alkyl; n=0-2 and R₂₈ represents C₁-C₁₀ alkyl optionally substituted with one or more hydroxy, halogen, alkoxy (such as C₁-₆ alkoxy) or amine.

In one group of compounds Y represents N.

In one group of compounds X represents O.

In one group of compounds Y represents N and X represents O.

Also provided is a method for the treatment or prophylaxis of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I) or a pharmaceutical acceptable salt.

Also provided is use of a compound described herein in the manufacture of a medicament for the treatment or prophylaxis of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia.

The compounds of formula I for use in the treatment of DMD will generally be administered in the form of a pharmaceutical composition.

Thus, according to a further aspect there is provided a pharmaceutical composition including in one embodiment less than 80% w/w, in another embodiment less than 50% w/w, e.g. 0.1 to 20%, of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above, in admixture with a pharmaceutically acceptable diluent or carrier.

Also provided is a process for the production of such a pharmaceutical composition which comprises mixing the ingredients. Examples of pharmaceutical formulations which may be used, and suitable diluents or carriers, are as follows:
for intravenous injection or infusion - purified water or saline solution;

for inhalation compositions - coarse lactose;

for tablets, capsules and dragees - microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin;

for suppositories - natural or hardened oils or waxes.

When the compound is to be used in aqueous solution, e.g. for infusion, it may be necessary to incorporate other excipients. In particular there may be mentioned chelating or sequestering agents, antioxidants, tonicity adjusting agents, pH-modifying agents and buffering agents.

Solutions containing a compound of formula I may, if desired, be evaporated, e.g. by freeze drying or spray drying, to give a solid composition, which may be reconstituted prior to use.

When not in solution, the compound of formula I is, in one embodiment, in a form having a mass median diameter of from 0.01 to 10μm. The compositions may also contain suitable preserving, stabilising and wetting agents, solubilisers, e.g. a water-soluble cellulose polymer such as hydroxypropyl methylcellulose, or a water-soluble glycol such as propylene glycol, sweetening and colouring agents and flavourings. Where appropriate, the compositions may be formulated in sustained release form.

The content of compound formula I in a pharmaceutical composition is generally about 0.01-about 99.9wt%, in one embodiment about 0.1-about 50wt%, relative to the entire preparation.

The dose of the compound of formula I is determined in consideration of age, body weight, general health condition, diet, administration time, administration method, clearance rate, combination of drugs, the level of disease for which the patient is under treatment then, and other factors.

While the dose varies depending on the target disease, condition, subject of administration, administration method and the like, for oral administration as a therapeutic agent for the treatment of Duchenne muscular dystrophy in a patient suffering from such a disease is from 0.01 mg - 10 g, in one embodiment 0.1 – 100 mg, is in certain embodiments administered in a single dose or in 2 or 3 portions per day.
The potential activity of the compounds of formula I for use in the treatment of DMD may be demonstrated in the following predictive assay and screens.

1. **Luciferase reporter assay (murine H2K cells)**

   The cell line used for the screen is an immortalized mdx mouse H2K cell line that has been stably transfected with a plasmid containing \( \approx 5\text{kb} \) fragment of the Utrophin A promoter including the first untranslated exon linked to a luciferase reporter gene (see Figure 1).

   Under conditions of low temperature and interferon containing media, the cells remain as myoblasts. These are plated into 96 well plates and cultured in the presence of compound for three days. The level of luciferase is then determined by cell lysis and reading of the light output from the expressed luciferase gene utilising a plate luminometer.

   Example of pharmacological dose response of compounds in the assay is shown in Figure 2.

2. **mdx mouse**

   Data obtained from the ADMET data was prioritised and the compounds with the best in vitro luciferase activity and reasonable ADMET data were prioritised for testing in the mdx proof of concept study where the outcome was to identify whether any of the compounds had the ability to increase the levels of utrophin protein in dystrophin deficient muscle when compared to vehicle only dosed control animals.

   There were two animals injected with 10mg/kg of compound administered ip daily for 28 days plus age matched controls. Muscle samples were taken and processed for sectioning (to identify increases in sarcolemmal staining of utrophin) and Western blotting (to identify overall increases in utrophin levels).

   Figure 3 shows an example of TA muscle sections stained with antibody specific for mouse utrophin. Comparison to the mdx muscle only injected with vehicle shows an increase in the amount of sarcolemmal bound utrophin.

   Muscles from the above treated mice were also excised and processed for Western blotting and stained with specific antibodies (see Figure 4). Again using muscle dosed with CPD-A
shows a significant increase in the overall levels of utrophin present in both the TA leg muscle and the diaphragm. Both mice exposed to CPD-A (V2 and V3) showed increased levels of utrophin expression compared to control.

Positive upregulation data from the first 28 day study were then repeated in a further two mouse 28 day study. A total of three different compounds have shown in duplicate the ability to increase the level of utrophin expression in the mdx mouse when delivered daily by ip for 28 days. This data demonstrates the ability of the compound when delivered ip causes a significant increase in the levels of utrophin found in the mdx muscle and therefore gives us the confidence that this approach will ameliorate the disease as all the published data to date demonstrates that any increase of utrophin levels over three fold has significant functional effects on dystrophin deficient muscle.

The H2K/mdx/Utro A reporter cell line maintenance

The H2K/mdx/Utro A reporter cell line was passaged twice a week until ≤30% confluent. The cells were grown at 33°C in the presence of 10% CO₂.

To remove the myoblasts for platting, they were incubated with Trypsin / EDTA until the monolayer started to detach.

Growth Medium

DMEM Gibco 41966

20% FCS

1% Pen/Strep

1% glutamine

10mls Chick embryo extract

Interferon(1276 905 Roche) Add fresh 10μl / 50mls medium

Luciferase Assay for 96 Well Plates

The H2K/mdx/Utro A reporter cell line cells were plated out into 96 well plates (Falcon 353296, white opaque) at a density of approximately 5000 cells/well in 190μl normal growth medium. The plates were then incubated at 33°C in the presence of 10% CO₂ for 24 hrs.
Compounds were dosed by adding 10μl of diluted compound to each well giving a final concentration of 10μM. The plates were then incubated for a further 48hrs.

Cells were then lysed in situ following the manufacture’s protocols (Promega Steady-Glo Luciferase Assay System E2520), then counted for 10 seconds using a plate luminometer (Victor1420).

**Compound Storage**

Compounds for screening were stored at -20°C as 10mM stocks in 100% DMSO until required.

**Injection of mdx mice with compounds**

Mdx from a breeding colony were selected for testing. Mice were injected daily with either vehicle or 10mg/kg of compound using the intraperitoneal route (ip). Mice were weighed and compounds diluted in 5% DMSO, 0.1% tween in PBS.

Mice were sacrificed by cervical dislocation at desired time points, and muscles excised for analysis.

**Muscle Analysis**

**Immunohistochemistry**

Tissues for sectioning were dissected, immersed in OCT (Bright Cryo-M-Bed) and frozen on liquid nitrogen cooled isopentane. Unfixed 8μM cryosections were cut on a Bright Cryostat, and stored at -80°C.

In readiness for staining, sections were blocked in 5% fetal calf serum in PBS for 30 mins. The primary antibodies were diluted in blocking reagent and incubated on sections for 1.5 hrs in a humid chamber then washed three times for 5mins in PBS. Secondary antibodies were also diluted in blocking reagent, and incubated for 1 hr in the dark in a humid chamber. Finally sections were washed three times 5mins in PBS and coverslips were mounted with hydromount. Slides were analysed using a Leica fluorescent microscope.
Results

Biological activity was assessed using the luciferase reporter assay in murine H2K cells, and is classified as follows:

- **+** Up to 200% relative to control
- **++** Between 201% and 300% relative to control
- **+++** Between 301% and 400% relative to control
- **++++** Above 401% relative to control

**Table 1: Compounds made by methods described herein**

<table>
<thead>
<tr>
<th>Example</th>
<th>Chemical Name</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,4-dichloro-N-(2-isopropylbenzo[d]oxazol-5-yl)benzamide</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>5-ethylsulfonyl-1,3-benzoazoxol-2-amine</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-methylbutanamide</td>
<td>+++</td>
</tr>
<tr>
<td>4</td>
<td>N-(4-(6-benzoylbenzo[d]oxazol-2-yl)phenyl)-2-methylbutanamide</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>N-(4-(5-(ethylsulfonyl)benzo[d]oxazol-2-yl)phenyl)isobutyramide</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>5-(ethylsulfonyl)-2-(3-phenoxypyhenyl)benzo[d]oxazole</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>2-(benzo[d]oxazol-2-yl)-5-chlorophenol</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>5-chloro-2-(5-methylbenzo[d]oxazol-2-yl)phenol</td>
<td>+++</td>
</tr>
<tr>
<td>9</td>
<td>5-amino-2-(5-methylbenzo[d]oxazol-2-yl)phenol</td>
<td>+++</td>
</tr>
<tr>
<td>10</td>
<td>5-(ethylsulfonyl)-2-(1H-indol-5-yl)benzo[d]oxazole</td>
<td>+++</td>
</tr>
<tr>
<td>11</td>
<td>N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(quinolin-2-ythio)acetamide</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>2-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)acetamide</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>2-(4-methyl-4H-1,2,4-triazol-3-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)butanamide</td>
<td>+++</td>
</tr>
<tr>
<td>14</td>
<td>N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(quinazolin-4-ylthio)acetamide</td>
<td>+++</td>
</tr>
<tr>
<td>15</td>
<td>2-(5-isopropyl-4H-1,2,4-triazol-3-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)acetamide</td>
<td>+++</td>
</tr>
<tr>
<td>16</td>
<td>2-(1,3,4-thiadiazol-2-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)propanamide</td>
<td>+++</td>
</tr>
<tr>
<td>17</td>
<td>5-(ethylsulfonyl)-2-(furan-2-yl)benzo[d]oxazole</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>3-(5-methylbenzo[d]oxazol-2-yl)pyridin-2-ol</td>
<td>+++</td>
</tr>
<tr>
<td>19</td>
<td>5-(5-methylbenzo[d]oxazol-2-yl)pyridin-2-ol</td>
<td>+++</td>
</tr>
<tr>
<td>20</td>
<td>5-(5-methylbenzo[d]oxazol-2-yl)pyridin-2-amine</td>
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<td>21</td>
<td>5-(5-methylbenzo[d]oxazol-2-yl)pyrimidine-2,4-diol</td>
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<td>22</td>
<td>N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(4-phenyl-4H-1,2,4-triazol-3-ylthio)acetamide</td>
<td>+++</td>
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<tr>
<td>23</td>
<td>N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(phenylthio)acetamide</td>
<td>++</td>
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<tr>
<td></td>
<td>Chemical Structure</td>
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<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>24</td>
<td>N-(4-(6-methylbenzo[d]oxazol-2-yl)phenyl)-2-(phenylthio)acetamide</td>
<td>+++</td>
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<tr>
<td>25</td>
<td>N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-phenoxacetamide</td>
<td>++++</td>
</tr>
<tr>
<td>26</td>
<td>methyl 2-(naphthalen-2-yl)benzo[d]oxazole-6-carboxylate</td>
<td>+</td>
</tr>
<tr>
<td>27</td>
<td>5-amino-2-(5-(trifluoromethoxy)benzo[d]oxazol-2-yl)phenol</td>
<td>++++</td>
</tr>
<tr>
<td>28</td>
<td>5-amino-2-(naphtho[1,2-d]oxazol-2-yl)phenol</td>
<td>++++</td>
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<tr>
<td>29</td>
<td>5-amino-2-(5-phenylbenzo[d]oxazol-2-yl)phenol</td>
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</tr>
<tr>
<td>30</td>
<td>2-(4H-1,2,4-triazol-3-ylthio)-N-(4-(6-methylbenzo[d]oxazol-2-yl)phenyl)acetamide</td>
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</tr>
<tr>
<td>31</td>
<td>2-(3',4'-dichlorophenyl)-6-(ethylsulfonyl)benzoxazole</td>
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</tr>
<tr>
<td>32</td>
<td>2-(4'-chlorophenyl)-6-(ethylsulfonyl)benzoxazole</td>
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</tr>
<tr>
<td>33</td>
<td>(2-(naphthalen-2-yl)benzo[d]oxazol-6-yl)methanol</td>
<td>+</td>
</tr>
<tr>
<td>34</td>
<td>2-(5-methylbenzo[d]oxazol-2-yl)phenol</td>
<td>++++</td>
</tr>
<tr>
<td>35</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-(beta-D-galactopyranosyloxy)acetamide</td>
<td>+</td>
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<tr>
<td>36</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-3-(beta-D-galactopyranosyloxy)propanamide</td>
<td>+</td>
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<td>37</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-hydroxyacetamide</td>
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</tr>
<tr>
<td>38</td>
<td>5-(ethylsulfonyl)-2-(isoquinolin-3-yl)benzo[d]oxazole</td>
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</tr>
<tr>
<td>39</td>
<td>5-(ethylsulfonyl)-2-(quinolin-6-yl)benzo[d]oxazole</td>
<td>++++</td>
</tr>
<tr>
<td>40</td>
<td>5-(ethylsulfonyl)-2-(quinolxalin-6-yl)benzo[d]oxazole</td>
<td>+</td>
</tr>
<tr>
<td>41</td>
<td>2-(dimethylamino)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
<td>++++</td>
</tr>
<tr>
<td>42</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-3-hydroxypropanamide</td>
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</tr>
<tr>
<td>43</td>
<td>3-(5-isobutryramidobenzo[d]oxazol-2-yl)quinoline 1-oxide</td>
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<tr>
<td>44</td>
<td>2-(1H-imidazol-1-yl)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
<td>+</td>
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<tr>
<td>45</td>
<td>2-(1H-imidazol-4'-yl)-N-(2'-(naphthalen-2'-yl)benzo[d]oxazol-5''-y)acetamide hydrochloride</td>
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<td>methyl ethyl(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)phosphinate</td>
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<td>(S)-N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-(methylamino)propanamide</td>
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<td>48</td>
<td>2-hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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<tr>
<td>49</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)-2-(beta-D-galactopyranosyloxy)acetamide</td>
<td>+++</td>
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<tr>
<td>50</td>
<td>3,3,3-trifluoro-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide</td>
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<td>51</td>
<td>2-methoxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
<td>++++</td>
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<tr>
<td>52</td>
<td>2-(2-methoxyethoxy)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
<td>++++</td>
</tr>
<tr>
<td>53</td>
<td>(S)-2-amino-N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)propanimide</td>
<td>+++</td>
</tr>
<tr>
<td>54</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propionimidamide</td>
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<tr>
<td>55</td>
<td>5-(ethyisulfanyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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<tr>
<td>56</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)methanesulfonamide</td>
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</tr>
<tr>
<td>57</td>
<td>2-(4,4-difluorocyclohexyl)-5-(ethylsulfonyl)benzo[d]oxazole</td>
<td>+</td>
</tr>
<tr>
<td>58</td>
<td>3-hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide</td>
<td>++++</td>
</tr>
<tr>
<td>59</td>
<td>ethyl 2-(naphthalen-2-yl)benzo[d]oxazol-5-yl(phenyl)phosphinate</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Effect</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------------------------------------------------------------</td>
<td>--------</td>
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<tr>
<td>60</td>
<td>methyl 2-(3,4-dichlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate</td>
<td>+</td>
</tr>
<tr>
<td>61</td>
<td>methyl 2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate</td>
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<tr>
<td>62</td>
<td>5-(ethylsulfonyl)-2-(naphthalen-2-ylmethyl)benzo[d]oxazole</td>
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</tr>
<tr>
<td>63</td>
<td>2-(4-chlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphoric acid</td>
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<td>64</td>
<td>2-morpholino-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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</tr>
<tr>
<td>65</td>
<td>N-methyl-2-(naphthalen-2-yl)benzo[d]oxazole-5-sulfonamide</td>
<td>++++</td>
</tr>
<tr>
<td>66</td>
<td>N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(pyridin-2-yl)oxacylamide</td>
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<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)-2-(piperidin-1-yl)acetamide</td>
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</tr>
<tr>
<td>68</td>
<td>5-(methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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</tr>
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<td>69</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-3-(beta-D-glucopyranosyloxy)propanamide</td>
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<td>70</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-(beta-D-mannopyranosyloxy)acetamide</td>
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<td>71</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-methylaminoacetamide</td>
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<tr>
<td>72</td>
<td>5-(2',2',2'-trideuteroethylsulfonyl)-2-(naphthalen-2'-'yl)benzo[d]oxazole</td>
<td>++++</td>
</tr>
<tr>
<td>73</td>
<td>(S)-2-amino-3-hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide</td>
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<tr>
<td>74</td>
<td>(S)-2-(methylamino)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide</td>
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</tr>
<tr>
<td>75</td>
<td>2-(6-nitromidazol[1,2-a]pyridin-2-yl)benzo[d]thiazole</td>
<td>+++</td>
</tr>
<tr>
<td>76</td>
<td>(E)-5-(ethylsulfonyl)-2-styrylbenzo[d]oxazole</td>
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<td>77</td>
<td>5-(ethylsulfonyl)-2-(1,2,3,4-tetrahydroquinophthalen-2-yl)benzo[d]oxazole</td>
<td>++++</td>
</tr>
<tr>
<td>78</td>
<td>5-(ethylsulfonyl)-2-(4-phenoxyphenyl)benzo[d]oxazole</td>
<td>+</td>
</tr>
<tr>
<td>79</td>
<td>2-(2,3-dihydro-1H-inden-5-yl)-5-(ethylsulfonyl)benzo[d]oxazole</td>
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</tr>
<tr>
<td>80</td>
<td>2-(4H-1,2,4-triazol-3-ythio)-N-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)acetamide</td>
<td>+++</td>
</tr>
<tr>
<td>81</td>
<td>1-(2'-(naphthalen-2'-yl)benzo[d]oxazol-5'-yl)pyrrolidin-2-one</td>
<td>+</td>
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<tr>
<td>82</td>
<td>2-(4H-1,2,4-triazol-3-ythio)-N-(5-(benzo[d]thiazol-2-yl)pyridine-3-yl)acetamide</td>
<td>++</td>
</tr>
<tr>
<td>83</td>
<td>2-(benzo[b]thiophen-1,1-dioxide-5-yl)-5-(ethylsulfonyl)benzo[d]oxazole</td>
<td>+</td>
</tr>
<tr>
<td>84</td>
<td>5-(morpholinomethyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
<td>++++</td>
</tr>
<tr>
<td>85</td>
<td>5-(ethylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
<td>+++</td>
</tr>
<tr>
<td>86</td>
<td>5-(methylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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<tr>
<td>87</td>
<td>5-(methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole</td>
<td>++</td>
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<tr>
<td>88</td>
<td>2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)methylaminioacetic acid</td>
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<tr>
<td>89</td>
<td>5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole</td>
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<tr>
<td>90</td>
<td>N-ethyl-2-(naphthalen-2-yl)benzo[d]oxazole-5-sulfonamide</td>
<td>++++</td>
</tr>
<tr>
<td>91</td>
<td>(S)-2-hydroxy-N,N,N-trimethyl-4-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylamino)-4-oxobutan-1-aminium</td>
<td>+</td>
</tr>
</tbody>
</table>

Further active compounds are 2-naphthalen-2-yl-5-(pyrrolidine-1-sulfonyl)-benzo[oxazole, 5-methoxy-2-(naphthalen-2-yl)benzo[d]oxazole, 2-(naphthalen-2-yl)benzo[d]oxazol-5-ol, 5-(2-
(benzyloxy)ethoxy)-2-(naphthalen-2-yl)benzo[d]oxazole, 2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)ethanol, (2-phenyl-1H-indol-3-yl)methanol and 2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylsulfonyl)ethanol.

Other active compounds include 5-methoxy-2-(naphthalen-2-yl)benzo[d]oxazole (++) , 2-(naphthalen-2-yl)benzo[d]oxazol-5-ol (++) , 5-(2-(benzyloxy)ethoxy)-2-(naphthalen-2-yl)benzo[d]oxazole (+), 2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylsulfonyl)ethanol (++) , 2-(naphthalen-2-yl)-5-(pyrrolidin-1-ylsulfonyl)benzo[d]oxazole (+), and 2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)ethanol (+), where (++) and (+) have the meanings shown for Table 1.

**Experimental**

HPLC-UV-MS was performed on a Gilson 321 HPLC with detection performed by a Gilson 170 DAD and a Finnigan AQA mass spectrometer operating in electrospray ionisation mode. The HPLC column used is a Phenomenex Gemini C18 150x4.6mm. Preparative HPLC was performed on a Gilson 321 with detection performed by a Gilson 170 DAD. Fractions were collected using a Gilson 215 fraction collector. The preparative HPLC column used is a Phenomenex Gemini C18 150x10mm and the mobile phase is acetonitrile/water.

$^1$H NMR spectra were recorded on a Bruker instrument operating at 300 MHz. NMR spectra were obtained as CDCl$_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm) or DMSO-D$_6$ (2.50 ppm). When peak multiplicities are reported, the following abbreviations are used s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets). Coupling constants, when given, are reported in Hertz (Hz).

Column chromatography was performed either by flash chromatography (40-65μm silica gel) or using an automated purification system (SP1™ Purification System from Biotage®). Reactions in the microwave were done in an Initiator 8™ (Biotage).

The abbreviations used are DMSO (dimethylsulfoxide), HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HCl (hydrochloric acid), MgSO$_4$ (magnesium sulfate), NaOH (sodium hydroxide), Na$_2$CO$_3$ (sodium carbonate), NaHCO$_3$ (sodium bicarbonate), STAB (sodium triacetoxyborohydride), THF (tetrahydrofuran).
EXAMPLE 1 (Compounds 1)

3-(5-Methylbenzo[d]oxazol-2-yl)pyridin-2-ol

To polyphosphoric acid at 110°C were added simultaneously 2-amino-4-methylphenol (123mg, 1.0mmol) and 2-hydroxynicotinic acid (139mg, 1.0mmol). The resulting mixture was then heated to 180°C for 5h. The solution was then poured into water. The resulting precipitate was basified with aqueous NaOH solution and then collected by filtration to afford 70mg (31%) of the title compound (LCMS RT = 5.19min, MH⁺ 227.1)

¹H NMR (DMSO): 8.06 (1H, dd, J 7.4 2.3 Hz), 7.89 (1H, dd, J 5.2 2.3 Hz), 7.54-7.48 (2H, m), 7.10 (1H, dd, J 8.3 1.2 Hz), 6.17 (1H, dd, J 7.4 5.8 Hz), 2.41 (3H, s)

All compounds below were prepared following the same general method and purified either by trituration, recrystallisation or column chromatography.

3-(5-Methylbenzo[d]oxazol-2-yl)pyridin-2-ol
LCMS RT = 5.19 min, MH⁺ 227.1; ¹H NMR (DMSO): 8.06 (1H, dd, J 7.4 2.3 Hz), 7.89 (1H, dd, J 5.2 2.3 Hz), 7.54-7.48 (2H, m), 7.10 (1H, dd, J 8.3 1.2 Hz), 6.17 (1H, dd, J 7.4 5.8 Hz), 2.41 (3H, s)

5-(5-Methylbenzo[d]oxazol-2-yi)pyridin-2-ol
LCMS RT = 5.34 min, MH⁺ 227.1; ¹H NMR (DMSO): 12.25 (1H, br), 8.23 (1H, d, J 2.2 Hz), 8.08 (1H, dd, J 9.6 2.6 Hz), 7.58 (1H, d, J 8.5 Hz), 7.52 (1H, s), 7.18 (1H, d, J 8.5 Hz), 6.53 (1H, d, J 9.6 Hz), 2.43 (3H, s)

5-(5-Methylbenzo[d]oxazol-2-yi)pyridin-2-amine
LCMS RT = 5.82 min, MH⁺ 226.1; ¹H NMR (DMSO): 11.74 (1H, br), 11.55 (1H, s), 8.32 (1H, s), 7.58 (1H, d, J 8.6 Hz), 7.51 (1H, s), 7.18 (1H, d, J 9.3 Hz), 2.43 (3H, s)

5-(5-Methylbenzo[d]oxazol-2-yi)pyrimidine-2,4-diol
LCMS RT = 4.98 min, MH⁺ 244.0; ¹H NMR (DMSO): 11.21 (1H, s), 8.40 (1H, d, J 8.2 Hz), 7.36-7.34 (1H, m), 7.67 (1H, d, J 8.8 Hz), 7.35-7.30 (1H, m), 6.29 (1H, dd, J 8.6 2.2 Hz), 6.20-6.16 (3H, m)

5-Amino-2-(5-(trifluoromethoxy)benzo[d]oxazol-2-yi)phenol
LCMS RT = 7.14 min, MH⁺ 311.1; ¹H NMR (DMSO): 10.93 (1H, br), 7.82 (1H, d, J 8.8 Hz), 7.76-7.74 (1H, m), 7.67 (1H, d, J 8.8 Hz), 7.35-7.30 (1H, m), 6.29 (1H, dd, J 8.6 2.2 Hz), 6.20-6.16 (3H, m)

5-Amino-2-(naphtho[1,2-d]oxazol-2-yi)phenol
LCMS RT = 7.38 min, MH⁺ 277.0; ¹H NMR (DMSO): 11.21 (1H, s), 8.40 (1H, d, J 8.2 Hz), 8.10 (1H, d, J 8.4 Hz), 7.96-7.89 (2H, m), 7.73-7.67 (2H, m), 7.63-7.56 (1H, m), 6.31 (1H, dd, J 8.7 2.1 Hz), 6.23 (1H, d, J 2.1 Hz), 6.05 (2H, s)

5-Amino-2-(5-phenylbenzo[d]oxazol-2-yi)phenol
LCMS RT = 7.75 min, MH⁺ 303.1; ¹H NMR (DMSO): 11.18 (1H, s), 7.95 (1H, d, J 1.8 Hz), 7.78 (1H, d, J 8.6 Hz), 7.75-7.71 (2H, m), 7.67 (1H, d, J 8.8 Hz), 7.62 (1H, dd, J 8.6 1.9 Hz), 7.52-7.45 (2H, m), 7.41-7.35 (1H, m), 6.30 (1H, dd, J 8.6 2.1 Hz), 6.20 (1H, d, J 2.0 Hz), 6.11 (2H, s)
5-(Ethylsulfonyl)-2-(isoquinolin-3-yl)benzo[d]oxazole
LCMS RT= 5.94min, MH⁺ 339.2; ¹H NMR (DMSO): 9.55 (1H, s), 8.99 (1H, s), 8.38 (1H, dd, J 1.9 0.6 Hz), 8.32-8.27 (2H, m), 8.16 (1H, dd, J 8.5 0.5 Hz), 8.01 (1H, dd, J 8.6 1.9 Hz), 7.98-7.85 (2H, m), 3.42 (2H, q, J 7.4 Hz), 1.15 (3H, t, J 7.4 Hz)

5-(Ethylsulfonyl)-2-(quinolin-6-yl)benzo[d]oxazole
LCMS RT= 5.78min, MH⁺ 339.2; ¹H NMR (DMSO): 9.05 (1H, dd, J 4.3 1.8 Hz), 8.99 (1H, d, J 1.9 Hz), 8.67 (1H, dd, J 8.7 1.3 Hz), 8.54 (1H, dd, J 8.9 1.9 Hz), 8.37 (1H, d, J 1.6 Hz), 8.25 (1H, d, J 9.0 Hz), 8.13 (1H, d, J 8.6 Hz), 8.00 (1H, dd, J 8.6 1.7 Hz), 7.69 (1H, dd, J 8.4 4.2 Hz), 3.42 (2H, q, J 7.4 Hz), 1.14 (3H, t, J 7.4 Hz)

5-(Ethylsulfonyl)-2-(quinoxalin-6-yl)benzo[d]oxazole
LCMS RT= 5.57min, MH⁺MeCN⁺ 380.9; ¹H NMR (DMSO): 9.10 (2H, dd, J 5.9 1.9 Hz), 8.89 (1H, d, J 1.8 Hz), 8.64 (1H, dd, J 8.9 2.0 Hz), 8.41 (1H, dd, J 1.8 0.5 Hz), 8.36 (1H, d, J 8.8 Hz), 8.17 (1H, dd, J 8.5 0.5 Hz), 8.02 (1H, dd, J 8.5 1.8 Hz), 3.42 (2H, q, J 7.4 Hz), 1.14 (3H, t, J 7.4 Hz)

Modified procedure 1A:

5-(Ethylsulfonyl)-2-(naphthalen-2-ylmethyl)benzo[d]oxazole
A mixture of 2-amino-4-(ethylsulfonyl)phenol (300mg, 1.49mmol) and 2-naphthylacetic acid (417mg, 2.24mmol) was heated at 125°C in polyphosphoric acid (PPA) for 5 hours. After cooling to room temperature, the reaction mixture was poured into ice water and neutralized with NaOH (5M) to pH = 7. The reaction mixture was extracted 3 times with EtOAc, the organic phase combined, dried over sodium sulfate and concentrated in vacuo to give a yellow oil. Purification using biotage 30% EtOAc/70% petroleum gave 160mg of a yellow solid
30% Yield, 97% UV purity.

LCMS RT= 6.50min, MH⁺ 352.0
¹H NMR (CDCl₃): 8.19ppm (1H, d, J 1.77 Hz), 7.77ppm (5H, m), 7.55ppm (1H, d, J 8.52 Hz), 7.42ppm (3H, m ), 4.41ppm (2H , s), 3.06ppm (2H, q, J 7.42 Hz), 1.19ppm (3H,t, J 7.42 Hz).

5-(Ethylsulfonyl)-2-(1,2,3,4-tetrahydronaphthalen-2-yl)benzo[d]oxazole
A mixture of 2-amino-4-(ethylsulfonyl)phenol (201 mg; 2 mmol) and 1,2,3,4-tetrahydro-2-naphthoic acid (352 mg; 2 mmol) was heated at 180°C in polyphosphoric acid (PPA) for 16 hours.

After cooling to room temperature, the reaction mixture was poured into ice water and neutralized with NaOH (5 M) to pH = 7. The reaction mixture was extracted 3 times with EtOAc, the organic phase combined, dried over magnesium sulfate and concentrated in vacuo. The crude product was purified on silica with 5:1 Petrol ether/Ethyl acetate. The product was then further purified by HPLC to give the title compound as a white solid, 97 % pure by UV LCMS.

**LCMS RT= 6.77min, MH+ = 342.1; 1H NMR (CDCl3):** 8.19 (1H, d, J 1.8 Hz), 7.83 (1H, dd, J 8.6 and 1.8 Hz), 7.60 (1H, d, J 8.6 Hz), 7.13-7.04 (4H, m), 3.44-3.33 (1H, m), 3.28-3.20 (2H, m), 3.12-3.04 (2H, q, J 7.4 Hz), 2.97-2.90 (2H, m), 2.48-2.37 (1H, m), 2.15-1.99 (1H, m), 1.24-1.16 (3H t, J 7.5 Hz).

The following two compounds were prepared using the same general method:

**5-(Ethylsulfonyl)-2-(4-phenoxyphenyl)benzo[d]oxazole**

**LCMS RT= 7.46min, MH+ = 379.9; 1H NMR (DMSO):** 8.28-8.23 (3H, m), 8.06 (1H, d, J 8.6 Hz), 7.93 (1H, dd, J 8.6, J 1.8 Hz), 7.52-7.47 (2H, m), 7.30-7.25 (1H, m), 7.21-7.18 (4H, m), 3.40 (2H, q, J 7.4 Hz), 1.12 (3H, t, J 7.3 Hz).

**2-(2,3-Dihydro-1H-inden-5-yl)-5-(ethylsulfonyl)benzo[d]oxazole**

**LCMS RT= 7.42min, MH+ = 328.0; 1H NMR (DMSO):** 8.27 (1H, d, J 1.5 Hz), 8.09-8.02 (3H, m), 7.93 (1H, dd, J 8.6, J 1.8 Hz), 7.49 (1H, d, J 8.0 Hz), 3.38 (2H, q, J 7.4 Hz), 2.98 (4H, q, J 7.1 Hz), 2.14-2.04 (2H, m), 1.12 (3H, t, J 7.3 Hz).

**Method 1A (Compounds Ic)**

**5-(Methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole**

**Preparation of 2-amino-4-(methylsulfonyl)phenol**

Boron tribromide (1M in dichloromethane, 39mL, 39.8 mmol) was added to a solution of 2-methoxy-5-(methylsulfonyl)aniline (2g, 9.94 mmol) in dichloromethane (30mL) and the
resultant solution was allowed to stir at room temperature for 10 minutes before being heated at reflux for 5 hours. After this time the reaction mixture was cooled to 0°C and quenched by the cautious addition of water. The organic layer was separated and the aqueous layer was concentrated **in vacuo**. The crude reaction mixture was suspended in toluene and concentrated **in vacuo** to give the title compound as a beige powder (4.4g), contaminated with boron salts after drying under vacuum for 24 hours.

**1H NMR (d6-DMSO)** 11.67 (1H, br s), 7.70-7.76 (2H, m), 7.16-7.19 (1H, m), 3.18 (3H, s).

**Preparation of 5-(methylsulfonyl)-2-(naphthalen-2'-yl)benzo[d]oxazole**

2-amino-4-(methylsulfonyl)phenol (approx. 44% by mass, 2g, 4.700mmol) and 2-naphthoic acid (890mg, 5.170mmol) were mixed and added in one portion to a heated flask of polyphosphoric acid (30mL, heated at 110°C). The resultant reaction mixture was heated at 120°C for 16 hours before being diluted with water (200mL). The mixture was adjusted to pH 8 with solid potassium carbonate and the title compound collected as an off-white solid by filtration (1.157g, 76%) (LCMS RT=6.73min, MH+ 324).

**1H NMR (300MHz, DMSO)** 8.93 (1H, s), 8.41 (1H, d, J 1.4 Hz), 8.32 (1H, dd, J 8.6 1.7 Hz), 8.23-8.26 (1H, m), 8.20 (1H, d, J 8.8 Hz), 8.13 (1H, d, J 8.6 Hz), 8.03-8.10 (2H, m), 3.34 (3H, s).

**Method 1Ai**

2-(4,4-Difluorocyclohexyl)-5-(ethylsulfonyl)benzo[d]oxazole

A solution of 4,4-difluorocyclohexane carboxylic acid (0.10g, 0.62mmol) and oxalyl chloride (64 µL, 0.74mmol) in DCM (2 mL), containing one drop of DMF, was stirred at room temperature for 1h. The solvents were removed in vacuo and the residue dissolved in xylene (2 mL), 2-amino-4-(ethylsulfonyl)phenol (0.13g, 0.62mmol) was added and the resulting reaction mixture was heated under reflux at 155 C for 1h. PTSA (59mg, 0.31mmol) was added and refluxing was continued for a further 2h, after which the reaction mixture was absorbed onto silica gel. Purification by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 3/7 v/v, afforded 117 mg (57%) of the title compound. (LCMS RT= 6.00min, MH+ 330.1)

**1H NMR (CDCl3):** 8.28 (1H, d, J 1.6 z), 7.93 (1H, dd, J 1.8 z, J 8.6 z), 7.68 (1H, d, J 8.6 Hz), 3.17 (2H, q, J 7.5 Hz), 2.31-1.90 (8H, m), 1.57 (1H, bs), 1.30 (3H, t, J 7.5 Hz).
**Method 1B (Compounds I)**

_N-Methyl-(2-naphthalen-2-yl)benzo[d]oxazol-5-yl)sulfonamide_

A mixture of 2-aminophenol-4-sulfomethylamide (252mg, 1.248mmol) and 2-naphthoyl chloride (285mg, 1.497mmol) in 1,4-dioxane (1.7ml) was heated at 200°C for 15mins under microwave activation. After cooling, 1M aq. sodium hydroxide was added (pH13) and the resultant solid collected by filtration. Drying in vacuo gave the title compound as an off-white solid (280mg, 66%).

**LCMS RT=** 6.62min, peak includes [M+MeCN]⁺; **¹H NMR (CDCl₃):** 8.84 (1H, br s); 8.34 (2H, m); 8.04 (2H, m); 7.95 (2H, m); 7.78 (1H, m); 7.64 (2H, m); 4.36 (1H, m); 2.74 (3H, d, J = 5.4 Hz).

**(E)-5-(Ethylsulfonyl)-2-styrylbenzo[d]oxazole**

**LCMS RT=** 6.49min, MH⁺ 314.1; **¹H NMR (DMSO):** 8.23 (1H, dd, J 1.7, J 0.5 Hz), 8.01 (1H, dd, J 8.5 J 0.5 Hz), 7.93 (1H, d, J 16.4 Hz), 7.92 (1H, dd, J 8.6, J 1.8 Hz), 7.87-7.84 (2H, m), 7.48-7.44 (2H, m), 7.42 (2H, d, J 16.4 Hz), 3.39 (2H, q, J 7.4 Hz), 1.12 (3H, t, J 7.3 Hz).

**Modified procedure**

_5-(Ethylsulfonyl)-2-(furan-2-yl)benzo[d]oxazole_

To 2-amino-4-(methylsulfonyl)phenol (201mg, 1.00mmol) in dry dioxane (2mL) was added furan-2-carbonyl chloride (98μL, 1.00mmol) at room temperature. The reaction vessel was heated in the microwave at 210°C for 15min. After cooling, the mixture was slowly poured into water, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄ and evaporated. The resulting solid was purified by column chromatography eluting with ethyl acetate/hexanes 1:2 v/v to afford 40mg (14%) of the title compound (**LCMS RT=** 5.73min, MH⁺ 277.9); **¹H NMR (DMSO):** 8.20 (1H, d, J 1.9 Hz), 8.08-8.07 (1H, m), 7.98 (1H, dd, J 8.6 0.5 Hz), 7.87 (1H, dd, J 8.6 1.8 Hz), 7.52 (1H, dd, J 3.6 0.7 Hz), 6.80 (1H, dd, J 3.6 1.7 Hz), 3.31 (2H, q, J 7.4 Hz), 1.05 (3H, t, J 7.4 Hz)

All compounds below were prepared following the same general method. The acid chloride used was either a commercially available compound or synthesized from the corresponding carboxylic acid using standard conditions.
**2-(3',4'-Dichlorophenyl)-6-(ethylsulfonyl)-benzoxazole**

LCMS RT= 7.45min; \(^1\)H NMR (DMSO): 8.40 (1H, d, \(J 2.0\) Hz), 8.36 (1H, d, \(J 1.7\) Hz), 8.20 (1H, dd, \(J 8.4\) 2.0 Hz), 8.10 (1H, d, \(J 8.5\) Hz), 7.97-7.93 (2H, m), 3.40 (2H, q, \(J 7.4\) Hz), 1.13 (3H, t, \(J 7.4\) Hz)

**2-(4'-Chlorophenyl)-6-(ethylsulfonyl)-benzoxazole**

\(^1\)H NMR (CDCl\(_3\)): 8.25 (2H, d, \(J 8.6\) Hz), 8.20-8.19 (1H, m), 7.95-7.94 (2H, m), 7.58 (2H, d, \(J 8.5\) Hz), 3.21 (2H, q, \(J 7.3\) Hz), 1.33 (3H, t, \(J 7.4\) Hz)

**Method 1C (Compounds 1)**

**5-(Ethylsulfonyl)-2-(naphthalen-2-ylmethyl)benzo[d]oxazole**

A mixture of 2-amino-4-(ethylsulfonyl)phenol (300mg, 1.49mmol) and 2-naphthylacetic acid (417mg, 2.24mmol) was heated at 125°C in polyphosphoric acid (PPA) for 5 hours. After cooling to room temperature, the reaction mixture was poured into ice water and neutralized with NaOH (5M) to pH =7. The reaction mixture was extracted 3 times with EtOAc, the organic phase combined, dried over sodium sulfate and concentrated \textit{in vacuo} to give a yellow oil. Purification using biotage 30% EtOAc/70% petroleum gave 160mg of a yellow solid 30% Yield, 97% UV purity.

LCMS RT= 6.50min, MH\(^+\) 352.0; \(^1\)H NMR (CDCl\(_3\)): 8.19ppm (1H, d, \(J 1.77\) Hz), 7.77ppm (5H, m), 7.55ppm (1H, d, \(J 8.52\) Hz), 7.42ppm (3H, m), 4.41ppm (2H, s), 3.06ppm (2H, q, \(J 7.42\) Hz), 1.19ppm (3H, t, \(J 7.42\) Hz).

**5-(Ethylsulfonyl)-2-(1,2,3,4-tetrahydronaphthalen-2-yl)benzo[d]oxazole**

A mixture of 2-amino-4-(ethylsulfonyl)phenol (201 mg; 2 mmol) and 1,2,3,4-tetrahydro-2-naphthoic acid (352 mg; 2 mmol) was heated at 180°C in polyphosphoric acid (PPA) for 16 hours. After cooling to room temperature, the reaction mixture was poured into ice water and neutralized with NaOH (5M) to pH =7. The reaction mixture was extracted 3 times with EtOAc, the organic phase combined, dried over magnesium sulfate and concentrated \textit{in vacuo}. The crude product was purified on silica with 5:1 Petrol ether/Ethyl acetate. The
product was then further purified by HPLC to give the title compound as a white solid, 97 % pure by UV LCMS.

**LCMS RT** = 6.77min, **MH** = 342.1; **¹H NMR (CDCl₃)**: 8.19 (1H, d, J 1.8 Hz), 7.83 (1H, dd, J 8.6 and 1.8 Hz), 7.60 (1H, d, J 8.6 Hz), 7.13-7.04 (4H, m), 3.44-3.33 (1H, m), 3.28-3.20 (2H, m), 3.12-3.04 (2H, q, J 7.4 Hz), 2.97-2.90 (2H, m), 2.48-2.37 (1H, m), 2.15-1.99 (1H, m), 1.24-1.16 (3H, t, J 7.5 Hz).

The following two compounds were prepared using the same general method:

5-(Ethylsulfonyl)-2-(4-phenoxyphenyl)benzo[d]oxazole
**LCMS RT** = 7.46min, **MH** = 379.9; **¹H NMR (DMSO)**: 8.28-8.23 (3H, m), 8.06 (1H, d, J 8.6 Hz), 7.93 (1H, dd, J 8.6, J 1.8 Hz), 7.52-7.47 (2H, m), 7.49-7.45 (1H, d, J 8.0 Hz), 3.38 (2H, q, J 7.4 Hz), 2.98 (4H, q, J 7.1 Hz), 2.14-2.04 (2H, m), 1.12 (3H, t, J 7.3 Hz).

2-(2,3-Dihydro-1H-inden-5-yI)-5-(ethylsulfonyl)benzo[d]oxazole
**LCMS RT** = 7.42min, **MH** = 328.0; **¹H NMR (DMSO)**: 8.27 (1H, d, J 1.5 Hz), 8.09-8.02 (3H, m), 7.93 (1H, dd, J 8.6, J 1.8 Hz), 7.49 (1H, d, J 8.0 Hz), 3.38 (2H, q, J 7.4 Hz), 2.98 (4H, q, J 7.1 Hz), 2.14-2.04 (2H, m), 1.12 (3H, t, J 7.3 Hz).
**EXAMPLE 2**

(2-(Naphthalen-2-yl)benzo[d]oxazol-6-yl)methanol

To a stirred suspension of methyl 2-(naphthalen-2-yl)benzo[d]oxazole-6-carboxylate (152mg, 0.5mmol) in dry tetrahydrofuran was added lithium aluminium hydride (38mg, 1.0mmol). The resulting solution was stirred at room temperature for 16h. The crude mixture was then diluted with ethyl acetate, washed with aqueous 1M HCl solution and brine. The combined organic layers were dried over anhydrous MgSO₄ and evaporated. The resulting product was purified by column chromatography eluting with ethyl acetate/hexanes 1:1 v/v to afford 90mg (66%) of the title compound (LCMS RT= 6.40min, MH⁺ 276.1)

¹H NMR (DMSO): 8.83 (1H, s), 8.27 (1H, dd, J 8.9 1.8 Hz), 8.21-8.17 (1H, m), 8.14 (1H, d, J 8.9 Hz), 8.06-8.02 (1H, m), 7.78 (1H, d, J 8.2 Hz), 7.74 (1H, s), 7.70-7.62 (2H, m), 7.39 (1H, dd, J 8.0 0.8 Hz), 5.40 (1H, t, J 5.9 Hz), 4.67 (2H, d, J 5.6 Hz)

**EXAMPLE 3 (Compounds II)**

2-(Dimethylamino)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide

To a solution of 2-(naphthalen-2-yl)benzo[d]oxazol-5-amine (390mg, 1.50mmol) in dichloromethane (20mL) at room temperature was added diisopropylethylamine (784μL, 4.50mmol) and a catalytic amount of DMAP, followed immediately after by the addition of 2-(dimethylamino)acetyl chloride (296mg, 1.88mmol). After 4h at room temperature, a further addition of diisopropylethylamine (784μL, 4.50mmol) and 2-(dimethylamino)acetyl chloride (237mg, 1.50mmol) was made, and the resulting mixture was stirred at room temperature for 16h. Dichloromethane was then removed in vacuo, water was added, and a solid precipitated out. The obtained solid was washed with aqueous potassium carbonate solution to afford 430.2mg (83%) of the title compound (LCMS RT= 7.52min, MH⁺ 346.2)

¹H NMR (DMSO): 9.94 (1H, s), 8.83 (1H, s), 8.28-8.11 (4H, m), 8.06-8.01 (1H, m), 7.75 (1H, d, J 8.6 Hz), 7.70-7.62 (3H, m), 3.12 (2H, s), 2.31 (6H, s).

LCMS RT= 7.52min, MH⁺ 346.2; ¹H NMR (DMSO): 9.94 (1H, s), 8.83 (1H, s), 8.28-8.11 (4H, m), 8.06-8.01 (1H, m), 7.75 (1H, d, J 8.6 Hz), 7.70-7.62 (3H, m), 3.12 (2H, s), 2.31 (6H, s).

3,3,3-Trifluoro-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide
LCMS RT= 6.98min, MH⁺ 371; ¹H NMR (DMSO): 10.52 (1H, s), 8.85 (1H, s), 8.27 (1H, dd, J 8.6 1.7 Hz), 8.21-8.12 (3H, m), 8.07-8.02 (1H, m), 7.81 (1H, d, J 8.6 Hz), 7.69-7.64 (2H,m), 7.53 (1H, dd, J 8.7 2.0 Hz), 3.56 (2H, q, J 11.2 Hz).

Precursors to the two compounds below were obtained using this general method for the coupling, but the title compounds product were obtained after deprotection using TFA/DCM 3:10 v/v at room temperature for 2h:

(S)-N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-2-(methylamino)propanamide
LCMS RT= 6.29min, MH⁺ 364.1; ¹H NMR (DMSO): 8.26 (1H, d, J 1.5 Hz), 8.10 (1H, dd, J 7.8 1.5 Hz), 7.90 (1H, dd, J 8.1 1.5 Hz), 7.79-7.69 (2H, m), 7.60 (1H, t, J 8.0 Hz), 3.61 (1H, q, J 7.4 Hz), 2.44 (3H, s), 1.40 (3H, d, J 6.9 Hz).

(S)-2-Amino-N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)propanamide
LCMS RT= 5.96min, MH⁺ 350.1; ¹H NMR (DMSO): 8.29 (1H, d, J 2.0 Hz), 8.11 (1H, dd, J 7.8 1.5 Hz), 7.93 (1H, dd, J 8.1 1.5 Hz), 7.78 (1H, d, J 8.8 Hz), 7.67 (1H, dd, J 8.8 2.1 Hz), 7.60 (1H, t, J 8.0 Hz), 3.50 (1H, q, J 6.6 Hz), 1.26 (3H, d, J 6.9 Hz).

The compounds below were obtained using the same general method for the coupling, and didn’t require a deprotection step:

2-(1H-Imidazol-1-yl)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide
LCMS RT= 5.79min, MH⁺ 369; ¹H NMR (DMSO): 10.52 (1H, s), 8.84 (1H, s), 8.26 (1H, dd, J 8.6 1.6 Hz), 8.20-8.11 (3H, m), 8.06-8.02 (1H, m), 7.80 (1H, d, J 8.9 Hz), 7.70-7.61 (3H, m), 7.56 (1H, dd, J 8.8 2.0 Hz), 7.20 (1H, s), 6.92 (1H, s), 4.96 (2H, s).

2-(1H-Imidazol-4-yl)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide
LCMS RT= 5.66min, MH⁺ 369; ¹H NMR (DMSO): 12.00-11.87 (1H, m), 10.31 (1H, s), 8.83 (1H, s), 8.26 (1H, dd, J 8.6 1.7 Hz), 8.22-8.11 (3H, m), 8.06-8.01 (1H, m), 7.76 (1H, d, J 9.0 Hz), 7.68-7.63 (2H, m), 7.60-7.54 (2H, m), 3.59 (2H, s).

**EXAMPLE 4 (Compounds II)**
As Method 3A, except instead of diisopropylamine, triethylamine was used as a base.

2-Methoxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide

LCMS RT = 6.69 min, \( MH^+ 333.2 \); \( ^1H \) NMR (CDCl\(_3\)): 8.80 (1H, s), 8.40 (1H, br), 8.32 (1H, dd, \( J \) 8.5 1.8 Hz), 8.09-8.08 (1H, m), 8.03-7.98 (2H, m), 7.94-7.90 (1H, m), 7.63-7.56 (4H, m), 4.09 (2H, s), 3.57 (3H, s).

2-(2-Methoxyethoxy)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide

LCMS RT = 6.77 min, \( MH^+ 377.1 \); \( ^1H \) NMR (CDCl\(_3\)): 9.08 (1H, s), 8.80 (1H, s), 8.33 (1H, dd, \( J \) 8.9 1.8 Hz), 8.09 (1H, d, \( J \) 1.9 Hz), 8.04-7.98 (2H, m), 7.94-7.90 (1H, m), 7.69-7.56 (4H, m), 4.19 (2H, s), 3.85-3.81 (2H, m), 3.70-3.66 (2H, m), 3.54 (3H, s).

**EXAMPLE 5**

2-Bromo-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide

2-(naphthalen-2-yl)benzo[d]oxazol-5-amine (1eq, 2g, 7.7 mmol) was added to a stirred solution of dichloromethane (40 ml), to this was added triethylamine (1.2eq, 0.934g, 9.2 mmol, 1.28ml) and 2-bromoacetyl bromide (1.1eq, 1.706g, 8.4 mmol, 0.734ml). This was stirred at room temperature for 18 hours. The crude product was extracted in dichloromethane and washed with water. The organic layer was dried over magnesium sulphate and solvent removed in vacuo. Flash column chromatography of the crude product using a gradient (ethyl acetate/hexanes 1:1 run to ethyl acetate/hexanes 1:0) afforded 2.8 g (96%) of the title compound.

**EXAMPLE 6**

2-Morpholino-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide

2-bromo-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide (1eq, 0.5g, 1.3 mmol) and potassium carbonate (1.2eq, 0.218g, 1.6 mmol) were added in one portion to stirred dimethylformamide, to this was added morpholine (1.1eq, 0.126g, 1.4 mmol, 0.12ml). The reaction mixture was stirred at room temperature for 18 hours. The crude product was then extracted in dichloro methane and washed with brine. The organic layer was dried over magnesium sulphate and solvent removed in vacuo. Flash column chromatography of the
crude product using a gradient (ethyl acetate/hexanes 1:1 run to ethyl acetate/hexanes 9:1) afforded 0.280g (55%) of the title compound.

**LCMS RT:** 9.11 min, **MH⁺ 386.5**; ¹H NMR (DMSO): 9.88 (1H, s), 8.83 (1H, bs), 8.26 (1H, dd, J 8.61 1.71), 8.23-8.17 (2H, m), 8.14 (1H, d, J 8.79), 8.06-8.03 (1H, m), 7.77 (1H, d, J 8.70), 7.68-7.62 (3H, m), 3.11 (2H, s), 1.63-1.56 (4H, m), 1.43-1.41 (2H, m).

## EXAMPLE 7

**N-(2-Naphthalen-2-yl)benzo[d]oxazol-5-yl)methanesulfonamide**

A mixture of **N-(2-naphthalen-2-yl)benzo[d]oxazol-5-amine** (92mg, 0.353mmol), methanesulfonyl chloride (30µL, 0.388mmol) and pyridine (5mL) was stirred at room temperature for 3.5h. The mixture was partitioned between ethyl acetate and water and the two layers separated. The aqueous layer was extracted further with ethyl acetate and the combined extracts were dried (over anhydrous MgSO₄) and concentrated in vacuo. Purification by column chromatography (eluting with 30% ethyl acetate in 60:40 petroleum ether) gave the title compound as a yellow solid.

**LCMS RT:** 6.48 min, **MH⁺ 339.1**

¹H NMR (d6-DMSO): 9.81 (1H, br m); 8.84 (1H, m); 8.27 (1H, m); 8.14-8.22 (2H, m); 8.05 (1H, m); 7.81 (1H, m); 7.67 (3H, m); 7.30 (1H, dd, J = 8.7 & 2.1 Hz); 2.99 (3H, s).

## EXAMPLE 8

**N-(2-Naphthalen-2-yl)benzo[d]oxazol-5-yl)propionimidamide**

To a stirred solution of **N-(2-naphthalen-2-yl)benzo[d]oxazol-5-amine** (298mg, 1.137mmol) in propionitrile (2mL, 28.03mmol) was added trimethylsilyltrifluoromethane sulfonate (236µL, 1.304mmol) dropwise at room temperature. After stirring for 24h at room temperature, the mixture was partitioned between 1N aq. sodium hydroxide and ethyl acetate and the layers separated. The aqueous layer was extracted further with ethyl acetate and the combined extracts were dried (over anhydrous MgSO₄) and concentrated in vacuo. Purification by column chromatography (gradient elution using 30%-90% ethyl acetate in 60:40 petroleum ether, then neat ethyl acetate and methanol) gave the title compound as a brown solid (73mg, 20%).

**LCMS RT:** 4.43 min, **MH⁺ 316.2**

¹H NMR (d6-DMSO): 8.85 (1H, s); 8.27 (1H, m); 8.13-8.22 (2H, m); 8.05 (1H, m); 7.78 (1H, m); 7.67 (3H, m); 7.40 (1H, br); 7.03 (1H, br); 2.36 (2H, m); 1.23 (3H, br).
2-Amino-4-iodophenol
A 1M solution of BBr₃ in DCM (40 mL, 40.15mmol) was added slowly to dry DCM (40mL) at room temperature under an atmosphere of dry nitrogen, followed by 5-iodo-2-methoxyaniline (2.50 g, 10.04mmol). The resulting mixture was refluxed for 18 h under nitrogen and quenched with distilled water (50mL). The pink solid precipitated was collected by filtration and washed with water. It was then taken up in a saturated aqueous solution of sodium bicarbonate (200mL) and the aqueous layer was extracted with ethyl acetate (3 x 100mL). The combined organic extracts were washed with water until pH = 7, dried over anhydrous MgSO₄ and evaporated to afford 1.37 g (58%) of 2 as a yellow solid.

^1H NMR (DMSO): 9.26 (1H, s), 6.87 (1H, d, J 2.2 Hz), 6.66 (1H, dd, J 8.2 2.2 Hz), 6.44 (1H, d, J 8.2 Hz), 4.72 (2H, s)

5-Iodo-2-(naphthalen-2-yl)benzo[d]oxazole
To 2-amino-4-iodophenol (250mg, 1.06mmol) in dioxane (3mL) was added 2-naphthoyl chloride (203mg, 1.06mmol) at room temperature. The reaction vessel was heated in the microwave at 197°C for 15min. After cooling, the mixture was partitioned between ethyl acetate (100mL) and water (70mL) and the two layers were separated. The aqueous layer was extracted further with ethyl acetate (2 x 50mL), the combined extracts were dried over anhydrous MgSO₄ and evaporated in vacuo. The resulting solid was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 1:9 v/v) to afford 300mg (76%) of the title compound.

^1H NMR (DMSO): 8.83 (1H, s), 8.25-8.12 (4H, m), 8.05-8.02 (1H, m), 7.76 (1H, dd, J 8.5 1.7 Hz), 7.69-7.62 (3H, m)
The compounds below were prepared following the same general method.

2-(3,4-Dichlorophenyl)-5-iodobenzo[d]oxazole
LC RT= 11.45min; \(^1\)H NMR (DMSO): 8.31 (1H, d, J 2.0 Hz), 8.21 (1H, d, J 1.6 Hz), 8.12 (1H, dd, J 8.4 2.0 Hz), 7.89 (1H, d, J 8.4 Hz), 7.77 (1H, dd, J 8.5 1.6 Hz), 7.66 (1H, d, J 8.5 Hz)

2-(2,3-Dichlorophenyl)-5-iodobenzo[d]oxazole
\(^1\)H NMR (DMSO): 8.29 (1H, d, J 1.5 Hz), 8.10 (1H, dd, J 8.0 1.5 Hz), 7.94 (1H, dd, J 8.0 1.5 Hz), 7.81 (1H, dd, J 8.5 1.5 Hz), 7.70 (1H, d, J 8.5 Hz), 7.60 (1H, t, J 8.0 Hz)

**EXAMPLE 10**

Ethyl 2-(naphthalen-2-yl)benzo[d]oxazol-5-yl(phenyl)phosphinate
Tetrakis(triphenylphosphine)palladium(0) (47mg, 0.04mmol) was added in one portion to a stirred solution of 5-iodo-2-(naphthalen-2-yl)benzo[d]oxazole (147mg, 0.4mmol) and ethyl phenylphosphinate (89µL, 0.6mmol) in toluene (5mL) in the presence of triethylamine (170µL, 1.19mmol) and the resulting mixture was heated in a sealed tube at 100°C for 3 h under an atmosphere of dry nitrogen. After cooling, the mixture was partitioned between ethyl acetate (100mL) and water (70mL) and the two layers were separated. The aqueous layer was extracted further with ethyl acetate (2 x 50mL), the combined extracts were dried over anhydrous MgSO\(_4\) end evaporated in vacuo. The resulting brown oil was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 8:2 v/v) to afford 109mg (66%) of the title compound (LCMS RT= 7.54min, MH\(^+\) 414.1).

\(^1\)H NMR (DMSO): 8.86 (1H, s), 8.29-8.14 (4H, m), 8.06-7.97 (2H, m), 7.88-7.81 (3H, m), 7.71-7.51 (5H, m), 4.10-4.00 (2H, m), 1.33 (3H, t, J 7.0 Hz)

The compounds below were prepared following the same general method.

Methyl ethyl(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)phosphinate
LCMS RT= 6.41min, 2MH+ 703.2; H NMR (DMSO): 8.88 (1H, s), 8.29 (1H, dd, J 8.6 1.7), 8.23-8.15 (3H, m), 8.07-8.00 (2H, m), 7.85-7.78 (1H, m), 7.70-7.66 (2H, m), 3.55 (3H, d, J 10.9 Hz), 2.09-1.95 (2H, m), 1.05-0.93 (3H, m)

Methyl 2-(3,4-dichlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate
LCMS RT= 6.65min, MH+ 370.0; H NMR (DMSO): 8.37 (1H, d, J 2.0 Hz), 8.19-8.15 (2H, m), 8.00 (1H, dd, J 8.3 2.3 Hz), 7.92 (1H, d, J 8.4 Hz), 7.86-7.79 (1H, m), 3.53 (3H, d, J 11.0 Hz), 2.08-1.95 (2H, m), 1.03-0.92 (3H, m)

Methyl 2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate
LCMS RT= 6.23min, MH+ 370.0; H NMR (DMSO): 8.24 (1H, d, J 11.2 Hz), 8.13 (1H, d, J 7.9 Hz), 8.05-8.02 (1H, m), 7.97 (1H, d, J 8.1 Hz), 7.89-7.83 (1H, m), 7.63 (1H, t, J 7.9 Hz), 3.53 (3H, d, J 11.0 Hz), 2.09-1.96 (2H, m), 1.03-0.92 (3H, m)

(2-(4-Chlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinic acid
Trimethylsilyl bromide (120µL, 0.88mmol) was added dropwise to a stirred solution of methyl 2-(4-chlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate (161mg, 0.44mmol) in dry dichloromethane (5mL) at 0°C. The resulting solution was allowed to reach room temperature over a period of 2 h and stirred for 16 h. The crude was then diluted with dichloromethane (100mL) and the organic layer was washed with water (50mL). The aqueous layer was extracted further with dichloromethane (2 x 30mL), the combined extracts were dried over anhydrous MgSO4 and evaporated in vacuo. The resulting colorless solid was purified by column chromatography eluting using a gradient (ethyl acetate/methanol 1:0 v/v to ethyl acetate/methanol 0:1 v/v) to afford 77mg (50%) of the title compound (LCMS RT=4.44min, (M-H)+ 320.1).
H NMR (MeOH-d4): 8.12 (2H, d, J 8.8), 8.10-8.06 (1H, m), 7.78-7.72 (1H, m), 7.58 (1H, dd, J 8.1, 1.4), 7.50 (2H, d, J 8.8), 4.49 (1H, br-s), 1.65-1.53 (2H, m), 0.95-0.84 (3H, m).
**EXAMPLE 11 (Compound XXXI)**

*N-(3-(Methylsulfonyl)phenyl)naphthamide*

2-Naphthoylchloride (1.13g, 5.9mmol) was added to a solution of 3-methylsulfonyl aniline hydrochloride (1.12g, 5.4mmol) in pyridine (15mL). After stirring for 4h, the reaction mixture was partitioned between water and EtOAc and the organic phase was dried over MgSO₄ and concentrated in vacuo. The crude title compound was used in the next reaction without further purification.

**LCMS RT= 5.95min, MH⁺ 326; ¹H NMR (DMSO):** 10.81 (1H, s), 8.63 (1H, s), 8.47 (1H, s), 8.20-8.17 (1H, m), 8.12-7.99 (4H, m), 7.69-7.64 (4H, m), 3.25 (3H, s).

*N-(3-(Methylsulfonyl)phenyl)naphthalene-2-carbothioamide*

A stirred solution of N-(3-(methylsulfonyl)phenyl)naphthamide (1.67g, 5.1mmol), and lawessons reagent (1.25g, 3.1 mmol) in toluene (36mL) was heated under reflux for 16h. After cooling to room temperature the solvent was evaporated under reduced pressure and the residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/0, v/v, to afford 1.5g (85%) of the title compound.

**LCMS RT= 6.26min, MH⁺ 342.0; ¹H NMR (DMSO):** 12.20 (1H, s), 8.53 (1H, s), 8.41 (1H, s), 8.26 (1H, d, J 7.9 Hz), 8.10-8.06 (1H, m), 7.99 (3H, m), 7.85 (1H, d, J 8.1 Hz), 7.75 (1H, t, J 8.0 Hz), 7.67-7.60 (2H, m), 3.26 (3H, s).

5-(Methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole
A solution of potassium hexacyanoferrate(III) (5.96g, 18.1mmol) in water (40mL) was heated to 90°C. To it, a solution of N-(3-(methylsulfonyl)phenyl)naphthalene-2-carbothioamide (1.54g, 4.5mmol) and 3M sodium hydroxide (20mL) in IMS (15mL) was added dropwise over 5 minutes. After stirring for 30 minutes, the reaction was cooled to room temperature, filtered over a vacuum and washed with water. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/4, v/v, to afford 137mg (9%) of the title compound.

LCMS RT= 7.45min, MH⁺ 340.1; ¹H NMR (DMSO): 8.78 (1H, d, J 1.4 Hz), 8.40 (1H, dd, J 8.1, J 1.0 Hz), 8.24 (1H, dd, J 8.6, J 1.8 Hz), 8.17-8.14 (1H, m), 8.08 (1H, d, J 8.7 Hz), 8.02 (1H, dd, J 7.7, J 1.0 Hz), 8.00-7.97 (1H, m), 7.80 (1H, t, J 8.0 Hz), 7.62-7.58 (2H, m), 3.34 (3H, s).

**EXAMPLE 12 (Compound XLV)**

5-(2,2,2-Trideuteroethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole

LHMDS (1M in THF, 1.36mL, 1.36mmol) was added to a solution of 5-(methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (400mg, 1.237mmol) in THF (30mL) at -78°C under N₂. The resultant solution was allowed to stir at -78°C for 1 hour before the addition of d₃-methyl iodide. The reaction mixture was allowed to warm to room temperature over 16 hours before the addition of saturated aqueous ammonium chloride (25mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (x3). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to furnish the title compound as an off-white solid (106mg, 25%) after column chromatography (4:1 to 2:1 petrol:ethyl acetate) (LCMS RT=7.00=6min, MH⁺ 341).

¹H NMR (d6-DMSO) 8.93 (1H, s), 8.36 (1H, dd, J 1.8 0.5 Hz), 8.32 (1H, dd, J 8.7 1.8 Hz), 8.23-8.26 (1H, m), 8.19 (1H, d, J 8.8 Hz), 8.14 (1H, dd, J 8.6 0.5 Hz), 8.07-8.10 (1H, m), 8.00 (1H, dd, J 8.6 1.8 Hz), 3.41 (2H, s).

**EXAMPLE 13**

Benzyl (2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyloxy)acetate.
BF₃ OEt₂ (0.39mL, 3.1mmol) was added to a solution of 1,2,3,4,6-penta-O-acetyl-beta-D-glucopyranose (1g, 2.56mmol) and benzyl glycolate (0.44mL, 3.1mmol) in anhydrous DCM (15mL) and the resulting reaction mixture was stirred for 5hr at room temperature. The solution was neutralized with Et₃N and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/1, v/v, to afford 1g (78%) of the title compound. (LCMS RT= 5.91min, M+NH₄= 514).

1H NMR (CDCl₃): 7.35 (5H, bs), 5.23 (1H, t, J 9.5 Hz), 5.17 (2H, s), 5.07 (1H, t, J 9.8 Hz), 5.03 (1H, dd, J 7.9 Hz, J 9.6 Hz), 4.66 (1H, d, J 7.9 Hz), 4.32 (2H, s), 4.23 (1H, dd, J 4.7 Hz, J 12.4 Hz), 4.11 (1H, dd, J 2.4 Hz, J 12.4 Hz), 3.68 (1H, m), 2.06 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 1.99 (3H, s).

(2,3,4,6-Tetra-O-acetyl-beta-D-glucopyranosyloxy)acetic acid
A solution of benzyl (2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosylox)acetate (1g, 2 mmol) was degassed, Pd-C (10%, 50mg) was added and the solution was degassed again. After stirring for 2.5h under a hydrogen atmosphere the reaction mixture was filtered over celite and the filtrate concentrated in vacuo. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/0, v/v, to afford 524 mg (65%) of the title compound. (LCMS RT= 4.32min, M= 405.1).

1H NMR (CDCl₃): 9.18 (1H, bs), 5.23 (1H, t, J 9.5 Hz), 5.07 (1H, t, J 9.8 Hz), 5.02 (1H, dd, J 7.9 Hz, J 9.5 Hz), 4.66 (1H, d, J 7.9 Hz), 4.32 (2H, s), 4.24 (1H, dd, J 4.7 Hz, J 12.4 Hz), 4.11 (1H, dd, J 2.3 Hz, J 12.4 Hz), 3.71 (1H, m), 2.07 (3H, s), 2.05 (3H, s), 2.01 (3H, s), 1.99 (3H, s).

N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-2-(2',3',4',6'-tetra-O-acetyl-beta-D-glucopyranosyloxy)acetamide
A solution of 2-(2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyloxy)acetic acid (524mg, 1.3mmol) and 2-(2,3-dichlorophenyl)benzo[d]oxazol-5-amine (362mg, 1.3mmol) in DMF (6mL) was cooled to 0°C, HATU (593 mg, 1.56mmol) and DIPEA (0.68mL, 3.9mmol) were added and the resulting reaction mixture was slowly warmed to room temperature. After stirring for 16h the reaction mixture was partitioned between EtOAc(200mL) and brine (150mL), the aqueous phase was extracted with EtOAc (2x150mL) and the combined organic phase was washed with brine (200mL) and dried
over MgSO₄. After removal of the solvent under reduced pressure the residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 7/3, v/v, to afford 762 mg (88%) of a pink solid.

**¹H NMR (CDCl₃):** 8.23 (1H, bs), 8.06 (d, J 1.6 Hz), 8.03 (1H, dd, J 1.6 Hz, J 7.9 Hz), 7.68-7.58 (3H, m), 7.39 (1H, t, J 7.9), 5.32 (1H, dd, J 9.5 Hz, J 11.9 Hz), 5.19-5.12 (2H, t, J 9.8 Hz), 5.02 (1H, dd, J 7.9 Hz, J 9.5 Hz), 4.64 (1H, d, J 7.8 Hz), 4.52 (1H, d, J 9.8 Hz), 4.34 (1H, dd, J 9.5 Hz, J 11.9 Hz), 5.32 (1H, dd, J 9.5 Hz, J 11.9 Hz), 5.02 (1H, d, J 7.8 Hz), 4.52 (1H, d, J 15.0 Hz), 4.34 (1H, dd, J 4.9 Hz, J 12.5 Hz), 4.26 (1H, d, J 15.0 Hz), 4.161 (1H, dd, J 2.3 Hz, J 12.5 Hz), 3.80 (1H, m), 2.13 (3H, s), 2.10 (3H, s), 2.08 (3H, s), 2.07 (3H, s).

N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-2-(beta-D-glucopyranosyloxy)acetamide

A solution of N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-(2',3',4',6'-tetra-O-acetyl-beta-D-glucopyranosyloxy)acetamide (0.76 g, 1.14 mmol) and ammonia (7N solution in MeOH, 14 mL) was stirred for 16h at ambient temperature. The reaction mixture was diluted with MeOH and concentrated under reduced pressure. The residue was triturated with hot MeOH and Et₂O to give 527 mg (93%) of the title compound as a white powder. (LCMS RT= 4.98 min, MH⁺ 500.8).

**¹H NMR (DMSO):** 10.08 (1H, s), 8.24 (d, J 1.6 Hz), 8.13 (1H, dd, J 1.5 Hz, J 7.9 Hz), 7.93 (1H, dd, J 1.6 Hz, J 8.1 Hz), 7.82 (1H, d, J 8.9 Hz), 7.70 (1H, dd, J 2.0 Hz, J 8.9 Hz), 7.61 (1H, t, J 7.9), 6.12 (1H, d, J 3.9 Hz), 5.15 (1H, d, J 4.7 Hz), 5.01 (1H, d, J 5.2 Hz), 4.59 (1H, t, J 5.9 Hz), 4.41-4.36 (2H, m), 4.264 (1H, d, J 16.1 Hz), 3.69 (1H, dd, J 6.3 Hz, J 10.2 Hz), 3.51-3.43 (1H, m), 3.21-3.14 (4H, m).

N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-2-(beta-D-galactopyranosyl)oxy)acetamide

The title compound was prepared using the same method for the building block synthesis, coupling and deprotection. (LCMS RT = 5.10 min, MH⁺ 499.0)

**¹H NMR (DMSO):** 10.21 (1H, s), 8.26 (1H, d, J 1.8 Hz), 8.12 (1H, dd, J 7.9 Hz, J 1.4 Hz), 7.93 (1H, dd, J 8.1 1.5 Hz), 7.81 (1H, d, J 9.0 Hz), 7.73 (1H, dd, J 9.0 1.8 Hz), 7.61 (1H, t, J 7.7 Hz), 6.03 (1H, d, J 4.0 Hz), 4.96 (1H, d, J 5.7 Hz), 4.71 (1H, t, J 6.4 Hz), 4.59 (1H, d, J 5.2 Hz), 4.41-4.17 (3H, m), 3.70-3.41 (6H, m).

2,3,4,6-Tetra-O-acetyl-alpha-D-mannopyranosyl bromide
A solution of 1,2,3,4,6-penta-O-acetyl-alpha-D-mannopyranose (5g, 12.8mmol) in 33%HBr/AcOH (60mL) was stirred at 0°C for 2h. The reaction mixture was poured into ice-water (100mL) and extracted with EtOAc (3x 150mL). The combined organic phase was washed with NaHCO₃ (3x 200mL), dried over MgSO₄ and concentrated in vacuo. The crude title compound was used in the next reaction without any further purification.

**H NMR (CDCl₃):** 6.31 (1H, d, J 1.2 Hz), 5.73 (1H, dd, J 3.4 Hz, J 10.1 Hz), 5.47 (1H, dd, J 1.6 Hz, J 3.4 Hz), 5.38 (1H, t, J 10.1 Hz), 4.35 (1H, dd, J 4.87 Hz, J 12.3 Hz), 4.26 (1H, m), 4.15 (1H, dd, J 2.1 Hz, J 12.3 Hz), 2.20 (3H, s), 2.13 (3H, s), 2.09 (3H, s).

**Benzyl (2,3,4,6-tetra-O-acetyl-alpha-D-mannopyranosyloxy)acetate.**

A solution of AgOTf (3.6g, 14.1mmol) in anhydrous toluene (20mL) was added to a cooled (0°C) solution of 2,3,4,6-tetra-O-acetyl-alpha-D-mannopyranosyl bromide (12.8 mmol) and benzyl glycolate (1.82mL, 12.8mmol) in anhydrous DCM (50mL). The resulting reaction mixture was stirred for 16hr, then diluted with DCM (200mL), washed with NaHCO₃ (2x 100mL) and brine (100mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/1, v/v, to afford 2.03g (32%) of the title compound.

**H NMR (CDCl₃):** 7.30 (5H, bs), 5.34-5.25 (3H, m), 5.14 (2H, s), 4.91 (1H, d J 1.4 Hz), 4.27 (1H, d, J 16.4 Hz), 4.20 (1H, dd, J 4.9 Hz, J 12.2 Hz), 4.15 (1H, d, J 16.4 Hz), 4.14-4.08 (1H, m), 3.99 (1H, dd, J 2.2 Hz, J 12.2 Hz), 2.07 (3H, s), 2.04 (3H, s), 2.02 (3H, s), 1.99 (3H, s).

**25 (2,3,4,6-Tetra-O-acetyl-beta-D-mannopyranosyloxy)acetic acid**

The title compound was prepared as described for (2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyloxy)acetic acid, without the column chromatography step.

**NMR (CDCl₃):** 9.18 (1H, bs), 5.35-5.27 (3H, m), 4.93 (1H, bs), 4.32-4.21 (3H, m), 4.14-4.06 (2H, m), 2.13 (3H, s), 2.09 (3H, s), 2.03 (3H, s), 1.97 (3H, s).
N-(2-(2,3-Dichlorophenyl)benzol[d]oxazol-5-yl)-2-(2',3',4',6'-tetra-O-acetyl-beta-D-mannopyranosyloxy)acetamide

The title compound was prepared using the same general method for the coupling. (LCMS RT= 6.62 min, MH+ 667.54)

$^1$H NMR (CDCl$_3$): 8.36 (1H, bs), 8.17 (d, J 1.4 Hz), 8.01 (1H, dd, J 1.6 Hz, J 7.9 Hz), 7.62 (1H, dd, J 1.6 Hz, 8.0 Hz), 7.55 (2H, s), 7.35 (1H, t, J 7.9), 5.44-5.29 (3H, m), 4.99 (1H, s), 4.37 (1H, d, J 15.3 Hz), 4.30 (1H, dd, J 5.9 Hz, J 12.5 Hz), 4.18 (1H, d, J 15.3 Hz), 4.16-4.03 (2H, m), 2.17 (3H, s), 2.09 (3H, s), 2.06 (3H, s), 2.04 (3H, s).

N-(2-(2,3-Dichlorophenyl)benzol[d]oxazol-5-yl)-2-(beta-D-mannopyranosyloxy)acetamide

The title compound was prepared using the same general method for the deprotection. (LCMS RT= 5.01 min, MH+ 501.12)

$^1$H NMR (CDCl$_3$): 10.02 (1H, s), 8.24 (d, J 1.9 Hz), 8.11 (1H, dd, J 1.5 Hz, J 7.9 Hz), 7.93 (1H, dd, J 1.5 Hz, J 8.1 Hz), 7.80 (1H, d, J 8.9 Hz), 7.65 (1H, dd, J 1.9 Hz, J 8.9 Hz), 7.60 (1H, t, J 8.1), 4.85 (1H, d, J 4.4 Hz), 4.77 (2H, m), 4.61 (1H, d, J 6.1 Hz), 4.52 (1H, t, J 5.6 Hz), 3.83 (2H, m), 3.66 (1H, dd, J 6.3 Hz, J 10.8 Hz), 3.62-3.56 (1H, m), 3.47-3.31 (3H, m).

3'-Benzyloxypropyl 2,3,4,6-tetra-O-acetyl-beta-D-galactopyranoside

BF$_3$ OEt$_2$ (0.71mL, 5.6mmol) was added to a solution of 1,2,3,4,6-penta-O-acetyl-beta-D-glucopyranose (2g, 5.1mmol) and 3-benzyloxypropanol (0.90mL, 5.6mmol) in anhydrous DCM (25mL) and the resulting reaction mixture was stirred for 16hr at room temperature. The solution was neutralised with Et$_3$N and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/1, v/v, to afford 2.1g (85%) of the title compound.

$^1$H NMR (CDCl$_3$): 7.40-7.33 (5H, m), 5.42 (1H, dd, J 1.1 Hz, J 3.4 Hz), 5.24 (1H, dd, J 7.9 Hz, J 10.5 Hz), 5.05 (1H, dd, J 3.4 Hz, J 10.5 Hz), 4.54 (2H, m), 4.49 (1H, d, J 7.9 Hz), 4.22-4.14 (2H, m), 4.04-4.00 (1H, m), 3.93 (1H, dt, J 1.1 Hz, J 6.7 Hz), 3.83 (1H, t, J 5.6 Hz), 3.74-3.69 (1H, m), 3.60-3.55 (1H, m), 2.19 (3H, s), 2.09 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.96-1.90 (2H, m).

3'-Hydroxypropyl 2,3,4,6-tetra-O-acetyl-beta-D-galactopyranoside
A solution of 3'-benzyloxypropyl 2,3,4,6-tetra-O-acetyl-beta-D-galactopyranoside (8.6g, 17mmol) was degassed, Pd-C (10%, 500mg) was added and the solution was degassed again. After stirring for 3h under a hydrogen atmosphere the reaction mixture was filtered over celite and the filtrate concentrated in vacuo. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/0, v/v, to afford 4.9g (70%) of the title compound.

\[
\begin{align*}
{^1}\text{H NMR (CDCl}_3\text{):} & \ 5.44 (1\text{H, dd}, J 1.1 \text{ Hz}, J 3.4 \text{ Hz}), 5.25 (1\text{H, dd}, J 7.9 \text{ Hz}, J 10.5 \text{ Hz}), 5.06 (1\text{H, dd}, J 3.4 \text{ Hz}, J 10.5 \text{ Hz}), 4.53 (1\text{H, d}, J 7.9 \text{ Hz}), 4.22-4.14 (2\text{H, m}), 4.09-4.04 (1\text{H, m}), 3.96 (1\text{H, dt}, J 1.1 \text{ Hz}, J 6.6 \text{ Hz}), 3.80-3.72 (3\text{H, m}), 2.20 (3\text{H, s}), 2.12 (3\text{H, s}), 2.03 (3\text{H, s}), 1.91-1.86 (2\text{H, m}).
\end{align*}
\]

3'-{\text{(2,3,4,6-Tetra-O-acetyl-beta-D-galactopyranosyloxy)propanoic acid}}

A solution of NaCl (sat. aq. 3mL), NaHCO\textsubscript{3} (sat. aq. 1.5 mL) and NaOCl (13%, 3mL) was added to a solution of 3'-hydroxypropyl 2,3,4,6-tetra-O-acetyl-beta-D-galactopyranoside (0.5g, 1.2mmol), TEMPO (3mg, 0.02mmol), KBr (12mg, 0.098mmol), TBABr (16mg, 0.062mmol) and NaHCO\textsubscript{3} (sat. aq. 3mL) in DCM (10mL) at 0°C. After stirring for 30 min at 0°C the reaction mixture was neutralized with 1N HCl, extracted with DCM (3 x 10mL) and the combined organic layers dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/0, v/v, to afford 0.45g (88%) of the title compound.

\[
\begin{align*}
{^1}\text{H NMR (CDCl}_3\text{):} & \ 5.32 (1\text{H, dd}, J 0.9 \text{ Hz}, J 3.4 \text{ Hz}), 5.10 (1\text{H, dd}, J 7.9 \text{ Hz}, J 10.5 \text{ Hz}), 4.95 (1\text{H, dd}, J 3.4 \text{ Hz}, J 10.5 \text{ Hz}), 4.46 (1\text{H, d}, J 7.9 \text{ Hz}), 4.13-4.01 (3\text{H, m}), 3.87-3.78 (2\text{H, m}), 2.62-2.56 (2\text{H, m}), 2.08 (3\text{H, s}), 1.99 (3\text{H, s}), 1.97 (3\text{H, s}), 1.91 (3\text{H, s}).
\end{align*}
\]

N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-3-(beta-D-galactopyranosyl oxy)propanamide

The title compound was prepared using the standard method for the coupling and deprotection.

\[
\begin{align*}
{\text{LCMS RT=}} & \ 5.09\text{min, M}\text{H}^+ 513.0) ; \ \text{^1H NMR (DMSO):} \ 10.13 (1\text{H, s}), 8.23 (1\text{H, d}, J 1.9 \text{ Hz}), 8.10 (1\text{H, dd}, J 7.9 \text{ 1.6 Hz}), 7.92 (1\text{H, dd}, J 8.2 14.8 Hz), 7.76 (1\text{H, d}, J 8.8 \text{ Hz}), 7.63-7.56 (2\text{H, m}), 4.87 (1\text{H, d}, J 4.0 \text{ Hz}), 4.71 (1\text{H, d}, J 5.0 \text{ Hz}), 4.62 (1\text{H, t}, J 5.7 \text{ Hz}),
\end{align*}
\]
N-(2-(Naphthalen-2-yl)benzo[d]oxazol-5-yl)-2-(beta-D-galactopyranosyl oxy)propanamide

The title compound was prepared using the standard method for the coupling and deprotection.

**LCMS RT= 5.05 min, MH+ 495.2; **

\[ ^1H \text{NMR (DMSO): } 10.08 \text{ (1H, s), } 8.83 \text{ (1H, s), } 8.27 \text{ (1H, d, } J 8.6 \text{ Hz), } 8.21-8.11 \text{ (3H, m), } 8.06-8.02 \text{ (1H, m), } 7.76 \text{ (1H, d, } J 8.7 \text{ Hz), } 7.68-7.63 \text{ (2H, m), } 7.57 \text{ (1H, dd, } J 8.6 \text{ Hz), } 4.88-4.85 \text{ (1H, m), } 4.72-4.68 \text{ (1H, m), } 4.64-4.58 \text{ (1H, m), } 4.38-4.35 \text{ (1H, m), } 4.16 \text{ (1H, d, } J 6.7 \text{ Hz), } 4.10-4.01 \text{ (1H, m), } 3.87-3.78 \text{ (1H, m), } 3.66-3.62 \text{ (1H, m), } 3.56-3.49 \text{ (2H, m), } 2.69-2.62 \text{ (2H, m).}

2-(Benzyloxy)-N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)acetamide

The title compound was obtained using the standard method for coupling.

**LCMS RT = 7.87 min, MH+ 427.2; **

\[ ^1H \text{NMR (CDCl3): } 8.47 \text{ (1H, bs), } 8.06 \text{ (t, } J 1.4 \text{ Hz), } 7.67 \text{ (1H, dd, } J 1.6 \text{ Hz, } J 8.0 \text{ Hz), } 7.59 \text{ (2H, m), } 7.45-7.36 \text{ (6H, m), } 4.72 \text{ (2H, s), } 4.18 \text{ (2H, s).}

N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-2-hydroxyacetamide

A solution of 2-(benzyloxy)-N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)acetamide (0.97g, 2.28 mmol) was degassed, Pd-C (10%, 100mg) was added and the solution was degassed again. After stirring for 6h under a hydrogen atmosphere the reaction mixture was filtered over celite and the filtrate concentrated in vacuo. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/0, v/v. The white solid was triturated with Et2O (2x) to afford 380mg (50%) of the title compound. (LCMS RT = 5.76 min, M 336.9).

\[ ^1H \text{NMR (DMSO): } 9.94 \text{ (1H, s), } 8.31 \text{ (1H, s), } 8.10 \text{ (1H, dd, } J 1.5 \text{ Hz, } J 7.9 \text{ Hz), } 7.92 \text{ (1H, dd, } J 1.5 \text{ Hz, } J 8.0 \text{ Hz), } 7.78 \text{ (2H, m), } 7.60 \text{ (1H, t, } J 8.0 \text{ Hz), } 5.74 \text{ (1H, t, } J 6.0 \text{ Hz), } 4.04 \text{ (2H, d, } J 6.0 \text{ Hz).}

The compounds below were made by the same coupling and deprotection as for N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-2-hydroxyacetamide
N-(2-(2,3-Dichlorophenyl)benzo[d]oxazol-5-yl)-3-hydroxypropanamide
LCMS RT= 5.71 min, MH⁺ 352.6; ¹H NMR (DMSO): 10.13 (1H, s), 8.25 (1H, d, J 1.9 Hz), 8.10 (1H, dd, J 7.9 1.7 Hz), 7.92 (1H, dd, J 8.3 1.6 Hz), 7.76 (1H, d, J 8.8 Hz), 7.62-7.56 (2H, m), 4.71 (1H, t, J 5.3 Hz), 3.74 (2H, q, J 5.6 Hz), 2H (m, obscured).

N-(2-(Naphthalen-2-yl)benzo[d]oxazol-5-yl)-3-hydroxypropanamide
LCMS RT = 8.03 min, MH⁺ 333.2; ¹H NMR (DMSO): 10.11 (1H, s), 8.82 (1H, s), 8.28-8.12 (4H, m), 8.06-8.02 (1H, m), 7.75 (1H,d, J 8.8 Hz), 7.68-7.64 (2H, m), 7.56 (1H, dd, J 2.0 Hz, J 8.8 Hz), 4.70 (1H, t, J 5.1 Hz), 3.74 (2H, d, J 5.2 Hz), & 2H (m, obscured).

2-Hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide
The title compound was obtained using the standard method for coupling: no deprotection required.
LCMS RT= 5.95 min, MH⁺ 319.1; ¹H NMR (DMSO): 9.90 (1H, s), 8.83 (1H, s), 8.28-8.24 (2H, m), 8.20-8.11 (2H, m), 8.06-8.01 (1H, m), 7.76-7.74 (2H,m), 7.68-7.63 (2H, m), 5.74 (1H, t, J 6.2 Hz), 4.04 (2H, d, J 6.0 Hz).

EXAMPLE 14
5-(Ethylsulfinyl)-2-(naphthen-2-yl)benzo[d]oxazole

(i) 4-(Ethylthio)phenol

4-mercaptophenol (4.2 g, 33.3 mmol) was dissolved in acetone (35 mL). K₂CO₃ (4.8 g, 35 mmol) and EtBr (3.6 mL, 49.9 mmol) were added and the mixture stirred at room temperature for 17 h. The mixture was filtered, and the residue washed with Et₂O (3 x 30 mL). The combined organics were washed with 1 M NaOH (2 x 50 mL). The aqueous extracts were combined and acidified with 2 M HCl. The acidic solution was extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a brown oil which crystallized on standing. The crude sulfide was purified by column chromatography (10% EtOAc/hexanes) to give the title compound as a pale yellow oil that crystallized on standing (3.9 g, 75%).

$^1$H NMR (CDCl₃): 7.31 (2 H, app d, AA'BB'), 6.79 (2 H, app d, AA'BB'), 4.81 (1 H, m), 2.85 (2 H, q, J 7.3) and 1.26 (3 H, t, J 7.3).

(ii) 4-(Ethylthio)-2-nitrophenol

4-(Ethylthio)phenol (3.2 g, 20.5 mmol) was dissolved in AcOH (10 mL) and cooled to 0°C. Concentrated HNO₃ (approx. 16 M, 1.28 mL, 20.5 mmol) was added dropwise. On completion of the addition, the mixture was diluted with H₂O (20 mL) and extracted with CHCl₃ (2 x 25 mL). The combined CHCl₃ extracts were washed with H₂O (25 mL) and brine (25 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure. The crude mixture was then purified by column chromatography (25% EtOAc/hexanes) to give the title compound as an orange oil (310 mg, 8%).

$^1$H NMR (CDCl₃): 10.54 (1 H, s), 8.09 (1 H, d, J 2.1), 7.59 (1 H, dd, J 8.8 and 2.2), 7.13 (1 H, d, J 8.8), 2.92 (2 H, q, J 7.3) and 1.31 (3 H, t, J 7.4).

(iii) 2-Amino-4-(ethylthio)phenol

4-(ethylthio)-2-nitrophenol (200 mg, 1.0 mmol) was dissolved in IMS/H₂O (5:1, 12 mL). NH₄Cl (107 mg, 2.0 mmol) was added and the mixture heated to 80°C. Fe powder (280 mg, 5.0 mmol) was added and the mixture heated at this temperature for 1 h, by which time TLC analysis (50% EtOAc/hexanes) indicated no starting material remained. The mixture was cooled and filtered through celite, washing with MeOH...
until the filtrate ran colourless. The filtrate was concentrated, then redissolved in EtOAc/H₂O. The solution was extracted with EtOAc (2 x 30mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound as a brown solid (100mg, 59%).

(iv) 5-(Ethylthio)-2-(naphthalen-2-yl)benzo[d]oxazole

2-amino-4-(ethylthio)phenol (100mg, 0.59mmol) was dissolved in xylene (5mL) and 2-naphthoyl chloride (113mg, 0.59mmol) was added. The mixture was heated to 160°C for 15 minutes, by which time TLC analysis (50% EtOAc/hexanes) indicated no starting material was present. pTsOH (225mg, 1.18mmol) was added and the mixture heated at reflux for 2h. The mixture was cooled, diluted with EtOAc and absorbed onto silica. Column chromatography (gradient: 100% hexanes – 20% EtOAc/hexanes) afforded the title compound as an off-white solid (130mg, 72%).

(v) 5-(Ethylsulfinyl)-2-(naphthalen-2-yl)benzo[d]oxazole

5-(ethylthio)-2-(naphthalen-2-yl)benzo[d]oxazole (64mg, 0.21mmol) was dissolved in dichloromethane (10mL) and cooled to -78°C. mCPBA (77%, 47mg, 0.21mmol) was added and the mixture stirred for 1h, allowing the temperature to rise to -50°C. Aqueous Na₂SO₃ (1mL) was added and the mixture warmed to room temperature. The mixture was washed with 1M NaOH (3 x 5mL) and brine (10mL). The organic layer was dried (MgSO₄), filtered and concentrated. The crude product was combined with a second batch of equivalent scale and purified by column chromatography (gradient: 50% EtOAc/hexanes – EtOAc to afford the title compound as a white solid (40mg, 56%). 0226-56-4

LCMS RT= 6.55min, MH⁺ 322.1; ¹H NMR (CDCl₃): 8.82 (1 H, s), 8.33 (1 H, dd, J 8.6 and 1.7), 8.07-8.01 (3 H, m), 7.95-7.92 (1 H, m), 7.79 (1 H, d, J 8.5), 7.68 (1 H, dd, J 8.5 and 1.6), 7.64-7.59 (2 H, m), 3.04-2.80 (2 H, m) and 1.24 (3 H, t, J 7.4).

EXAMPLE 15
General synthetic scheme for (2-(4H-1,2,4-triazol-3-ylthio)-N-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)acetamide & 2-(4H-1,2,4-triazol-3-ylthio)-N-(5-(benzo[d]thiazol-2-yl)pyridin-3-yl)acetamide

4-(Benzo[d]thiazol-2-yl)thiazol-2-amine

2-Aminobenzenethiol (1.00mL, 9.35mmol) and 2-aminothiazole-4-carboxylic acid (1.59g, 11.21mmol) were added simultaneously to PPA at 120°C and the resulting mixture was stirred at 210°C for 18h. The hot crude was poured onto ice/water (150mL) and basified with NaOH pellets until pH=14. The aqueous layer was then extracted with ethyl acetate (3x70mL), the combined extracts were washed with brine until pH=7 and dried over anhydrous magnesium sulfate. The resulting solid was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 7:3 v/v to ethyl acetate/hexanes 1:0 v/v then ethyl acetate/methanol 1:0 v/v to ethyl acetate/methanol 98:2 v/v) to afford 407mg (12%) of the title compound.

**LCMS RT= 5.53min, MH+ 234.1; **1H NMR (DMSO): 8.09-8.07 (1H, m), 7.99-7.96 (2H, m), 7.54-7.48 (2H, m), 7.44-7.39 (3H, m).

The compounds below were prepared following the same general method.

5-(Benzo[d]thiazol-2-yl)pyridin-3-amine
LCMS RT= 5.37min, MH⁺ 228.1; ¹H NMR (DMSO): 8.41 (1H, d, J 1.95), 8.18-8.15 (1H, m), 8.09-8.05 (2H, m), 7.61-7.45 (3H, m), 5.72 (2H, s).

N-(4-(Benzo[d]thiazol-2-yl)thiazol-2-yl)-2-chloroacetamide

Chloroacetyl chloride (340μL, 4.29mmol) was added dropwise to a stirred solution of 4-(benzo[d]thiazol-2-yl)thiazol-2-amine (250mg, 1.07mmol) in dichloromethane/tetrahydrofuran (20mL; 1:1 v/v) in the presence of diisopropylethylamine (1.12mL, 6.43mmol). The resulting mixture was stirred at room temperature for 18h, then the crude was diluted with dichloromethane (150mL) and the organic layer was washed with brine (50mL). The aqueous layer was extracted with dichloromethane (2x50mL) and the combined extracts were dried over anhydrous magnesium sulphate. The resulting oil was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 3:7 v/v) to afford 211mg (64%) of the title compound.

LCMS RT= 6.07min, MH⁺ 310.0; ¹H NMR (DMSO): 12.94 (1H, bs), 8.13 (1H, d, J 7.50), 8.12 (1H, s), 8.04 (1H, d, J 7.50), 7.55 (1H, td, J 7.50 1.20), 7.46 (1H, td, J 7.50 1.20), 4.45 (2H, s).

The compounds below were prepared following the same general method.

N-(5-(Benzo[d]thiazol-2-yl)pyridin-3-yl)-2-chloroacetamide

A mixture of N-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)-2-chloroacetamide 2 (205mg, 0.66mmol), 1H-1,2,4-triazole-5(4H)-thione (74mg, 0.73mmol) and potassium carbonate (110mg, 0.8mmol) in acetone (20mL) was refluxed for 2h. The solvent was removed in vacuo and the resulting solid was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 1:0 v/v) to afford 120mg (48%) of the title compound.
The compounds below were prepared following the same general method.

2-(4H-1,2,4-triazol-3-ylthio)-N-(5-(benzo[d]thiazol-2-yl)pyridin-3-yl)acetamide

LCMS RT= 5.17min, MH⁺ 369.0; ¹H NMR (DMSO): 14.00 (1H, bs), 10.80 (1H, bs), 8.95 (1H, d, J 1.77), 8.86-8.83 (2H, m), 8.48 (1H, s), 8.20 (1H, d, J 7.30), 8.13 (1H, d, J 7.30), 7.59 (1H, td, J 7.30 1.30), 7.51 (1H, td, J 7.30 1.30), 4.14 (2H, s).

EXAMPLE 16

1-(2-(Naphthalen-2-yl)benzo[d]oxazol-5-yl)pyrrolidin-2-one

4-Chloro-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)butanamide

4-bromobutyryl chloride (195µL, 1.69mmol) was added dropwise to a solution of 2-(naphthalen-2-yl)-5-amino-benzo[d]oxazole (400mg, 1.537mmol) in anhydrous pyridine (7.5mL) at 0°C and the resultant reaction mixture allowed to warm to room temperature over 16 hours. After this time, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous copper sulphate solution (x2) then saturated aqueous potassium carbonate solution (x2). The organic layer was dried over MgSO₄ and concentrated in vacuo to furnish 4-chloro-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)butanamide (115mg, 21%) after column chromatography (2:1 to 1:1 40-60 petrol:ethyl acetate) (LCMS RT=7.42min, MH⁺ 365).

¹H NMR (300MHz, DMSO) 10.19 (1H, s), 8.83 (1H, s), 8.26 (1H, dd, J 8.6, 1.7 Hz), 8.17-8.20 (2H, m), 8.14 (1H, d, J 8.7 Hz), 8.03-8.06 (1H, m), 7.76 (1H, d, J 8.8 Hz), 7.62-7.70 (2H, m), 7.55 (1H, dd, J 8.8 2.1 Hz), 3.74 (1H, t, J 6.5 Hz), 2.54 (obsc.), 2.08 (2H, quintet, J 6.9 Hz).

1-(2-(Naphthalen-2-yl)benzo[d]oxazol-5-yl)pyrrolidin-2-one

Diethylamine (20µL, 0.187mmol) and potassium carbonate (26mg, 0.187mmol) were added to a solution of 4-chloro-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)butanamide (62mg, 0.170mmol) in anhydrous DMF under nitrogen and the reaction mixture heated to 50°C for 16 hours. After cooling to room temperature, the reaction mixture was
diluted with ethyl acetate and washed with brine (x3). The organic layer was dried over MgSO$_4$ and concentrated in vacuo to furnish the title compound (28mg, 50%) as a pale yellow powder after column chromatography (2:1 to 1:1 40-60 petrol:ethyl acetate) (LCMS RT=7.02min, MH$^+$ 329).

$^1$H NMR (300MHz, DMSO) 8.84 (1H, s), 8.27 (1H, dd, J 8.6 1.7 Hz), 8.13-8.21 (2H, m), 8.03-8.08 (2H, m), 7.83 (1H, d, J 8.7 Hz), 7.78 (1H, dd, J 8.9 2.0 Hz), 7.63-7.70 (2H, m), 3.95 (2H, t, J 7.0 Hz), 2.54 (obsc.), 2.11 (2H, quintet, J 7.5 Hz).

**EXAMPLE 17**

2-(Benzo[b]thiophen-1,1-dioxide-6-yl)-5-(ethylsulfonyl)benzo[d]oxazole

m-chloroperbenzoic acid (0.65g, 3.8mmol) was added to a solution of 2-(benzo[b]thiophen-6-yl)-5-(ethylsulfonyl)benzo[d]oxazole (0.56g, 1.5mmol) in chloroform (15mL). After stirring for 16h, sodium sulfite solution (10%) was added and shaken with the reaction mixture, which was then partitioned. The organic phase was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 4/1, v/v, then recrystallised using ethanol to afford 88mg (15%) of the title compound.

LCMS RT= 5.66min, MH$^+$ n/a; $^1$H NMR (DMSO): 8.48 (1H, d, J 0.9 Hz), 8.44 (1H, dd, J 7.9, J 1.4 Hz), 8.38 (1H, d, J 1.3 Hz), 8.15-8.12 (2H, m), 8.02 (1H, dd, J 8.6, J 1.8 Hz), 7.83 (1H, dd, J 6.9, J 0.8 Hz), 7.56 (1H, d, J 6.9 Hz), 3.38 (2H, q, J 7.4 Hz), 1.12 (3H, t, J 7.3 Hz).

**EXAMPLE 18**

General scheme to synthesise common intermediate A

Step1: 1. naphth-CHO, MeOH, 50$^\circ$C

2. DDQ, DCM, rt

Step2: benzoylperoxide, NBS

chlorobenzene, reflux

\[ \text{Step1} \quad \text{Step2} \]

\[ \text{A} \]

Step1:
A solution of 2-amino-4-methylphenol (900mg, 7.30mmol, 1eq) and 2-naphthaldehyde (1.14g, 7.30mmol, 1eq) in MeOH (30mL) was heated for 30 minutes at 50°C. After concentration in vacuo, the residue was suspended in DCM (40mL) and treated with DDQ (2,3 dichloro,5,6-dicyano-1,4-benzoquinone, 1.74g, 1.05eq, 766mmol). The reaction mixture was stirred at room temperature for 10 minutes and diluted with DCM. The organic phase was washed with brine and NaHCO₃ aq, dried over Na₂SO₄, concentrated in vacuo. This reaction gave us the desired compound in a quantitative yield, no further purification needed.

**LCMS RT** = 9.39min, **MH⁺** = 260.1, 97% UV

**¹H NMR (CDCl₃):** 8.69 (1H, s), 8.23 (1H, dd, J 3.41Hz), 7.90 (2H, m, J 4.35 Hz), 7.82 (1H, m, J 4.62Hz), 7.50 (3H, m, J 4.71Hz), 7.42 (1H, d, J 8.28Hz), 7.11 (1H, dd, J 4.11 Hz), 2.5 (3H, s).

**Step 2:**

To a stirred solution of the methyl compound (1.9g, 7.33mmol, 1eq) in chlorobenzene (60mL) at 90°C was added NBS (1.3g, 7.33mmol, 1eq) and benzoyl peroxide (catalytic amount) in one portion. The reaction mixture was heated at 90°C for 1 hour and heated at reflux for 4 more hours. After cooling down, the reaction mixture was concentrated in vacuo, suspended in EtOAc. The residue was filtered and gave 350mg of the desired product. The organic phase was washed with brine, NaHCO₃ aq, dried over Na₂SO₄, concentrated in vacuo. The solid was triturated in EtOAc and provided 400mg of desired Bromo compound. No further purification was attempted.

**LCMS RT** = 9.00min, **MH⁺** = 338.1, 96% UV

**¹H NMR (CDCl₃):** 8.70 (1H, s), 8.23 (1H, dd, J 8.23Hz), 7.91 (2H, m, J 4.02 Hz), 7.82 (1H, m, J 4.69Hz), 7.75 (1H, d, J 1.50Hz), 7.51 (3H, m, J 2.81Hz), 7.36 (1H, dd, J 3.37 Hz), 4.59 (3H, s).

**5-(Morpholinomethyl)-2-(naphthalen-2-yl)benzo[d]oxazole**

The Bromo compound A (200mg, 0.592mmol, 1eq) was dissolved in dry DMF, (V=6mL), potassium carbonate (91mg, 0.651mmol, 1.1eq) and morpholine (0.0057mL, 0.651mmol, 1.1eq) were added at room temperature. The reaction mixture was stirred at room temperature for 18 hours. Water was added. The aqueous phase was extracted
three times with EtOAc, the organic phases were washed with water and brine, dried over Na$_2$SO$_4$, concentrated in vacuo. Purification by Flash Jones chromatography gave 68mg of the desired compound in 34% yield.

**LCMS**

RT = 8.08min, MH$^+$ = 345.3, 100% UV

$^1$H NMR (DMSO): 8.89 (1H, s), 8.32 (1H, dd, J 3.40Hz), 8.25 (2H, m, J 4.66Hz and J 7.84Hz), 8.09 (1H, dd, J 4.60Hz), 7.82 (2H, d, J 8.44Hz), 7.73 (2H, q, J 4.09Hz), 7.47 (1H, dd, J 4.09Hz), 3.65 (6H, m), 2.47 (4H, m, J 4.23Hz).

**5-(Ethylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole & 5-(methylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole**

Step 3:

The bromo compound A (300mg, 0.887mmol, 1eq) was dissolved in dry THF (15mL); Sodium ethanethiolate (82mg, 0.976mmol, 1.1eq) or sodium thiomethoxide (68mg, 0.976mmol, 1.1eq) was added at room temperature. The reaction mixture was refluxed for 4 hours. After cooling down the mixture was diluted with water, extracted three times with DCM. The organics phases were washed with brine, dried over Na$_2$SO$_4$, concentrated in vacuo.

Bromo starting material and desired product were co-spotting by TLC. In the crude mixture 59% desired compound was present by LCMS (a). No further purification was attempted in both cases.

**LCMS (a)**

RT = 9.83min, MH$^+$ = 320.2, 59% UV

a: 5-(ethylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole

$^1$H NMR (CDCl$_3$):

8.71 (1H, s), 8.25 (1H, m, J 2.54Hz), 7.87 (3H, m, J 6.44Hz), 7.70 (1H, d, J 7.28Hz), 7.53 (3H, m, J 3.44Hz), 7.37 (1H, m), Other impurities present from the starting material bromo compound, 3.80 (2H,s), 2.41 (2H, q, J 10.21Hz) I impurity underneath the peak, 1.18 (3H, t, J 7.37Hz).

b: 5-(methylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole

$^1$H NMR (DMSO):

8.24 (1H,s), 8.33 (1H, dd, J 3.44Hz), 8.23 (2H, m, J 4.69Hz), 8.11 (1H, m, J 3.14Hz), 7.85 (2H, dd, J 8.46Hz), 7.73 (2H, q, J 2.92Hz), 7.48 (1H, dd, J 3.37 Hz), 3.93 (2H,s), 2.05 (3H, s).
Step 4:

5 a (or b) was dissolved in 10mL of chloroform, 4 eq of MPCBA was added in one portion at 0°C. The reaction mixture was stirred at room temperature overnight.

a: The reaction mixture was diluted with DCM, washed twice with NaOH 1N and water. The organic phase was dried over Na₂SO₄, concentrated in vacuo. Purification by trituration in DCM and ether gave the desired product in 20% yield.

b: A solid crashed out, it was filtered and washed with ether to give the desired product in 25% yield.

LCMS (a) RT= 6.59min, MH⁺ = 352.2, 93.6% UV
LCMS (b) RT= 6.46min, MH⁺ = 338.2, 99.5% UV

10 a: ¹H NMR (DMSO): 8.86 (1H, s), 8.28 (1H, dd, J3.43Hz), 8.17 (2H, m, J5.62Hz), 8.04 (1H, m, J4.47Hz), 7.87 (2H, d, J8.61Hz), 7.66 (2H, q, J2.98Hz), 7.49 (1H, dd, J3.35Hz), 4.64 (2H, s), 3.06 (2H, q, J7.42Hz), 1.24 (3H, t, J7.44Hz).

b: ¹H NMR (DMSO): 8.86 (1H, s), 8.28 (1H, dd, J3.43Hz), 8.17 (2H, m, J4.55Hz), 8.04 (1H, m, J4.60Hz), 7.88 (2H, m, J3.97Hz), 7.66 (2H, q, J2.98Hz), 7.50 (1H, dd, J3.35Hz), 4.66 (2H, s), 2.94(3H, s).

EXAMPLE 19
[(S)-(9H-Fluoren-9-yl)methyl 3-(tert-butyldimethylsilyloxy)-1-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylamino)-1-oxopropan-2-ylcarbamate], 4

HATU (1.271g, 3.34mmol) was added in one portion at room temperature to a stirred solution of (S)-N-Boc-O-TBDMS-serine (1.477g, 3.34mmol) in DMF (50mL) in the presence of diisopropylethylamine (1.59mL, 9.12mmol), followed by 2-(naphthalen-2-yl)benzo[d]oxazol-5-amine (791mg, 3.04mmol); the resulting mixture was stirred at room temperature for 18h. The crude was partitioned between ethyl acetate (200mL) and brine (150mL) and the two layers were separated. The aqueous layer was extracted further with ethyl acetate (2 x 50mL) and the combined extracts were dried over anhydrous magnesium sulphate. The resulting solid was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 1:0 v/v) to afford 2.05g (98%) of the title compound.

\[ \text{H NMR (DMSO): } 10.30 \ (1H, s), \ 8.80 \ (1H, s), \ 8.25-8.09 \ (4H, m), \ 8.02-7.99 \ (1H, m), \ 7.92-7.85 \ (2H, m), \ 7.76-7.70 \ (3H, m), \ 7.64-7.55 \ (4H, m), \ 7.41-7.27 \ (4H, m), \ 4.39-4.32 \ (1H, m), \ 4.28-4.17 \ (3H, m), \ 3.86-3.74 \ (2H, m), \ 0.78 \ (9H, s), \ -0.01 \ (6H, d, } J 8.28 \).\]

The compounds below were prepared following the same general method.
(S)-Tert-butyl methyl(1-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylamino)-1-oxopropan-2-yl)carbamate, 7

LCMS RT= 8.19 min, MH$^+$ 446.4; $^1$H NMR (DMSO): 10.12 (0.5H, bs), 10.02 (0.5H, bs), 8.83 (1H, s), 8.26 (1H, dd, $J$ 8.61 1.70), 8.20-8.12 (3H, m), 8.05-8.02 (1H, m), 7.77 (1H, d, $J$ 8.80), 7.70-7.61 (2H, m), 7.58 (1H, dd, $J$ 8.80 2.04), 4.73 (0.5H, bm), 4.41 (0.5H, bm), 2.89 (3H, s), 1.39 (3H, d, $J$ 7.17), 1.34 (9H, s).

[(S)-2-Amino-3-(tert-butyldimethylsilyloxy)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide], 5

Piperidine (4mL, 40.5mmol) was added dropwise at room temperature to a stirred solution of 4 (2.08g, 3.04mmol) in dimethylformamide (16mL) and the resulting mixture was stirred for 18h. The crude was partitioned between ethyl acetate (150mL) and brine (100mL) and the two layers were separated. The aqueous layer was extracted further with ethyl acetate (2 x 50mL) and the combined extracts were dried over anhydrous magnesium sulfate. The resulting oil was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 3:7 v/v to ethyl acetate/hexanes 1:0 v/v) to afford 1.39 (99%) of the title compound.

LCMS RT= 9.59 min, MH$^+$ 462.3; $^1$H NMR (DMSO): 8.81 (1H, s), 8.26-8.23 (2H, m), 8.18-8.15 (1H, m), 8.12 (1H, d, $J$ 8.80), 8.04-8.00 (1H, m), 7.94 (1H, s), 7.75 (1H, d, $J$ 8.80), 7.68-7.60 (3H, m), 3.79 (1H, dd, $J$ 9.72 5.10), 3.70 (1H, dd, $J$ 9.72 5.85), 3.47 (1H, t, $J$ 5.46), 0.81 (9H, s), 0.00 (6H, s).

[(S)-2-Amino-3-hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide], 6

TBAF (1M in THF, 12.16mL, 12.16mmol) was added dropwise at room temperature to a stirred solution of 5 (1.40g, 3.04mmol) in THF (10mL) and the resulting mixture was stirred for 60h. The crude was evaporated to dryness, dissolved in ethyl acetate (200mL) and washed with 1M NaOH in water (100mL). The aqueous layer was extracted further with ethyl acetate (2 x 50mL) brine (100mL) and the two layers were separated. The aqueous layer was extracted further with ethyl acetate (2x50mL) and the combined extracts were washed with brine (2 x 50mL) and dried over anhydrous
magnesium sulfate. The resulting solid was precipitated from IMS/methanol to afford 282mg (27%) of the title compound as a colourless solid.

**LCMS RT** = 5.52min, MH⁺ 348.1; **¹H NMR (DMSO)**: 8.83 (1H, s), 8.28-8.25 (2H, m), 8.20-8.12 (2H, m), 8.05-8.02 (1H, m), 7.76 (1H, d, J 8.80), 7.67-7.64 (3H, m), 4.87 (1H, t, J 5.18), 3.62-3.57 (2H, m), 3.44-3.40 (1H, m).

[(S)-2-(Methylamino)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide], 8 TFA (2mL) was added dropwise at room temperature to a stirred solution of 7 (557mg, 1.25mmol) in DCM (10mL) and the resulting mixture was stirred for 3h. The reaction was quenched with NaHCO₃ (sat.) (10mL) and the aqueous layer was extracted with DCM (3 x 50mL). The combined extracts were dried over anhydrous magnesium sulphate and evaporated to dryness. The resulting yellow solid was purified by column chromatography eluting using a gradient (ethyl acetate/methanol 1:0 v/v to ethyl acetate/methanol 7:3 v/v) to afford 310mg (72%) of the title compound.

**LCMS RT** = 6.64min, MH⁺ 346.1; **¹H NMR (DMSO)**: 10.04 (1H, s), 8.82 (1H, s), 8.27-8.24 (2H, m), 8.20-8.16 (1H, m), 8.12 (1H, d, J 8.80), 8.05-8.02 (1H, m), 7.76 (1H, d, J 8.80), 7.67-7.63 (3H, m), 3.17 (1H, q, J 6.82), 2.28 (3H, s), 1.24 (3H, d, J 6.82).

3-(5-Isobutyramidobenzo[d]oxazol-2-yl)quinoline 1-oxide
To a stirred suspension of N-(2-(quinolin-3-yl)benzo[d]oxazol-5-yl)isobutyramide (250mg, 0.75mmol) in dry dichloromethane (15mL) was added a solution of 2,2,2-trifluoroacetic anhydride (533µL, 3.77mmol) and hydrogen peroxide (35% wt in H₂O, 550µL, 5.66mmol) in dichloromethane (15mL). The resulting solution was refluxed for 16h. After cooling, the crude mixture was diluted with dichloromethane and washed with aqueous NaHCO₃ solution. The aqueous layer was extracted with dichloromethane and the organic layers were washed with water until neutral pH was reached. The combined organic layers were dried over anhydrous MgSO₄ and evaporated. The resulting product was purified by recrystallisation from dichloromethane to afford 24mg (9%) of the title compound (LCMS RT = 5.15min, (M+MeCN)⁺ 388.9)
\textbf{EXAMPLE 20}

2-(Dimethylamino)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide hydrochloride

4M HCl in 1,4-dioxane (4mL) was added to a stirred solution of 2-(dimethylamino)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide (50mg, 0.145mmol) in methanol (5mL) and the resultant solution allowed to stir for 10 minutes before being concentrated \textit{in vacuo}. The crude residue was resuspended in toluene and again concentrated in vacuo to give the crude product as a yellow solid. This was triturated with diethyl ether and the title compound isolated as a yellow powder (42mg, 76\%) by filtration under reduced pressure (LCMS RT=6.51min, \textit{MH}^+ 346).

\textbf{1H NMR (CDCl$_3$)} 11.05 (1H, s), 9.99 (1H, br s), 8.86 (1H, s), 8.28 (1H, dd, \textit{J} 8.6 1.7Hz), 8.15-8.24 (3H, m), 8.05-8.08 (1H, m), 7.86 (1H, d, \textit{J} 8.8), 7.65-7.73 (2H, m), 7.61 (1H, dd, \textit{J} 8.8 2.1Hz), 4.23 (2H, d, \textit{J} 4.6Hz), 2.92 (6H, d, \textit{J} 4.2Hz).

2-(1H-Imidazol-4-yl)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide hydrochloride

2-(1H-imidazol-4-yl)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide (50mg, 0.136mmol) was suspended in 4M HCl in 1,4-dioxane (4mL) and the resultant mixture heated at 150°C for 10minutes in a CEM Discover microwave. After this time the reaction mixture was concentrated \textit{in vacuo}. The crude residue was resuspended in toluene and again concentrated \textit{in vacuo} to give the crude product as a yellow solid. This was triturated with diethyl ether and the title compound isolated as a yellow powder (47mg, 85\%) by filtration under reduced pressure (LCMS RT=4.60min).

\textbf{1H NMR (CDCl$_3$)} 14.48 (1H, br s), 14.27 (1H, br s), 10.72 (1H, s), 9.08 (1H, d, \textit{J} 1.3Hz), 8.85 (1H, s), 8.28 (1H, dd, \textit{J} 8.6 1.7Hz), 8.14-8.24 (3H, m), 8.05-8.08 (1H, m), 7.82 (1H, d, \textit{J} 8.8), 7.59-7.72 (4H, m), 3.98 (2H, s).
EXAMPLE 21

**N-(4-(6-Methylbenzo[d]thiazol-2-yl)phenyl)-2-(pyridin-2-yl)oxy)acetamide**

HATU (442mg, 1.16mmol) was added in one portion to a stirred solution of 2-(pyridin-2-yl)oxy)acetic acid in DCM (30mL) in the presence of diisopropylethylamine (510µL, 2.90mmol), followed by 4-(6-methylbenzo[d]thiazol-2-yl)aniline (233mg, 0.97mmol); the resulting mixture was stirred at room temperature for 18h. The solid formed was filtered off, washed with methanol, collected and dried to afford 143mg (37%) of the title compound.

**¹H NMR (DMSO):** 10.67 (1H, s), 8.04 (2H, d, J 8.5), 7.91-7.88 (2H, m), 7.77 (2H, d, J 8.5), 7.69-7.67 (1H, bd), 7.50-7.45 (1H, bt), 7.36-7.33 (1H, bd), 6.42-6.39 (1H, bd), 6.29-6.24 (1H, bt), 4.78 (2H, s), 2.45 (3H, s).

The compounds below were prepared following the same general method.

**N-(4-(6-Methylbenzo[d]thiazol-2-yl)phenyl)-2-(phenylthio)acetamide**

**LCMS RT:** 7.77min, M⁺ 390.9; **¹H NMR (DMSO):** 10.52 (1H, s), 8.03 (2H, d, J 8.73), 7.91-7.89 (2H, m), 7.76 (2H, d, J 8.73), 7.44-7.41 (2H, m), 7.36-7.31 (3H, m), 7.24-7.19 (1H, m), 3.91 (2H, s), 2.46 (3H, s).

**N-(4-(6-Methylbenzo[d]oxazol-2-yl)phenyl)-2-(phenylthio)acetamide**

**LCMS RT:** 7.29min, M⁺ 374.9; **¹H NMR (DMSO):** 10.55 (1H, s), 8.12 (2H, d, J 8.77), 7.79 (2H, d, J 8.77), 7.63 (1H, d, J 8.10), 7.57 (1H, s), 7.44-7.41 (2H, m), 7.36-7.31 (2H, m), 7.24-7.19 (2H, m), 3.91 (2H, s), 2.46 (3H, s).

**N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-phenoxyacetamide**

**LCMS RT:** 7.77min, M⁺ 374.9; **¹H NMR (DMSO):** 10.40 (1H, s), 8.04 (2H, d, J 8.79), 7.91-7.89 (2H, m), 7.85 (2H, d, J 8.79), 7.36-7.30 (3H, m), 7.03-6.96 (3H, m), 7.63 (1H, d, J 8.10), 4.75 (2H, s), 2.45 (3H, s).
2-(4H-1,2,4-triazol-3-ylthio)-N-(4-(6-methylbenzo[d]oxazol-2-yl)phenyl)acetamide

**LCMS RT= 7.26 min, M+ 366.1;**

**^1H NMR (DMSO):**
14.09 (1H, bs), 10.62 (1H, s), 8.49 (1H, bs), 8.12 (2H, d, J 8.74), 7.80 (2H, d, J 8.74), 7.63 (1H, d, J 8.10), 7.57 (1H, s), 7.21 (1H, d, J 8.25), 4.11 (2H, s), 2.46 (3H, s).

**EXAMPLE 22**

2-((2-(Naphthalen-2-yl)benzo[d]oxazol-5-yl)methylamino)acetic acid

Glycine ethyl ester hydrochloride salt (91mg, 1.1eq, 0.653mmol) was dissolved in dry DMF (4mL), 1eq of triethylamine was added and the reaction mixture was stirred at room temperature for 5 minutes. In a separate flask the bromide (300mg, 1eq, 0.59mmol) was dissolved in dry DMF (6mL), potassium carbonate was added to the mixture following by the solution of free based glycine ethyl ester in DMF. The reaction mixture was stirred at room temperature overnight. After 18 hours, some starting material was still present by TLC (50% ethyl acetate, 50% petrol ether), 1.1eq of free based glycine ethyl ester was added and the reaction mixture was heated at 70°C for 3 hours. After cooling down, the reaction mixture was concentrated in vacuo, diluted with DCM. The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated in vacuo.

Purification by flash Jones chromatography provided a yellow solid in 42% yield.

**^1H NMR (CDCl₃):**
8.25 (1H, s), 8.23 (1H, dd, J 3.44Hz), 7.91 (2H, m, J 6.52Hz), 7.82 (1H, t, J 4.69Hz), 7.68 (1H, s), 7.50 (3H, m, J 3.47Hz), 7.31 (1H, dd, J 3.32Hz), 4.13 (2H, q, J 7.14Hz), 3.89 (2H, s), 3.78 (2H, s), 1.20 (3H, t, J 8.50Hz).

This ester (75mg, 0.208mmol, 1eq) was dissolved in a mixture of water THF 1/1 (V=4mL), 5mL of a 1M NaOH solution was added at room temperature. The reaction mixture was stirred at room temperature for 18 hours. A solution of 2N HCl was added to the mixture until pH=3. A white solid crashed out, it was filtered, washed with ether and dry in the vac oven for 4 hours. It gave the desired product in a 56% yield.
LC: RT= 4.93min, 99.17% UV.

\(^1H\) NMR (DMSO): 8.18 (1H, s), 8.28 (1H, dd, J 3.44Hz), 8.17 (2H, m, J 4.13Hz), 8.04 (2H, m, J 3.38Hz), 7.90 (1H, d, J 8.37Hz), 7.64 (3H, m), 4.33 (2H, s), 3.86 (2H, s).

**EXAMPLE 23**

![Chemical structure](image)

The compounds below were prepared following the same general method.

2-Naphthalen-2-yl-5-(pyrrolidine-1-sulfonyl)-benzoxazole

\(R_f\) = 8.5 (40:60 EtOAc:Pet Ether); \(^1H\) NMR (DMSO): 8.82 (1H, s), 8.30-8.04 (6H, m), 7.92-7.89 (1H, dd, \(J\)), 7.72-7.63 (2H, m), 7.44-7.41 (2H, m), 3.20 (4H, t, \(J\)), 1.65 (4H, t, \(J\)).

N-Ethyl-2-(naphthalen-2-yl)benzo[d]oxazole-5-sulfonamide

LC RT= 6.86min, UV; \(^1H\) NMR (DMSO): 8.94 (1H, s), 8.34 (1H, dd, \(J\) 8.6, \(J\) 1.6 Hz), 8.28-8.25 (2H, m), 8.22 (1H, d, \(J\) 8.8 Hz), 8.10 (2H, d, \(J\) 8.5 Hz), 7.95 (1H, dd, \(J\) 8.6, \(J\) 1.8 Hz), 7.77-7.68 (3H, m), 2.87 (2H, q, \(J\) 7.2 Hz), 1.03 (3H, t, \(J\) 7.2 Hz).

N-(3-(Ethylsulfonyl)phenyl)naphthalene-2-carbothioamide

LHMDS (1M, 0.62mmol) was added to a solution of 5-(methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole (0.19g, 0.56mmol) in dry THF (7mL) cooled to -78°C. After stirring for 1h, iodomethane (0.16g, 1.23mmol) was added, and the reaction was warmed to room temperature. After stirring for 16h, ammonium chloride (10mL) was added and the reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried over MgSO\(_4\) and concentrated *in vacuo*. The residue was
purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/4, v/v, to afford 102mg (51%) of the title compound.

**LC RT**= 7.74min, UV ; **¹H NMR (DMSO)**: 8.83 (1H, d, J 1.4 Hz), 8.46 (1H, dd, J 8.1, J 0.9 Hz), 8.29 (1H, dd, J 8.6, J 1.8 Hz), 8.22-8.19 (1H, m), 8.13 (1H, d, J 8.7 Hz), 8.05-8.01 (2H, m), 7.86 (1H, t, J 8.0 Hz), 7.70-7.62 (2H, m), 3.48 (2H, q, J 7.4 Hz), 1.16 (3H, t, J 7.3 Hz).

**EXAMPLE 24**

(5)-2-Hydroxy-N,N,N-trimethyl-4-(2-(naphtalen-2-yl)benzo[d]oxazol-5-ylamino)-4-oxobutan-1-aminium TFA salt

HATU (0.22g, 0.57mmol) and DiPEA (0.20mL, 1.14mmol) were added to a solution of L-Carnitine (89mg, 0.55mmol) and 2-(naphtalen-2-yl)benzo[d]oxazol-5-amine (100mg, 0.38 mmol) in DMF (2mL) at 0°C. After stirring for 16h at ambient temperature the reaction mixture was concentrated and the residue treated with DCM/MeOH. The precipitate was filtered off and purified by HPLC (H2O/MeCN, 0.1% TFA) to give 29mg (15%) of the title compound. (LCMS RT= 4.41min, **MH**⁺ = 404.2)

**¹H NMR (DMSO)**: 10.28 (1H, s), 8.82 (1H, s), 8.27-8.23 (2H, m), 8.20-8.12 (2H, m), 7.78 (1H, d, J 8.8 Hz), 7.68-7.64 (2H, m), 7.56 (1H, dd, J 2.0 Hz, J 8.8 Hz), 5.75 (1H, bs), 4.59 (1H, m), 3.44 (2H, d, J 5.7 Hz), 3.17 (9H, s), 2.57 (2H, m).

**EXAMPLE 25**

2-Amino-4-methoxyphenol

A mixture of 2-nitro-4-methoxyphenol (6.00g, 35.5mmol) and ammonium chloride (9.48g, 177.4mmol) in IMS/H2O (180mL, 2:1) was heated to 70°C, then iron (9.91g,
177.4 mmol) was added and the resulting mixture was refluxed for 18 h. The crude was cooled down and filtered through a pad of celite. The filter was washed with ethyl acetate and the filtrate evaporated to dryness to afford a brown solid, which was partitioned between ethyl acetate (250 mL) and brine (150 mL). The two layers were separated, the aqueous layer was extracted further with ethyl acetate (2 x 50 mL) and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a brown solid which was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 3:2 v/v) to afford 3.84 g (78%) of the title compound.

Rf = 0.47 (ethyl acetate/hexanes 1:1 v/v); 1H NMR (DMSO): 8.44 (1H, s), 6.51 (1H, d, J 8.46), 6.20 (1H, d, J 2.97), 5.94 (1H, dd, J 8.46, 2.97), 4.72 (2H, s)

5-Methoxy-2-(naphthalen-2-yl)benzo[d]oxazole
Prepared using previously described standard microwave route.

Rf = 0.79 (ethyl acetate/hexanes 1:1 v/v); 1H NMR (DMSO): 8.79 (1H, s), 8.24 (1H, dd, J 8.65, 1.71), 8.18-8.15 (1H, m), 8.12 (1H, d, J 8.65), 8.04-8.01 (1H, m), 7.71 (1H, d, J 8.88), 7.68-7.61 (2H, m), 7.39 (1H, d, J 2.52), 7.03 (1H, dd, J 8.88, 2.52), 3.85 (3H, s).

2-(Naphthalen-2-yl)benzo[d]oxazol-5-ol
A 1 M solution of BBr3 in DCM (21.3 mL, 21.3 mmol) was added slowly to dry DCM (20 mL) at room temperature under an atmosphere of dry nitrogen, followed by 5-methoxy-2-(naphthalen-2-yl)benzo[d]oxazole 2 (1.567 g, 5.33 mmol). The resulting mixture was refluxed for 18 h under nitrogen and quenched with distilled water (20 mL). The crude was then partitioned between ethyl acetate (200 mL) and water (100 mL) and the two layers were separated. The aqueous layer was extracted further with ethyl acetate (2 x 50 mL) and the combined extracts were dried over anhydrous MgSO4. Evaporation of the solvent afforded a yellow solid which was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 1:1 v/v) to afford 848 mg (57%) of the title compound.

Rf = 0.66 (ethyl acetate/hexanes 1:1 v/v); 1H NMR (DMSO): 9.58 (1H, s), 8.78 (1H, s), 8.22 (1H, dd, J 8.61, 1.71), 8.17-8.14 (1H, m), 8.11 (1H, d, J 8.76), 8.03-8.00 (1H, m), 7.68-7.59 (3H, m), 7.14 (1H, d, J 2.30), 6.88 (1H, dd, J 8.76, 2.30).
5-(2-(Benzylkoxy)ethoxy)-2-(naphthalen-2-yl)benzo[d]oxazole

NaH (60% dispersion in oil, 34mg, 0.86mmol) was added to a solution of 2-(naphthalen-2-yl)benzo[d]oxazol-5-ol (0.2g, 0.71mmol) in DMF (4mL) at room temperature. After stirring for 0.5h benzyl 2-chloroethyl ether (0.14mL, 0.92mmol) was added and the reaction mixture was stirred at 50°C for 16h and quenched with distilled water (0.5mL). The reaction mixture was partitioned between EtOAc (40mL) and water (30mL) and the organic phase was washed with water (2x 30mL) and brine (30mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography eluting using a gradient (ethyl acetate/hexanes 0:1 v/v to ethyl acetate/hexanes 3:7 v/v) to afford 170mg (61%) of the title compound.

Rf = 0.70 (ethyl acetate/hexanes 1:1 v/v).

1H NMR (DMSO): 8.79 (1H, s), 8.22 (1H, dd, J 8.6 1.7), 8.18-8.11 (2H, m), 8.04-8.00 (1H, m), 7.71 (1H, d, J 8.9), 7.66-7.629 (2H, m), 7.40 (1H, d, J 2.5), 7.36-7.34 (4H, m), 7.30-7.27 (1H, m), 7.05 (1H, d, J 8.9 2.5), 4.57 (2H, s), 4.22 (2H, m), 3.80 (2H).

EXAMPLE 26

(2-Phenyl-1H-indol-3-yl)methanol

To a solution of 2-phenylindole-3-carboxaldehyde (500mg, 2.62mmol, 1eq) in dry MeOH (30mL) was added sodium borohydride (103mg, 1.2eq, 2.71mmol) in one portion at 0 °C. The reaction mixture was stirred at room temperature for 18hours. Water was added to the reaction mixture and the aqueous phase was extracted three times with dichloromethane, dried over Na₂SO₄, concentrated in vacuo. Purification by recrystallisation in dichloromethane gave the title compound.

LCMS RT= 5.63min, 99.65% UV, Rf =0.46 in 20% Ethylacetate /80% Petrol ether

1H NMR (DMSO): 11.33 (1H, s, OH), 7.79 (2H, dd, J 4.47Hz), 7.66 (1H, d, J 7.71 Hz), 7.52 (2H, t, J 7.64Hz), 7.39 (2H, t, J 7.05Hz), 7.10 (2H, dt, J 4.50Hz), 4.94 (1H, d, J 9.66 Hz, NH), 4.68 (2H, d, J 4.56Hz).

EXAMPLE 27

5-(Ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole
LHMDS (1M, 0.62mmol) was added to a solution of 5-(methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole (0.19g, 0.56mmol) in dry THF (7mL) cooled to -78°C. After stirring for 1h, iodomethane (0.16g, 1.23mmol) was added, and the reaction was warmed to room temperature. After stirring for 16h, ammonium chloride (10mL) was added and the reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 1/4, v/v, to afford 102mg (51%) of the title compound.

**LCMS RT**= 7.74min; **¹H NMR (DMSO)**: 8.83 (1H, d, J 1.4 Hz), 8.46 (1H, dd, J 8.1, J 0.9 Hz), 8.29 (1H, dd, J 8.6, J 1.8 Hz), 8.22-8.19 (1H, m), 8.13 (1H, d, J 8.7 Hz), 8.05-8.01 (2H, m), 7.86 (1H, t, J 8.0 Hz), 7.70-7.62 (2H, m), 3.48 (2H, q, J 7.4 Hz), 1.16 (3H, t, J 7.3 Hz).

**EXAMPLE 28**

2-(2-(Naphthalen-2-yl)benzo[d]oxazol-5-yl)sulfonyl)ethanol

A solution of 2-(naphthalen-2-yl)benzo[d]oxazol-5-amine (0.15g, 0.57mmol) and hydrochloric acid (3mL) was stirred for 30 minutes at 50°C, then cooled to 0°C. A solution of sodium nitrite (0.044g, 0.63mmol) in water (0.5mL) was added to the reaction drop-wise and stirred for 45 minutes, before the pH was adjusted to pH 7 with 1M sodium hydroxide. The mixture was added drop-wise to a solution of 2-mercapoethanol (0.08mL) in 1M sodium hydroxide (1.2mL) containing a copper suspension (0.036g, 0.58mmol) and heated to 60°C. After stirring for 30 minutes, the reaction mixture was cooled and extracted twice with ethyl acetate. The combined organic layers were dried over MgSO4 and concentrated in vacuo. The crude compound was purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 3/7, v/v, to afford 127mg (69%) of 2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylthio)ethanol. mCPBA (0.17g, 0.99mmol) was added to a solution of 2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylthio)ethanol (0.13g, 0.40mmol) in chloroform (5mL) and stirred for 16 hours. Sodium sulfite solution (10%, 5mL) was added to the reaction mixture. The organic phase was washed with 1M sodium hydroxide, dried over MgSO4 and concentrated in vacuo. The crude compound was
purified by column chromatography, eluting with ethyl acetate/petroleum ether 0/1 to 6/4, v/v, to afford 22mg (11%) of the title compound.

**Rf value** (Petrol:EtOAc 1:1, v/v): 0.39

**1H NMR (DMSO):** 8.83 (1H, s), 8.27 (1H, d), 8.21 (1H, dd, J 8.6, J 1.7 Hz), 8.16-8.08 (2H, m), 8.03-7.97 (2H, m), 7.91 (1H, dd, J 8.6, J 1.8 Hz), 7.65-7.57 (2H, m), 4.80 (1H, t, J 5.4 Hz), 3.64 (2H, q, J 6.5 Hz), 3.48 (2H, t, 6.1 Hz).
WHAT IS CLAIMED IS:

1. A compound of Formula (1)

![Chemical Structure](image)

wherein

R₉ represents a C₅₋₁₀ carbocycle which is partially or fully aromatic containing 0-4 hetero atoms and optionally substituted by 1-4 halogen, C₁₋₆ alkyl, OC₁₋₆ alkyl or NR₉₀(C=Q)-M-Z-R₉₃ wherein R₉₀ represents H or C₁₋₆ alkyl, Q represents O, S, or NR₉₁ wherein R₉₁ represents H or C₁₋₆ alkyl, M represents C₁₋₃ alkyl optionally substituted with halogen, C₁₋₆ alkyl, or C₁₋₆ alkoxy, Z represents O, S or NR₂₉₂ wherein R₂₉₂ represents H or C₁₋₆ alkyl and R₉₃ represents a C₅₋₁₀ carbocycle which is partially or fully aromatic containing 0-4 hetero atoms and optionally substituted by 1-4 halogen, C₁₋₆ alkyl or OC₁₋₆ alkyl;

three of A₁, A₂, A₃ and A₄ represent CH, and one of A₁, A₂, A₃ and A₄ represents CR₁ wherein R₁ represents:

an alkyl group selected from C₂₋₃ alkyl, n-butyl and sec-butyl, optionally substituted with hydroxy, halogen, carboxylic acid, piperidin-1-yl, N-morpholino, -NMe₂ or alkoxy;

hydroxy, halogen, CO₂(C₁₋₆alkyl), or -O(C₁₋₆alkyl) or C₁ alkyl substituted with halogen, carboxylic acid, piperidin-1-yl, N-morpholino, -NMe₂ or alkoxy;

hydroxy, halogen, CO₂(C₁₋₆alkyl), or -O(C₁₋₆alkyl);

-N-(S)-2-amino-3-hydroxypropionamide;

-N-(S)-2-(methylamino)propionamide;

-N-(S)-2-aminopropionamide;

-N-2-methylaminoacetamide;

-(S=O)R₂₁, wherein R₂₁ represents C₁₋₆alkyl;

-SOₙR₂₂ wherein n = 0, 1 or 2 and R₂₂ represents CH₃, CH₂CD₃ or C₃₋₆alkyl, optionally substituted with OH or ethyl substituted with hydroxy;
-SO₂NR₃₅R₂₃, wherein R₂₃ and R₃₅ which may be the same or different each represent H or C₁₋₆ alkyl;
-NR₃₅SO₉R₂₄, wherein n = 0, 1 or 2 and R₂₄ and R₃₅ which may be the same or different each represent H or C₁₋₆ alkyl;
-K-SO₉-R₂₈, wherein K represents C₁₋₃ alkyl optionally substituted with C₁₋₆ alkyl, n=0-2 and R₂₈ represents C₁₋₁₀ alkyl optionally substituted with one or more hydroxy, halogen, alkoxy or amine;
-CO₂R₂₆, wherein R₂₆ represents C₁₋₆ alkyl;
disubstituted phosphinate, wherein each substituent which may be the same or different may represent C₁₋₆ alkyl or C₅₋₁₀ aryl;
an N-linked mono- or bicyclic ring substituted by one or more oxo, hydroxyl, halogen, C₁₋₆ alkyl, alkoxy or aryl substituent; or
NR₁₅C(=W)R₁₇ wherein W represents NH, S or O;
R₁₇ represents C₂-alkyl, n-propyl, or C₄₋₁₀ alkyl; C₁₋₁₀ alkyl substituted with one or more halogen, hydroxyl, alkoxy or amine; a mono or disaccharide unit attached at the anomeric position via a C₁₋₄ alkyl group which is optionally substituted with one or more C₁₋₆ alkyl group; CH₂aryl, wherein aryl represents an aromatic hydrocarbon or a 5 to 10 membered aromatic heterocycle containing 1 to 4 hetero atoms selected from an oxygen atom, a sulphur atom and a nitrogen atom as a ring constituent besides carbon; -CH₂OCH₃, -CH₂OCH₂CH₂OCH₃, CH₂piperidin-1-yl or CH₂-N-morpholinoyl; and
R₁₅ represents H, C₁₋₆ alkyl or together with R₁₇ represents -CH₂CH₂--; X is O or N; and
Y is O or N.

2. A compound according to claim 1, wherein A₁, A₂ and A₄ represent CH, and A₃ represents CR₁.

3. A compound according to any preceding claim, wherein R₉ represents 2-naphthyl.
4. A compound according to claim 1 wherein R\textsubscript{9} represents 2-naphthyl optionally substituted with halogen or phenyl optionally substituted with halogen; A\textsubscript{1}, A\textsubscript{2} and A\textsubscript{4} represent CH, and A\textsubscript{3} represents CR\textsubscript{1} wherein R\textsubscript{1} represents: NR\textsubscript{15}C(=W)R\textsubscript{17} wherein W represents NH, S or O;

R\textsubscript{17} represents C\textsubscript{2}-alkyl, n-propyl, or C\textsubscript{4}-C\textsubscript{10}alkyl; C\textsubscript{1}-C\textsubscript{10}alkyl substituted with one or more halogen, hydroxyl, alkoxy or amine; a mono or disaccharide unit attached at the anomeric position via a C\textsubscript{1}-C\textsubscript{4}alkyl group which is optionally substituted with one or more C\textsubscript{1}-C\textsubscript{6} alkyl group; CH\textsubscript{2}aryl, wherein aryl represents an aromatic hydrocarbon or a 5 to 10 membered aromatic heterocycle containing 1 to 4 hetero atoms selected from an oxygen atom, a sulphur atom and a nitrogen atom as a ring constituent besides carbon; CH\textsubscript{2}OCH\textsubscript{3}, CH\textsubscript{2}OCH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{3}, CH\textsubscript{2}piperidin-1-yl or CH\textsubscript{2}N-morpholino; and R\textsubscript{15} represents H, C\textsubscript{1}-C\textsubscript{6} alkyl or together with R\textsubscript{17} represents -CH\textsubscript{2}CH\textsubscript{2}-, -CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}- or -CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-.

5. A compound according to claim 1 wherein R\textsubscript{9} represents a 5-10 membered heterocyclic ring containing one or more SO\textsubscript{n} units, wherein n=0-2 and may be the same or different for each SO\textsubscript{n} unit.

6. A compound according to claim 1, wherein R\textsubscript{1} represents a N-linked mono- or bi-cylic ring which is a lactam.

7. A compound according to claim 1, wherein R\textsubscript{1} represents -K-SO\textsubscript{n}R\textsubscript{28}, wherein K represents C\textsubscript{1}-C\textsubscript{3} alkyl optionally substituted with C\textsubscript{1}-C\textsubscript{6} alkyl; n=0-2 and R\textsubscript{28} represents C\textsubscript{1}-C\textsubscript{10}alkyl optionally substituted with one or more halogen, alkoxy or amine.

8. A compound according to claim 1, wherein R\textsubscript{9} represents a C\textsubscript{5-10} carbocycle which is partially or fully aromatic containing 0-4 hetero atoms substituted by NR\textsubscript{90}(C=Q)-M-Z-R\textsubscript{93} wherein R\textsubscript{90} represents H or C\textsubscript{1-6} alkyl, Q represents O, S, or NR\textsubscript{91} wherein R\textsubscript{91} represents H or C\textsubscript{1-6} alkyl, M represents C\textsubscript{1-3} alkyl optionally substituted with halogen, C\textsubscript{1-6} alkyl, or C\textsubscript{1-6} alkoxy, Z represents O, S or NR\textsubscript{92} wherein R\textsubscript{92} represents H or C\textsubscript{1-6} alkyl and R\textsubscript{93} represents a C\textsubscript{5-10} carbocycle which is partially or
fully aromatic containing 0-4 hetero atoms and optionally substituted by 1-4 halogen, C₁-C₆ alkyl, OC₁-C₆ alkyl.

9. A compound according to claim 1 wherein Y represents N.

10. A compound according to claim 1 wherein X represents O.

11. A compound according to claim 1 wherein Y represents N and X represents O.

12. A compound selected from the following table:

<p>| 1 | 3,4-dichloro-N-(2-isopropylbenzo[d]oxazol-5-yl)benzamide |
| 2 | 5-ethylsulfonyl-1,3-benzo[d]oxazol-2-amine |
| 3 | N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-methylbutanamide |
| 4 | N-(4-(6-benzo[d]oxazol-2-yl)phenyl)-2-methylbutanamide |
| 5 | N-(4-(5-ethylsulfonyl)benzo[d]oxazol-2-yl)phenyl)isobutyramide |
| 6 | 5-(ethylsulfonyl)-2-(3-phenoxyphenyl)benzo[d]oxazole |
| 7 | 2-(benzo[d]oxazol-2-yl)-5-chlorophenol |
| 8 | 5-chloro-2-(5-methylbenzo[d]oxazol-2-yl)phenol |
| 9 | 5-amino-2-(5-methylbenzo[d]oxazol-2-yl)phenol |
| 10 | 5-(ethylsulfonyl)-2-(1H-indol-5-yl)benzo[d]oxazole |
| 11 | N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(quinolin-2-ylthio)acetamide |
| 12 | 2-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)acetamide |
| 13 | 2-(4-methyl-4H,1,2,4-triazol-3-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)butanamide |
| 14 | N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(quinazolin-4-ylthio)acetamide |
| 15 | 2-(5-isopropyl-4H,1,2,4-triazol-3-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)acetamide |
| 16 | 2-(1,3,4-thiadiazol-2-ylthio)-N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)propanamide |
| 17 | 5-(ethylsulfonyl)-2-(furan-2-yl)benzo[d]oxazole |
| 18 | 3-(5-methylbenzo[d]oxazol-2-yl)pyridin-2-ol |
| 19 | 5-(5-methylbenzo[d]oxazol-2-yl)pyridin-2-ol |
| 20 | 5-(5-methylbenzo[d]oxazol-2-yl)pyridin-2-amine |
| 21 | 5-(5-methylbenzo[d]oxazol-2-yl)pyrimidine-2,4-diol |
| 22 | N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(4-phenyl-4H,1,2,4-triazol-3-ylthio)acetamide |
| 23 | N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-(phenylthio)acetamide |</p>
<table>
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<th>Chemical Structure</th>
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<td>N-(4-(6-methylbenzo[d]oxazol-2-yl)phenyl)-2-(phenylthio)acetamide</td>
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<td>25</td>
<td>N-(4-(6-methylbenzo[d]thiazol-2-yl)phenyl)-2-phenoxyacetamide</td>
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<td>26</td>
<td>methyl 2-(naphthalen-2-yl)benzo[d]oxazole-6-carboxylate</td>
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<td>5-amino-2-(5-(trifluoromethoxy)benzo[d]oxazol-2-yl)phenol</td>
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<td>5-amino-2-(5-phenylbenzo[d]oxazol-2-yl)phenol</td>
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<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-hydroxyacetamide</td>
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<td>3-(5-isobutyramidobenzo[d]oxazol-2-yl)quinoline 1-oxide</td>
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<td>2-(1H-imidazol-4'-yl)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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<td>2-(1H-imidazol-4'-yl)-N-(2''-(naphthalen-2''-yl)benzo[d]oxazol-5''-yl)acetamide</td>
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<td>2-hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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<td>49</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)-2-(beta-D-galactopyranosyl)acetamide</td>
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<td>50</td>
<td>3,3,3-trifluoro-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide</td>
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<td>2-methoxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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<td>2-(2-methoxyethoxy)-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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<td>53</td>
<td>(S)-2-amino-N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)propanamide</td>
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<tr>
<td>54</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propionimidamide</td>
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<tr>
<td>55</td>
<td>5-(ethylsulfinyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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<td>56</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)methanesulphonamide</td>
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<td>57</td>
<td>2-(4,4-difluorocyclohexyl)-5-(ethylsulfonyl)benzo[d]oxazole</td>
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<td>58</td>
<td>3-hydroxy-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)propanamide</td>
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<tr>
<td>59</td>
<td>ethyl 2-(naphthalen-2-yl)benzo[d]oxazol-5-yl(phenyl)phosphinate</td>
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<td>60</td>
<td>methyl 2-(3,4-dichlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate</td>
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<td>61</td>
<td>methyl 2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinate</td>
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<td>62</td>
<td>5-(ethoxysulfonyl)-2-(naphthalen-2-ylmethyl)benzo[d]oxazole</td>
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<td>63</td>
<td>2-(4-chlorophenyl)benzo[d]oxazol-5-yl(ethyl)phosphinic acid</td>
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<td>64</td>
<td>2-morpholino-N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)acetamide</td>
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<td>65</td>
<td>N-methyl-2-(naphthalen-2-yl)benzo[d]oxazole-5-sulfonamide</td>
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<td>66</td>
<td>N-(4-(6-methylbenz[d]thiazol-2-yl)phenyl)-2-(pyridin-2-yl氧)acetamide</td>
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<td>67</td>
<td>N-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)-2-(piperidin-1-yl)acetamide</td>
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<td>68</td>
<td>5-(methylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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<td>69</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-3-(beta-D-glucopyranosyl)propanamide</td>
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<td>70</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-(beta-D-mannopyranosyl)acetamide</td>
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<td>71</td>
<td>N-(2-(2,3-dichlorophenyl)benzo[d]oxazol-5-yl)-2-methylaminocetamide</td>
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<td>72</td>
<td>5-(2',2',2'-trideuteroethylsulfonyl)-2-(naphthalen-2'-yl)benzo[d]oxazole</td>
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<td>5-(ethylsulfonyl)-2-(naphthalen-2'-yl)benzo[d]oxazole</td>
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<td>5-(ethylsulfonyl)-2-(1',2',3',4'-tetrahydronaphthalen-2-yl)benzo[d]oxazole</td>
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<td>2-(6-nitroimidazo[1,2-a]pyridin-2-yl)benzo[d]thiazole</td>
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<td>76</td>
<td>(E)-5-(ethylsulfonyl)-2-styrylbenzo[d]oxazole</td>
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<td>5-(ethylsulfonyl)-2-(1,2,3,4-tetrahydro-6-yl)benzo[d]oxazole</td>
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<td>5-(ethylsulfonyl)-2-(4-phenoxyphenyl)benzo[d]oxazole</td>
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<td>79</td>
<td>2-(2,3-dihydro-1H-inden-5-yl)-5-(ethylsulfonyl)benzo[d]oxazole</td>
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<td>80</td>
<td>2-(4H-1,2,4-triazol-3-ylthio)-N-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)acetamide</td>
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<td>81</td>
<td>1-(2'-naphthalen-2'-yl)benzo[d]oxazol-5'-ylpyrrolidin-2-one</td>
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<td>82</td>
<td>2-(4H-1,2,4-triazol-3-ylthio)-N-(5-(benzo[d]thiazol-2-yl)pyridine-3-yl)acetamide</td>
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<td>83</td>
<td>2-(benzo[b]thiophen-1,1-dioxide-6-yl)-5-(ethylsulfonyl)benzo[d]oxazole</td>
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<td>84</td>
<td>5-(morpholinomethyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
</tr>
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<td>85</td>
<td>5-(ethylsulfonyl)methyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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<td>86</td>
<td>5-(methylsulfonylmethyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
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<td>87</td>
<td>5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole</td>
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<td>88</td>
<td>2-(2-(naphthalen-2-yl)benzo[d]oxazol-5-yl)methylaminoacetic acid</td>
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<td>89</td>
<td>5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]thiazole</td>
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<td>90</td>
<td>N-ethyl-2-(naphthalen-2-yl)benzo[d]oxazole-5-sulfonamide</td>
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<td>91</td>
<td>(S)-2-hydroxy-N,N,N-trimethyl-4-(2-(naphthalen-2-yl)benzo[d]oxazol-5-ylamino)-4-oxobutan-1-aminium</td>
</tr>
</tbody>
</table>
13. A pharmaceutical composition, comprising the compound of any of claims 1-12 and a pharmaceutically acceptable carrier.

14. A method of treatment or prophylaxis of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia, comprising administering the compound of any of claims 1-12.
FIG. 2

<table>
<thead>
<tr>
<th></th>
<th>CPD A</th>
<th>CPD B</th>
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<tr>
<td>EC50</td>
<td>7.975e-007</td>
<td>9.532e-007</td>
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</tbody>
</table>

CPD A - 5-amino-2-[(5,6-dimethylbenzo[d]oxazol-2-yl)phenol
CPD B - 2-[(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine