

Treatment of Duchenne muscular dystrophy

The present invention relates to a method of treatment of Duchenne muscular dystrophy.

5 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
10 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
15 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
20 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-
25 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 *mdx* mouse is the most widely used model due to availability, short
30 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 (*mdx*) in the mouse. *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.

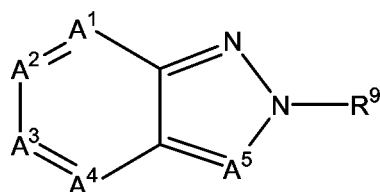
Pharmacological approaches for the treatment of muscular dystrophy differ from gene- and cell-based approaches in not being designed to deliver either the missing gene and/or protein. In general, the pharmacological strategies use drugs/molecules in an attempt to improve the phenotype by means such as 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 *mdx* mice it localizes

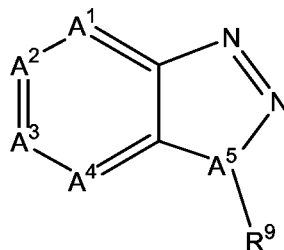
to the sarcolemma of muscle cells and restores the components of the dystrophin-associated protein complex (DAPC), which prevents the dystrophic development and in turn leads to functional improvement of skeletal muscle. Adenoviral delivery of utrophin in the dog has been shown to prevent pathology. 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.

We have now found a group of compounds which upregulate endogenous utrophin in predictive screens and, thus, may be useful in the treatment of DMD.

According to the invention, we provide use of a compound of Formula (I) or (II)



I



II

wherein

A^1 , A^2 , A^3 , A^4 and A^5 , which may be the same or different, represent N or CR^1 ,

R_9 represents $-L-R^3$, in which L is a single bond or a linker group and R^3 represents hydrogen or a substituent and

in addition,

when an adjacent pair of $A^1 - A^4$ each represent CR^1 , then the adjacent carbon atoms, together with their substituents may form a ring B,

when A^5 represents CR^1 , then A^5 and $N-R^9$, together with their substituents may form a ring C,

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia.

When R⁹ represents H, compounds of formula I are tautomers of compounds of formula II.

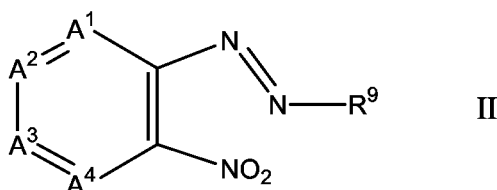
Compounds of formula I may exist in tautomeric, enantiomeric and diastereomeric forms, all of which are included within the scope of the invention.

Certain compounds of formula I are novel. According to the invention, we also provide 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. According to the invention, we claim compounds known in the art as such, but not previously described for use as pharmaceuticals, as pharmaceuticals.

All of the compounds of formula I may be made by conventional methods. Methods of making heteroaromatic ring systems are well known in the art. In particular, methods of synthesis are discussed in Comprehensive Heterocyclic Chemistry, Vol. 1 (Eds.: AR Katritzky, CW Rees), Pergamon Press, Oxford, 1984 and Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995 The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds, Alan R. Katritzky (Editor), Charles W. Rees (Editor), E.F.V. Scriven (Editor), Pergamon Pr, June 1996. Other general resources which would aid synthesis of the compounds of interest include March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley-Interscience; 5th edition (January 15, 2001).

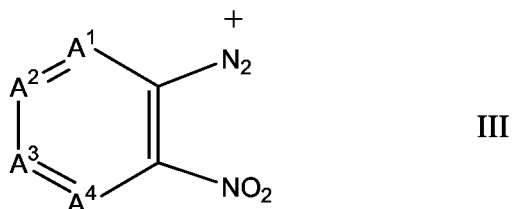
Compounds of formula I or pharmaceutically acceptable salts thereof may be prepared from a compound of formula II



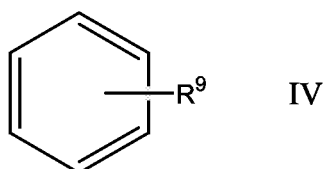
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in which A^1 , A^2 , A^3 , and A^4 are defined as above, in a reductive ring closure effected by reaction with thiourea-S,S-dioxide or a dithionite salt, for example an alkali metal salt, as described, for example, in EP 0 751 134. The reaction may be carried out in an aqueous solution, preferably an alcoholic aqueous solution, at a temperature of 60 to 80°C. Cyclisation will not occur in the presence of certain functionality, for example in the presence of $-NH_2$ or $-OH$ functionality. These groups will need to be protected before cyclisation. For example $-NH_2$ groups may be protected as amides, and OH groups may be protected as ethers. Suitable protecting strategies are disclosed, for example, in EP 0 751 134.

- 10 Compounds of formula II may be prepared by a diazonium coupling reaction of a diazonium compound of formula III,

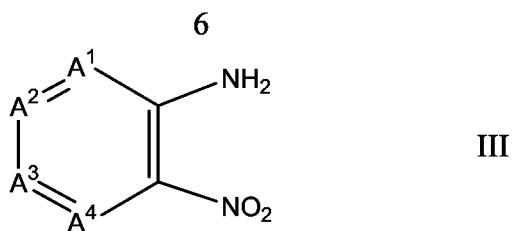


- 15 wherein A^1 , A^2 , A^3 , and A^4 are defined as above, with phenyl derivatives of formula IV



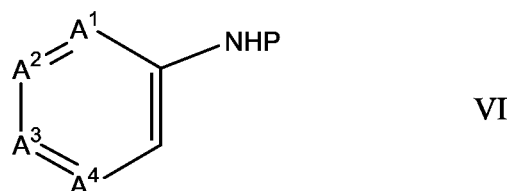
- 20 wherein R^9 is defined as above. Conditions for the coupling are well known to the synthetic chemist. For example, reaction may take place in methanol under slightly acidic conditions, over up to 24 hours.

Compounds of formula III may be prepared by diazotisation of appropriate amines of formula V



wherein A^1 , A^2 , A^3 , and A^4 are defined as above. Methods of diazotisation are well known in the art, e.g. by reaction with $\text{NaNO}_2/\text{AcOH}$ in an aqueous solution at 0 to 10°C.

Compounds of formula V may be synthesised by nitration, and subsequent deprotection, of a compound of formula VI,

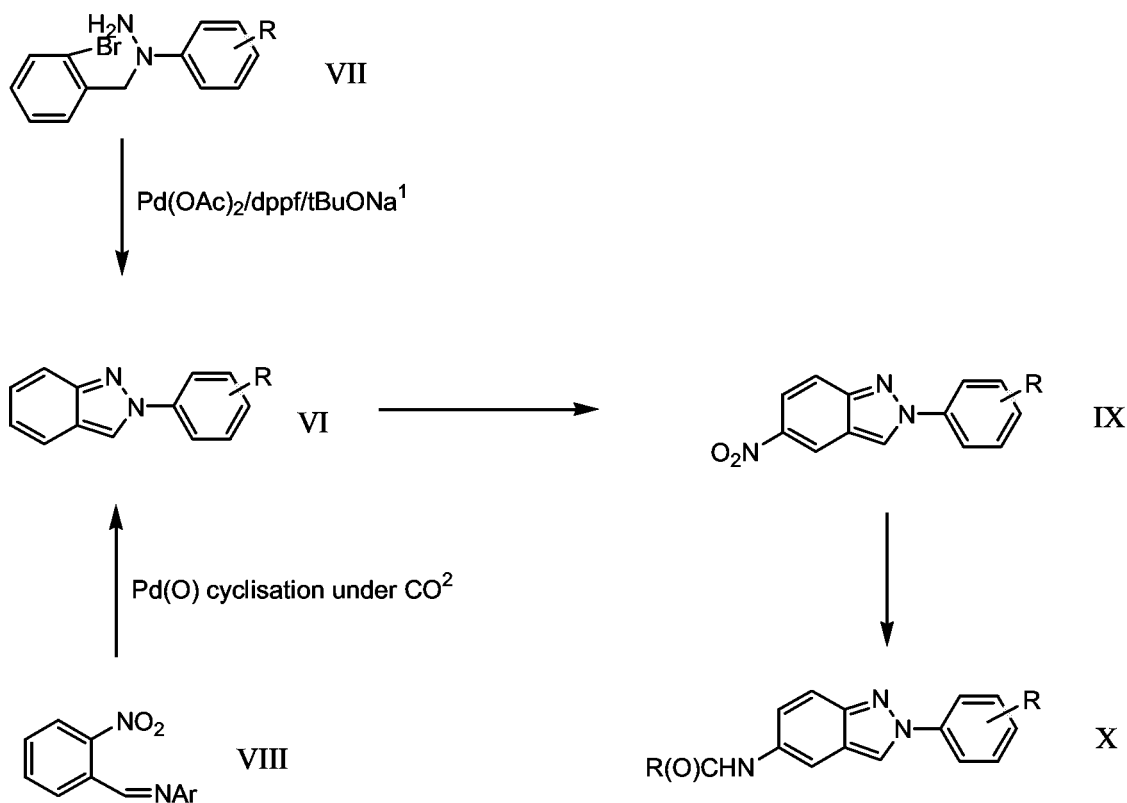


wherein A^1 , A^2 , A^3 , and A^4 are as defined above and P represents a protecting group appropriate to the nitrating conditions. Nitration could be effected by, for example, $\text{cHNO}_3/\text{cH}_2\text{SO}_4$ in a solvent appropriate to the reaction conditions.

Compounds of formulas IV and VI may be made by conventional techniques known per se.

2-Phenylindazoles of formula I can be made by a variety of processes, as outlined in the scheme below.

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10 Phenyl indazoles may be made using known processes. For example hydrazines of formula VII may be cyclised using Pd (II) catalysis as described by Song, J.J. et al, Organic Letters, 2000, 2(4), 519-521.

Alternatively, phenyl indazoles of formula VII may be synthesised from an imine VIII using Pd (0) mediated cyclisation as described by Akazome, M. et al, J. Chem. Soc. Chemical Communications, 1991, 20, 1466-7.

The phenyl indazoles may then be manipulated using processes known to the skilled man. For example, nitration (as described by Elguero, J. et al, Bulletin des Societes Chimiques Belges, 1996, 105(6), 355-358) gives nitro compound IX. The skilled man is well aware of processes by which nitro compounds may be manipulated

to give a wide range of functionality. For example, reduction of the nitro compound, for example using Sn/HCl, followed by acylation, for example using an acid chloride and triethyl amine in CH₂Cl₂ gives an amide X.

In the above processes it may be necessary for any functional groups, e.g.
5 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
10 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)- α -phenylethyl, diphenylmethyl or triphenylmethyl, and
15 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
20 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.

25 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
30 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. The non-toxic physiologically acceptable salts are preferred, 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.

Examples of substituents that R^3 in the compound of formula 1 may represent include alkyl, alkoxy or aryl, each optionally substituted by one or more, preferably one to three substituents, R_2 , which may be the same or different.

In addition, compounds that may be mentioned include those of:

formula I of claim 1 or of formula II of claim 1 in which A^5 represents N, wherein:

L is single bond and R^3 represents:

thioalkyl optionally substituted by alkyl or optionally substituted aryl,

- O-aryl or thioaryl, in which the aryl is optionally substituted,
optionally substituted aryl,
hydroxyl,
NR¹⁰R¹¹,
5 SO₂R¹²,
NR¹³SO₂R¹⁴,
C(=W)R¹⁶,
NR¹⁵C(=W)R¹⁷,
R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁶ and R¹⁷, which may be the same or different,
10 represent hydrogen, alkyl optionally substituted by optionally substituted aryl,
optionally substituted aryl,
in addition,
R¹⁰ and R¹¹ together with the nitrogen to which they are attached may form a
ring,
15 R¹² may have the same meaning as NR¹⁰R¹¹,
R¹⁶ and R¹⁷, which may be the same or different, may each represent
alkyl substituted by one or more of halogen, alkoxy optionally substituted aryl
or optionally substituted aryl,
optionally substituted aryloxy,
20 aryl or NR¹⁰R¹¹,
and when R¹⁶ or R¹⁷ represents NR¹⁰R¹¹, one of R¹⁰ and R¹¹ may additionally
represent CO alkyl optionally substituted or COaryl optionally substituted, and
in addition to the definitions shared with R¹⁷, R¹⁶ may represent hydroxyl;
25 or compounds of formula II of claim 1 in which A⁵ represents CH, and wherein
L is single bond and R³ represents:
thioalkyl optionally substituted by alkyl or optionally substituted aryl,
thioaryl, in which the aryl is optionally substituted,
optionally substituted aryl,
30 hydroxyl,
NO₂,
CN,
NR¹⁰R¹¹,

- halogen,
 SO_2R^{12} ,
 $\text{NR}^{13}\text{SO}_2\text{R}^{14}$,
 $\text{C}(=\text{W})\text{R}^{16}$,
5 $\text{OC}(=\text{W})\text{NR}^{10}\text{R}^{11}$
 $\text{NR}^{15}\text{C}(=\text{W})\text{R}^{17}$,
 R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{17} , which may be the same or different,
represent hydrogen, alkyl optionally substituted by optionally substituted aryl,
optionally substituted aryl,
10 in addition,
 R^{10} and R^{11} together with the nitrogen to which they are attached may form a
ring,
 R^{12} may have the same meaning as $\text{NR}^{10}\text{R}^{11}$,
 R^{16} and R^{17} , which may be the same or different, may each represent
15 alkyl substituted by one or more of halogen, alkoxy optionally substituted aryl
or optionally substituted aryl,
optionally substituted aryloxy,
aryl or $\text{NR}^{10}\text{R}^{11}$,
and when R^{16} or R^{17} represents $\text{NR}^{10}\text{R}^{11}$, one of R^{10} and R^{11} may additionally
20 represent CO alkyl optionally substituted or COaryl optionally substituted, and
in addition to the definitions shared with R^{17} , R^{16} may represent hydroxyl.

- Compounds that may be mentioned include those wherein R^1 and R^2 , which
may be the same or different, may represent:
25 alkyl optionally substituted by one or more halogen, alkoxy or optionally
substituted aryl, thioaryl or aryloxy,
alkoxy optionally substituted by optionally by alkyl or optionally substituted
aryl,
hydroxyl,
30 $\text{OC}(=\text{W})\text{NR}^{10}\text{R}^{11}$
aryl,
thioalkyl optionally substituted by alkyl or optionally substituted aryl,
thioaryl, in which the aryl is optionally substituted,

NO₂,

CN,

NR¹⁰R¹¹,

halogen,

5 SO₂R¹²,

NR¹³SO₂R¹⁴,

C(=W)R¹⁶,

NR¹⁵C(=W)R¹⁷,

P(=O)OR₄₀R₄₁,

10 R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₄₀ and R₄₁, which may be the same or different, represent hydrogen, alkyl optionally substituted by optionally substituted aryl, optionally substituted aryl,

in addition,

NR¹⁰R¹¹ together with the nitrogen to which they are attached may form a ring,

15 R¹² may have the same meaning as NR¹⁰R¹¹,

when R₁₇ represents NR¹⁰R¹¹, that NR¹⁰R¹¹ may represent hydrogen, COalkyl and CO optionally substituted aryl,

R¹⁶ may represent hydroxy, alkoxy, or NR¹⁰R¹¹,

and R¹⁷ may represent alkyl substituted by one or more of halogen, alkoxy,

20 optionally substituted aryl or NR¹⁰R¹¹.

Other compounds that may be mentioned include those of either:

formula I of claim 1 or of formula II of claim 1 in which A⁵ represents N, wherein:

25 L represents a linker group which is:

O, S or NR¹⁸,

alkylene, alkenylene, alkynylene, each of which may be optionally interrupted by one or more of O, S, NR¹⁸, or one or more C-C single, double or triple bonds,

and R¹⁸ represents hydrogen, alkyl, COR¹⁶.

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or a compound of formula II of claim 1 in which A⁵ represents CH, wherein:

L represents a linker group which is:

O, S, NR¹⁸,

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alkylene, alkenylene, alkynylene, each of which may be optionally interrupted by one or more of O, S, NR¹⁸, or one or more C-C single, double or triple bonds,

a -N-N- single or double bond,

and R¹⁸ represents hydrogen, alkyl, COR¹⁶.

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Alkyl may represent any alkyl chain. Alkyl includes straight and branched, saturated and unsaturated alkyl, as well as cyclic alkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However, preferably, when any of the substituents represents alkyl, alkyl is saturated, linear or branched and has from 1 to 10 carbon atoms, preferably from 1 to 8 carbon atoms and more preferably from 1 to 6 carbon atoms. When any of the substituents represents alkyl, a particularly preferred group is cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

15 Aryl may represent any aromatic system. Preferably, in the compounds of formula I, aryl is 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. We prefer heterocycles which contain one or two heteroatoms. Aromatic heterocycles that may be mentioned include
20 furan, thiophene, pyrrole, and pyridine.

Particularly preferably, when aryl is an aromatic hydrocarbon, aryl represents a 6 to 10 membered monocyclic or bicyclic system, for example phenyl or naphthalene.

25 Saturated and unsaturated heterocycles that may be mentioned include those containing 4 to 7 ring atoms, preferably 5 or 6 ring atoms, preferably containing one to two heteroatoms selected from N, S and O. Heterocycles that may be mentioned include pyrrolidine, piperidine, tetrahydrofuran, piperazine and morpholine. N-containing heterocycles are particularly preferred, eg when NR¹⁰R¹¹ forms a
30 heterocyclic ring.

As detailed above, when an adjacent pair of A¹ - A⁴ each represent CR¹, the adjacent carbon atoms, together with their substituents may form a ring B. Also, when

A^5 represents CR^1 , then A^5 and CR^1 together with their substituents may form a ring C. Preferably ring B and/or ring C is a saturated or unsaturated 3 to 10 membered carbocyclic or heterocyclic ring.

5 Particularly preferably ring B is benzene ring.

Particularly preferably ring C is a 3- 10 membered saturated or unsaturated heterocyclic ring.

10 We particularly prefer compounds in which at least one R_1 represents $NR^{15}C(=W)R^{17}$, most particularly the group $NR^{15}COR^{17}$.

We also prefer compounds in which at least one R^1 represents $CONR^{10}R^{11}$.

15 For one group of particularly preferred compounds at least one R_1 represents an amide group $NHCOR^{17}$, wherein R^{17} is selected from:

alkyl $C_1 - C_6$,

alkyl $C_1 - C_6$ substituted by phenyl

alkyl $C_1 - C_6$ substituted by alkoxy $C_1 - C_6$,

20 haloalkyl $C_1 - C_6$,

perfluoroalkyl $C_1 - C_6$,

phenyl optionally substituted by one or more of halogen, alkyl $C_1 - C_6$, alkoxy $C_1 - C_6$, amino, (alkyl $C_1 - C_6$)amino, di(alkyl $C_1 - C_6$) amino or phenyl,

CH:CH phenyl,

25 naphthyl, pyridinyl, thiophenyl and furanyl.

We prefer compounds in which one or both of R^1 and R^2 are other than $-COOH$.

30 For another group of particularly preferred compounds at least one R^1 represents a group $NR^{15}CONR^{10}R^{11}$, then in which R^{10} and R^{11} , which may be the same or different, are selected from optionally substituted aryl, alkyl and COaryl optionally substituted. A particularly preferred group which at least one of R^1 may represent is

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NHCONHR¹⁵ and R¹⁵ is selected from phenyl, alkyl C₁ to C₆ and COphenyl optionally substituted by one or more halogen.

For another group of particularly preferred compounds at least one R¹
5 represents alkyl C₁ to C₆, optionally substituted by phenyl or a 5 or 6- membered saturated or unsaturated heterocycle containing one to two heteroatoms selected from N, S and O. Preferred heterocycles include thiophene, furan, pyridine and pyrrole.

For another group of particularly preferred compounds at least one R¹
represents COR¹⁶ and R¹⁶ is alkoxy C₁ – C₆, amino, (alkyl C₁ – C₆)amino or di(alkyl C₁
10 – C₆) amino.

For another group of particularly preferred compounds at least one R₁ represents:

NO₂,
15 halogen,
amino or (alkyl C₁ – C₆)amino or di(alkyl C₁ – C₆) amino in which the alkyl C₁ to C₆ is optionally substituted by phenyl or a 5 or 6 membered saturated or unsaturated heterocycle,
NHSO₂alkyl C₁ – C₆, NHSO₂phenyl,
20 SO₂alkyl C₁ – C₆,
phenyl optionally substituted by C₁ to C₆ alkoxy C₁ – C₆,
a 5 – 10 membered, saturated or unsaturated, mono- or bi-cyclic heterocycle containing from 1 – 3 heteroatoms selected from N, S and O.

25 There is also wide scope for variation of the group R³. Preferably R³ represents aryl and is optionally substituted by one to three substituents, R², which may be the same or different.

Particularly preferably, R³ is a 5 – 10 membered aromatic mono- or bi-cyclic
30 system, especially a hydrocarbon 5 – 10 membered aromatic mono- or bi-cyclic system, for example benzene or naphthalene.

Alternatively, the 5 – 10 membered aromatic mono- or bi-cyclic system, may be a heterocyclic system containing up to three heteroatoms selected from N, O and S, for example a thiophene, furan, pyridine or pyrrole.

5 Preferably the substituent(s) R^2 is/are selected from:

alkyl $C_1 - C_6$, optionally substituted by thiophenyl or phenoxy, each optionally substituted by halogen,

alkoxy $C_1 - C_6$

phenyl,

10 thioalkyl $C_1 - C_6$

thiophenyl, optionally substituted by halogen,

NO_2 ,

CN

15 $NR^{10}R^{11}$, in which R^{10} and R^{11} , which may be the same or different represent hydrogen, alkyl $C_1 - C_6$, or together with the nitrogen to which they are attached form a 5 to 7 membered ring which may contain one or more additional heteroatoms selected from N, O and S,

halogen

20 SO_2R^{12} , in which R^{12} represents a 5 to 7 membered ring which may contain one or more additional heteroatoms selected from N, O and S

$NHCOR^{17}$, in which R^{17} represents

alkyl $C_1 - C_6$, optionally substituted by:

phenyl or halogen, or

phenyl optionally substituted by alkoxy $C_1 - C_6$, carboxy or

25 halogen, or

a 5 or 6 membered saturated or unsaturated heterocycle,

phenyl or a 5 or 6 membered saturated or unsaturated heterocycle

optionally substituted by halogen, alkoxy C_1 to C_6 , carboxy or a group $SO_2NR^{10}R^{11}$,

30 Particularly preferably when R^2 represents $NR^{10}R^{11}$, $NR^{10}R^{11}$ represents N-pyrrole, N-piperidine, $N'(C_1 - C_6)$ alkyl N piperazine or N-morpholine.

Preferably the linker group L represents:

-NH.NH-

-CH=CH-,

-C≡C-, or

-NCOR¹⁶ in which R¹⁶ represents phenyl or a 5 or 6 membered saturated

5 or unsaturated heterocycle optionally substituted by halogen, alkoxy C₁ to C₆, carboxy.

A¹ - A⁴ may represent N or CR¹. Consequently, the six membered ring may contain 1, 2, 3 or 4 nitrogen atoms. Embodiments of the invention exist in which two
10 of A¹ - A⁴ represent nitrogen, one of A¹ - A⁴ represents nitrogen and in which all of A¹ - A⁴ represents CR¹.

In a particularly preferred group of compounds:

A¹, A², A³, A⁴ and A⁵ which may be the same or different, represent N or CR¹,

15 R⁹ represents -L-R³, in which L is a single bond or a linker group,

either the compound is of formula I or of formula II wherein A⁵ represents N,
and

L is single bond and R³ represents:

thioalkyl optionally substituted by alkyl or optionally substituted aryl,

20 thioaryl, in which the aryl is optionally substituted,

optionally substituted aryl,

hydroxyl,

NR¹⁰R¹¹,

SO₂R¹²,

25 NR¹³SO₂R¹⁴,

C(=W)R¹⁶,

NR¹⁵C(=W)R¹⁷,

R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁶ and R¹⁷, which may be the same or different,
represent hydrogen, alkyl optionally substituted by optionally substituted aryl,
30 optionally substituted aryl,

in addition,

R¹⁰ and R¹¹ together with the nitrogen to which they are attached may form a
ring,

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R^{12} may have the same meaning as $NR^{10}R^{11}$,

R^{16} and R^{17} , which may be the same or different, may each represent

alkyl substituted by one or more of halogen, alkoxy optionally substituted aryl or optionally substituted aryl,

5 optionally substituted aryloxy,

aryl or $NR^{10}R^{11}$,

and when R^{16} or R^{17} represents $NR^{10}R^{11}$, one of R^{10} and R^{11} may additionally represent CO alkyl optionally substituted or COaryl optionally substituted, and

in addition to the definitions shared with R^{17} , R^{16} may represent hydroxyl;

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or the compound is of formula II in which A^5 represents CH, and wherein L is single bond and R^3 represents:

thioalkyl optionally substituted by alkyl or optionally substituted aryl,

thioaryl, in which the aryl is optionally substituted,

15 optionally substituted aryl,

hydroxyl,

NO_2 ,

CN,

$NR^{10}R^{11}$,

20 halogen,

SO_2R^{12} ,

$NR^{13}SO_2R^{14}$,

$C(=W)R^{16}$,

$OC(=W)NR^{10}R^{11}$

25 $NR^{15}C(=W)R^{17}$,

R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{17} , which may be the same or different, represent hydrogen, alkyl optionally substituted by optionally substituted aryl, optionally substituted aryl,

in addition,

30 R^{10} and R^{11} together with the nitrogen to which they are attached may form a ring,

R^{12} may have the same meaning as $NR^{10}R^{11}$,

R^{16} and R^{17} , which may be the same or different, may each represent

19

alkyl substituted by one or more of halogen, alkoxy optionally substituted aryl or optionally substituted aryl,

optionally substituted aryloxy,

aryl or $\text{NR}^{10}\text{R}^{11}$,

5 and when R^{16} or R^{17} represents $\text{NR}^{10}\text{R}^{11}$, one of R^{10} and R^{11} may additionally represent CO alkyl optionally substituted or COaryl optionally substituted, and in addition to the definitions shared with R^{17} , R^{16} may represent hydroxyl and in addition,

R^1 and R^2 , which may be the same or different, represent:

10 alkyl optionally substituted by one or more halogen, alkoxy or optionally substituted aryl, thioaryl or aryloxy,

alkoxy optionally substituted by optionally by alkyl or optionally substituted aryl,

hydroxyl,

15 $\text{OC}(=\text{W})\text{NR}^{10}\text{R}^{11}$

aryl,

thioalkyl optionally substituted by alkyl or optionally substituted aryl,

thioaryl, in which the aryl is optionally substituted,

NO_2 ,

20 CN ,

$\text{NR}^{10}\text{R}^{11}$,

halogen,

SO_2R^{12} ,

$\text{NR}^{13}\text{SO}_2\text{R}^{14}$,

25 $\text{C}(=\text{W})\text{R}^{16}$,

$\text{NR}^{15}\text{C}(=\text{W})\text{R}^{17}$,

R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{17} , which may be the same or different, represent hydrogen, alkyl optionally substituted by optionally substituted aryl, optionally substituted aryl,

30 in addition,

$\text{NR}^{10}\text{R}^{11}$ together with the nitrogen to which they are attached may form a ring,

R^{12} may have the same meaning as $\text{NR}^{10}\text{R}^{11}$,

20

when R_{17} represents $NR^{10}R^{11}$, that $NR^{10}R^{11}$ may represent hydrogen, COalkyl and CO optionally substituted aryl,

R^{16} may represent hydroxy, alkoxy, or $NR^{10}R^{11}$,

and R^{17} may represent alkyl substituted by one or more of halogen, alkoxy,
5 optionally substituted aryl or $NR^{10}R^{11}$.

when an adjacent pair of $A_1 - A_4$ each represent CR_1 , then the adjacent carbon atoms, together with their substituents may form a ring B,

or a pharmaceutically acceptable salt thereof,

10 in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia.

We also provide a method for the treatment or prophylaxis of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia in a patient in need thereof,

15 comprising administering to the patient an effective amount of a compound of formula (I) or (II) or a pharmaceutical acceptable salt.

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

20 Thus, according to a further aspect of the invention there is provided a pharmaceutical composition including preferably less than 80% w/w, more preferably 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.

25 We also provide 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.

5 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.

10 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.

15 When not in solution, the compound of formula I preferably is in a form having a mass median diameter of from 0.01 to 10 μ m. 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.

20 The content of compound formula I in a pharmaceutical composition is generally about 0.01-about 99.9wt%, preferably 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.

25 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, preferably 0.1 – 100 mg, is preferably administered in a single dose or in 2 or 3 portions per day.

30 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 ≈ 5 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.

15

The H2K/mdx/Utro A reporter cell line maintenance

The H2K/mdx/Utro A reporter cell line was passaged twice a week until $\leq 30\%$ confluent. The cells were grown at 33°C in the presence of $10\% \text{CO}_2$

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

20

Growth Medium

DMEM Gibco 41966

20% FCS

1% Pen/Strep

25

1% glutamine

10mls Chick embryo extract

Interferon(1276 905 Roche) Add fresh $10\mu\text{l}$ / 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.

- 5 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

- 10 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.

15

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.

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

Muscle Analysis

Immunohistochemistry

- 25 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% foetal calf serum in PBS for 30 mins. The primary antibodies were diluted in blocking reagent and incubated on

25

sections for 1.5 hrs in a humid chamber then washed three times for 5mins in PBS. Secondary antibodies also diluted in blocking reagent, were incubated for 1hr in the dark in a humid chamber. Finally sections were washed three times 5mins in PBS and coverslip Mounted with hydromount. Slides were analysed using a Leica fluorescent
5 microscope.

Results

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

- 5 + 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

10 Table 1: Compounds made by methods described herein

Example number	Chemical Name	Activity
1	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)nicotinamide	+++
2	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isonicotinamide	++
3	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)benzamide	+
4	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-4-methoxybenzamide	++
5	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-2-methoxybenzamide	+
6	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)thiophene-2-carboxamide	+++
7	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)propionamide	+
8	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)butyramide	++
9	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)pentanamide	++
10	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide	++
11	N-(2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)furan-2-carboxamide	++
12	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)nicotinamide	+++
13	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isonicotinamide	+++
14	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)propionamide	+
15	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)butyramide	+
16	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)pentanamide	+
17	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide	+

18	N-(2-(4-(diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)furan-2-carboxamide	+
19	2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+++
20	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)nicotinamide	++
21	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isonicotinamide	+
22	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)acetamide	++
23	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)propionamide	+
24	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)butyramide	+
25	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)pentanamide	+
26	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide	+
27	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)furan-2-carboxamide	+
28	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)thiophene-2-carboxamide	+
29	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)benzamide	+
30	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)-4-methoxybenzamide	+
31	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)-2-methoxybenzamide	+
32	4-chloro-N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)benzamide	+
33	N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)-4-(dimethylamino)benzamide	+
34	6-methyl-2-(4-morpholinophenyl)-2H-benzo[d][1,2,3]triazol-5-amine	++
35	N-(2-(4-chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)propionamide	++++
36	N-(2-(4-chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)butyramide	+++
37	N-(2-(4-chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide	++++
38	2-(4-chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+
39	N-(2-(4-chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)acetamide	++++
40	2-(4-(piperidin-1-yl)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine	++
41	2-(4-(dimethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+++
42	2-(4-(4-methylpiperazin-1-yl)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+
43	2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine	++++
44	2-(4-chlorophenyl)-6-(methylsulfonyl)-2H-indazole	++
45	2-(4-chlorophenyl)-6-nitro-2H-indazole	+
46	N-(2-(4-chlorophenyl)-2H-indazol-6-yl)isobutyramide	++++
47	2-(4-chlorophenyl)-6-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole 1-oxide	+
48	2-(4-chlorophenyl)-2H-indazole	++++
49	2-(4-chlorophenyl)-5-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole	+
50	2-(3,4-dichlorophenyl)-5-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole	++

51	2-(3',4'-dichlorophenyl)-5-(ethylsulfonyl)-benzotriazole	+++
52	2-(4'-chlorophenyl)-5-(ethylsulfonyl)-benzotriazole	++++
53	N-(2-(3,4-Dichlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide	++++
54	6-(Methylsulfonyl)-2-(naphthalen-2-yl)-2H-benzo[d][1,2,3]triazole 1-oxide	++
55	5-(Methylsulfonyl)-2-(naphthalen-2-yl)-2H-benzo[d][1,2,3]triazole	++++
56	2-(4'-Chlorophenyl)-6-(isopropylsulfonyl)-2H-indazole	++++

Table 2: Compounds made by analogues methods to those described herein, or by literature methods known or adapted by the persons skilled in the art.

Example number	Chemical Name	Activity
57	5-nitro-2-phenyl-2H-benzo[d][1,2,3]triazole	++
58	2-p-tolyl-2H-benzo[d][1,2,3]triazol-5-amine	+
59	2-(4-nitrophenyl)-2H-benzo[d][1,2,3]triazol-5-amine	++
60	2-(4-methoxyphenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+
61	2-(3-chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+
62	2-phenyl-2H-benzo[d][1,2,3]triazol-5-amine	++
63	2-(3,4-dimethylphenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+
64	2-(4-ethoxyphenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine	++
65	6-methyl-2-p-tolyl-2H-benzo[d][1,2,3]triazol-5-amine	++
66	N-(2-(4-methoxyphenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)acetamide	+
67	N-(6-methyl-2-phenyl-2H-benzo[d][1,2,3]triazol-5-yl)acetamide	++
68	2-(4-ethylphenyl)-2H-benzo[d][1,2,3]triazol-5-amine	++
69	N-(2-(4-fluorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)acetamide	++
57	N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)acetamide	+++
58	2-(4-Fluorophenyl)-2H-benzo[d][1,2,3]triazol-5-amine	+++
59	2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine	++++
60	2-(5-Amino-2H-benzo[d][1,2,3]triazol-2-yl)phenol	++++
61	6-Methyl-2-p-tolyl-2H-benzo[d][1,2,3]triazol-5-amine	++
62	6-Methyl-2-phenyl-2H-benzo[d][1,2,3]triazol-5-amine	++

5

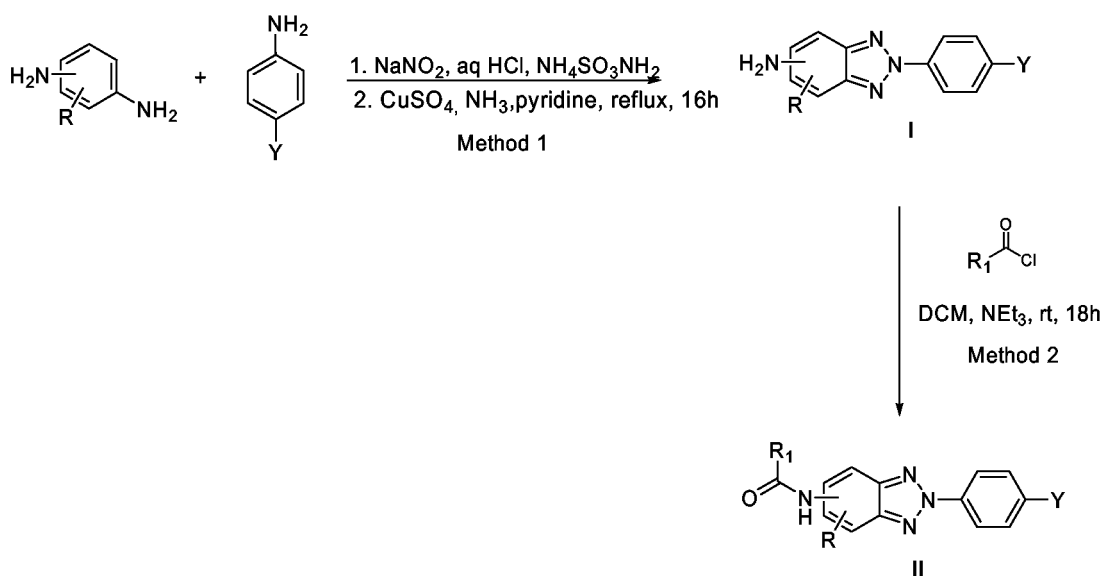
Experimental

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.

10

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.

- 5 ¹H NMR spectra were recorded on a Bruker instrument operating at 300 MHz. NMR spectra were obtained as CDCl₃ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm) or DMSO-D₆ (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).
- 10 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), HCl (hydrochloric acid),
 15 MgSO₄ (magnesium sulfate), NaOH (sodium hydroxide), Na₂CO₃ (sodium carbonate), NaHCO₃ (sodium bicarbonate), THF (tetrahydrofuran).



20

Method 1 : Compounds I

2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine

An aqueous solution (10mL) of sodium nitrite (764mg, 11.1mmol) was added dropwise to a solution of N,N-diethyl-p-phenylenediamine (1.54mL, 9.3mmol) in 10% aqueous hydrochloric acid (50mL) under ice cooling. After 15min, ammonium sulfamate (1.58g, 13.8mmol) was added and the resulting mixture was stirred for 15min. After
5 adjusting the pH to pH 5 using sodium acetate, 1,3-phenylenediamine (1g, 9.2mmol) was added; the mixture was further stirred for 2h and then basified to pH 9 using 1M sodium hydroxide. Ethyl acetate was added and the organic layer washed twice with brine. The combined organic layers were dried over anhydrous MgSO₄ and evaporated to afford a red solid. A solution of copper sulfate (10g) in aqueous ammonia (30mL of
10 28% ammonia in 30mL of water) was added to the previously obtained red solid in pyridine (40mL). The solution was then refluxed for 16h. After cooling, ethyl acetate was added, and the organic layer washed twice with brine. The combined organic layers were dried over anhydrous MgSO₄ and evaporated down to get a dark red solid, which was triturated with diethyl ether to afford 1.09g (42%) of the title compound
15 (LCMS RT= 7.06min, MH⁺ 282.1)

¹H NMR (DMSO): 8.02 (2H, d, *J* 9.3 Hz), 7.68 (1H, d, *J* 9.1 Hz), 6.96 (1H, dd, *J* 9.1 2.0 Hz), 6.86 (2H, d, *J* 9.3 Hz), 6.75 (1H, dd, *J* 1.9 0.6 Hz), 5.55 (2H, br), 3.46 (4H, q, *J* 7.1 Hz), 1.19 (6H, t, *J* 7.1 Hz)

20 All compounds below were prepared following the same general procedure and purified either by trituration with diethyl ether or by column chromatography on silica gel eluting with a gradient of ethyl acetate/hexanes .

6-Methyl-2-(4-morpholinophenyl)-2H-benzo[d][1,2,3]triazol-5-amine

25 LCMS RT= 5.95min, MH⁺ 311.9; ¹H NMR (DMSO): 8.03 (2H, d, *J* 9.2 Hz), 7.55 (1H, s), 7.11 (2H, d, *J* 9.3 Hz), 6.81 (1H, s), 5.32 (2H, s), 3.78-3.75 (4H, m), 3.19-3.16 (4H, m), 2.26 (3H, s)

2-(4-Chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-amine

30 LCMS RT= 6.72min, MH⁺ 245.0; ¹H NMR (DMSO): 8.19 (2H, d, *J* 9.0 Hz), 7.69 (1H, d, *J* 9.4 Hz), 7.66 (2H, d, *J* 9.1 Hz), 6.99 (1H, dd, *J* 9.1 2.0 Hz), 6.68 (1H, d, *J* 1.9 Hz), 5.71 (2H, s)

2-(4-(Piperidin-1-yl)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine

LCMS RT= 7.21min, MH^+ 294.2; 1H NMR (DMSO): 7.99 (2H, d, J 9.2 Hz), 7.65 (1H, d, J 9.2 Hz), 7.08 (2H, d, J 9.2 Hz), 6.92 (1H, dd, J 9.0 1.9 Hz), 6.70-6.69 (1H, m), 5.53 (2H, s), 3.28-3.23 (4H, m), 1.68-1.54 (6H, m)

5

2-(4-(Dimethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine

LCMS RT= 6.13min, MH^+ 254.1; 1H NMR (DMSO): 7.99 (2H, d, J 9.2 Hz), 7.64 (1H, d, J 9.2 Hz), 6.91 (1H, dd, J 9.0 2.0 Hz), 6.86 (2H, d, J 9.2 Hz), 6.70 (1H, d, J 1.5 Hz), 5.50 (2H, s), 2.99 (6H, s)

10

2-(4-(4-Methylpiperazin-1-yl)phenyl)-2H-benzo[d][1,2,3]triazol-5-amine

LCMS RT= 4.86min, MH^+ 309.1; 1H NMR (DMSO): 8.01 (2H, d, J 9.2 Hz), 7.65 (1H, d, J 9.2 Hz), 7.10 (2H, d, J 9.2 Hz), 6.93 (1H, dd, J 9.0 1.9 Hz), 6.70-6.69 (1H, m), 5.54 (2H, s), 2.23 (4H, s)

15

2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine

LCMS RT= 7.13min, MH^+ 259.0; 1H NMR (DMSO): 8.19 (2H, d, J 8.9 Hz), 7.65 (2H, d, J 8.9 Hz), 7.60-7.59 (1H, m), 6.80 (1H, s), 5.48 (2H, s), 2.27 (3H, s)

20 **Method 2 :Compounds II****N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)nicotinamide**

To a solution of 2-(4-chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-amine (50mg, 0.19mmol) and triethylamine (108 μ L, 0.77mmol) in dichloromethane (4mL) was added 3-nicotinoyl chloride hydrochloride (38mg, 0.21mmol). The resulting mixture was stirred at room temperature overnight. Dichloromethane was added and the organic layer was washed twice with aqueous saturated Na_2CO_3 . The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. The resulting solid was washed with diethyl ether to afford 7mg (10%) of the title compound (LCMS RT=

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6.30min, MH^+ 364.2)

1H NMR (DMSO): 10.26 (1H, s), 9.20 (1H, m), 8.82-8.79 (1H, m), 8.39-8.32 (3H, m), 8.13 (1H, s), 7.96 (1H, s), 7.74 (2H, d, J 8.9 Hz), 7.65-7.57 (1H, m)

All compounds below were prepared following the same general procedure.

N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isonicotinamide

LCMS RT= 6.37min, MH^+ 364.0; 1H NMR (DMSO): 10.33 (1H, s), 8.83 (2H, d, J 6.0 Hz), 8.33 (2H, d, J 8.8 Hz), 8.12 (1H, s), 7.96-7.92 (3H, m), 7.73 (2H, d, J 8.9 Hz)

N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)benzamide

LCMS RT= 7.63min, MH^+ 363.1; 1H NMR (DMSO): 10.05 (1H, s), 8.33 (2H, d, J 9.1 Hz), 8.10 (1H, s), 8.04-7.94 (3H, m), 7.73 (2H, d, J 9.1 Hz), 7.64-7.55 (3H, m)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-4-methoxybenzamide

LCMS RT= 7.63min, MH^+ 392.7; 1H NMR (DMSO): 9.88 (1H, s), 8.32 (2H, d, J 9.1 Hz), 8.08 (1H, s), 8.02 (2H, d, J 8.8 Hz), 7.93 (1H, s), 7.73 (2H, d, J 9.0 Hz), 7.09 (2H, d, J 8.8 Hz), 3.86 (3H, s)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-2-methoxybenzamide

LCMS RT= 9.42min; 1H NMR (DMSO): 10.23 (1H, s), 8.78 (1H, s), 8.32 (2H, d, J 9.0 Hz), 8.07-8.05 (1H, m), 7.96 (1H, s), 7.72 (2H, d, J 9.0 Hz), 7.66-7.59 (1H, m), 7.33-7.15 (2H, m), 4.08 (3H, s)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)thiophene-2-carboxamide

LCMS RT= 7.44min, MH^+ 369.0; 1H NMR (DMSO): 10.07 (1H, s), 8.32 (2H, d, J 9.1 Hz), 8.05-8.03 (2H, m), 7.95 (1H, s), 7.90 (1H, dd, J 5.0 1.0 Hz), 7.72 (2H, d, J 8.9 Hz), 7.28-7.25 (1H, m), 2.45 (3H, s)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)propionamide

LCMS RT= 6.86min, MH^+ 315.2; 1H NMR (DMSO): 9.48 (1H, s), 8.47 (2H, d, J 8.9 Hz), 8.32 (1H, s), 8.03 (1H, s), 7.88 (2H, d, J 8.9 Hz), 2.59 (3H, s), 1.30 (3H, t, J 7.1 Hz)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)butyramide

LCMS RT= 7.32min, MH^+ 329.1; **^1H NMR (DMSO):** 9.34 (1H, s), 8.29 (2H, d, J 8.9 Hz), 8.13 (1H, s), 7.86 (1H, s), 7.71 (2H, d, J 8.9 Hz), 2.42 (3H, s), 1.66-1.60 (2H, m), 0.97 (3H, t, J 7.1 Hz)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)pentanamide

LCMS RT= 7.82min, MH^+ 343.2; **^1H NMR (DMSO):** 9.34 (1H, s), 8.30 (2H, d, J 8.9 Hz), 8.13 (1H, s), 7.86 (1H, s), 7.71 (2H, d, J 8.9 Hz), 2.41 (3H, s), 1.66-1.58 (2H, m), 1.42-1.33 (2H, m), 0.94 (3H, t, J 7.1 Hz)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide

LCMS RT= 7.23min, MH^+ 329.2; **^1H NMR (DMSO):** 9.31 (1H, s), 8.30 (2H, d, J 8.9 Hz), 8.09 (1H, s), 7.87 (1H, s), 7.71 (2H, d, J 8.9 Hz), 2.77-2.73 (1H, m), 2.41 (3H, s), 1.17 (6H, d, J 6.8 Hz)

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N-(2-(4-Chlorophenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)furan-2-carboxamide

LCMS RT= 7.44min, MH^+ 353.1; **^1H NMR (DMSO):** 9.89 (1H, s), 8.32 (2H, d, J 9.1 Hz), 8.10 (1H, s), 7.98-7.93 (2H, m), 7.73 (2H, d, J 8.9 Hz), 7.36 (1H, dd, J 3.5 0.8 Hz), 6.74 (1H, dd, J 3.5 1.8 Hz), 2.44 (3H, s)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)nicotinamide

LCMS RT= 6.94min, MH^+ 401.0; **^1H NMR (DMSO):** 10.23 (1H, s), 9.20 (1H, m), 8.81-8.78 (1H, m), 8.39-8.33 (1H, m), 8.08 (2H, d, J 9.1 Hz), 8.01 (1H, s), 7.88-7.86 (1H, m), 7.63-7.56 (1H, m), 6.85 (2H, d, J 9.2 Hz), 3.43-3.40 (4H, m), 1.15 (6H, t, J 6.7 Hz)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isonicotinamide

LCMS RT= 6.99min, MH^+ 400.9; **^1H NMR (DMSO):** 10.31 (1H, s), 8.82 (2H, d, J 6.0 Hz), 8.08 (2H, d, J 9.2 Hz), 8.00 (1H, s), 7.93 (2H, d, J 5.9 Hz), 7.89-7.87 (1H, m), 6.85 (2H, d, J 9.2 Hz), 3.42-3.38 (4H, m), 2.43 (3H, s), 1.15 (6H, t, J 7.2 Hz)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)propionamide

LCMS RT= 7.51min, MH⁺ 352.2; ¹H NMR (DMSO): 9.28 (1H, s), 8.06-8.02 (3H, m), 7.78 (1H, s), 6.83 (2H, d, *J* 9.2 Hz), 3.42-3.37 (6H, m), 2.38 (3H, s), 1.16-1.10 (9H, m)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)butyramide

LCMS RT= 7.97min, MH⁺ 366.1; ¹H NMR (DMSO): 9.32 (1H, s), 8.04 (2H, d, *J* 8.9 Hz), 8.00 (1H, s), 7.78 (1H, s), 6.84 (2H, d, *J* 8.9 Hz), 1.70-1.62 (2H, m), 1.17-1.07 (6H, m), 0.97 (3H, t, *J* 7.1 Hz)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)pentanamide

LCMS RT= 8.53min, MH⁺ 379.9; ¹H NMR (DMSO): 9.32 (1H, s), 8.04 (2H, d, *J* 8.9 Hz), 8.00 (1H, s), 7.78 (1H, s), 6.83 (2H, d, *J* 8.9 Hz), 3.50-3.35 (6H, m), 2.39 (3H, s), 1.65-1.61 (2H, m), 1.41-1.34 (2H, m), 1.17-1.07 (6H, m), 0.94 (3H, t, *J* 7.1 Hz)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide

LCMS RT= 7.92min, MH⁺ 366.1; ¹H NMR (DMSO): 9.29 (1H, s), 8.05 (2H, d, *J* 8.9 Hz), 7.96 (1H, s), 7.78 (1H, s), 6.84 (2H, d, *J* 8.9 Hz), 3.42-3.37 (4H, m), 2.41 (3H, s), 1.17-1.07 (12H, m)

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N-(2-(4-(Diethylamino)phenyl)-6-methyl-2H-benzo[d][1,2,3]triazol-5-yl)furan-2-carboxamide

LCMS RT= 8.18min, MH⁺ 389.9; ¹H NMR (DMSO): 9.87 (1H, s), 8.07 (2H, d, *J* 9.1 Hz), 7.98 (1H, s), 7.98-7.96 (1H, m), 7.85 (1H, m), 7.34 (1H, dd, *J* 3.4 0.7 Hz), 6.87 (2H, d, *J* 9.2 Hz), 6.73 (1H, dd, *J* 3.5 1.7 Hz), 3.42-3.37 (4H, m), 2.41 (3H, s), 1.17-1.07 (6H, m)

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N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)nicotinamide

LCMS RT= 7.19min, MH⁺ 387.1; ¹H NMR (DMSO): 10.69 (1H, s), 9.16 (1H, s), 8.82-8.77 (1H, m), 8.54 (1H, s), 8.34 (1H, d, *J* 7.8 Hz), 8.08 (2H, d, *J* 9.3 Hz), 7.98

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(1H, d, *J* 9.3 Hz), 7.71 (1H, dd, *J* 9.1 1.7 Hz), 7.58-7.53 (1H, m), 6.85 (2H, d, *J* 9.2 Hz), 3.44 (4H, q, *J* 6.8 Hz), 1.18 (6H, t, *J* 6.8 Hz)

N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isonicotinamide

- 5 **LCMS RT= 7.23min, MH⁺ 387.1; ¹H NMR (DMSO):** 10.74 (1H, s), 8.82 (2H, d, *J* 5.6 Hz), 8.58-8.53 (1H, m), 8.08 (2H, d, *J* 9.4 Hz), 7.98 (1H, dd, *J* 9.1 0.6 Hz), 7.91 (2H, d, *J* 6.1 Hz), 7.71 (1H, dd, *J* 9.1 1.8 Hz), 6.86 (2H, d, *J* 9.1 Hz), 3.43 (4H, q, *J* 7.1 Hz), 1.15 (6H, t, *J* 7.1 Hz)

10 **N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)acetamide**

LCMS RT= 6.89min, MH⁺ 324.2; ¹H NMR (DMSO): 10.20 (1H, s), 8.38 (1H, d, *J* 1.8 Hz), 8.04 (2H, d, *J* 9.2 Hz), 7.89 (1H, dd, *J* 9.1 0.6 Hz), 7.42 (1H, dd, *J* 9.2 1.8 Hz), 6.84 (2H, d, *J* 9.2 Hz), 3.43 (4H, q, *J* 6.9 Hz), 2.11 (3H, s), 1.14 (6H, t, *J* 6.9 Hz)

15 **N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)propionamide**

LCMS RT= 7.50min, MH⁺ 338.2; ¹H NMR (DMSO): 10.12 (1H, s), 8.41 (1H, d, *J* 1.0 Hz), 8.04 (2H, d, *J* 9.2 Hz), 7.89 (1H, d, *J* 9.2 Hz), 7.44 (1H, dd, *J* 9.1 1.8 Hz), 6.84 (2H, d, *J* 9.4 Hz), 3.42 (4H, q, *J* 6.9 Hz), 2.39 (2H, q, *J* 7.4 Hz), 1.17-1.09 (9H, m)

20 **N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)butyramide**

LCMS RT= 8.00min, MH⁺ 352.1; ¹H NMR (DMSO): 10.13 (1H, s), 8.42-8.40 (1H, m), 8.04 (2H, d, *J* 9.2 Hz), 7.89 (1H, d, *J* 9.2 Hz), 7.44 (1H, dd, *J* 9.1 1.7 Hz), 6.84 (2H, d, *J* 9.4 Hz), 3.42 (4H, q, *J* 6.9 Hz), 2.36 (2H, q, *J* 7.4 Hz), 1.72-1.60 (2H, m), 1.14 (6H, t, *J* 7.0 Hz), 0.95 (3H, t, *J* 7.4 Hz)

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N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)pentanamide

LCMS RT= 8.60min, MH⁺ 365.9; ¹H NMR (DMSO): 10.13 (1H, s), 8.42-8.40 (1H, m), 8.04 (2H, d, *J* 9.2 Hz), 7.89 (1H, d, *J* 9.2 Hz), 7.44 (1H, dd, *J* 9.1 1.7 Hz), 6.84 (2H, d, *J* 9.4 Hz), 3.42 (4H, q, *J* 6.9 Hz), 2.38 (2H, q, *J* 7.4 Hz), 1.67-1.57 (2H, m), 1.42-1.30

- 30 (2H, m), 1.14 (6H, t, *J* 7.0 Hz), 0.92 (3H, t, *J* 7.4 Hz)

N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide

LCMS RT= 7.95min, MH⁺ 352.2; ¹H NMR (DMSO): 10.09 (1H, s), 8.42-8.35 (1H, m), 8.04 (2H, d, *J* 9.2 Hz), 7.89 (1H, d, *J* 9.2 Hz), 7.46 (1H, dd, *J* 9.1 1.8 Hz), 6.84 (2H, d, *J* 9.4 Hz), 3.42 (4H, q, *J* 6.9 Hz), 2.70-2.61 (1H, m), 1.18-1.12 (12H, m)

- 5 **N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)furan-2-carboxamide LCMS RT= 7.98min, MH⁺ 376.3; ¹H NMR (DMSO):** 10.43 (1H, s), 8.48-8.47 (1H, m), 8.07 (2H, d, *J* 9.2 Hz), 7.99-7.98 (1H, m), 7.94 (1H, d, *J* 9.2 Hz), 7.74 (1H, dd, *J* 9.3 1.9 Hz), 7.40 (1H, d, *J* 3.5 Hz), 6.85 (2H, d, *J* 9.3 Hz), 6.75-6.72 (1H, m), 3.43 (4H, q, *J* 7.1 Hz), 1.15 (6H, t, *J* 7.0 Hz)

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N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)thiophene-2-carboxamide

- LCMS RT= 8.47min, MH⁺ 391.9; ¹H NMR (DMSO):** 10.45 (1H, s), 8.46-8.45 (1H, m), 8.09-8.06 (3H, m), 7.96 (1H, d, *J* 9.3 Hz), 7.91 (1H, dd, *J* 5.0 1.0 Hz), 7.70 (1H, dd, *J* 9.2 1.8 Hz), 7.28-7.25 (1H, m), 6.84 (2H, d, *J* 9.4 Hz), 3.43 (4H, q, *J* 7.0 Hz), 1.15 (6H, t, *J* 7.0 Hz)
- 15

N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)benzamide

- LCMS RT= 8.62min, MH⁺ 385.9; ¹H NMR (DMSO):** 10.50 (1H, s), 8.54-8.53 (1H, m), 8.08 (2H, d, *J* 9.2 Hz), 8.02-7.99 (2H, m), 7.96 (1H, dd, *J* 9.1 0.6 Hz), 7.74 (1H, dd, *J* 9.2 1.8 Hz), 7.67-7.54 (3H, m), 6.85 (2H, d, *J* 9.3 Hz), 3.44 (4H, q, *J* 7.0 Hz), 1.15 (6H, t, *J* 7.0 Hz)
- 20

N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)-4-

- methoxybenzamide LCMS RT= 8.58min, MH⁺ 416.2; ¹H NMR (DMSO):** 10.33 (1H, s), 8.52-8.51 (1H, m), 8.06 (2H, d, *J* 9.2 Hz), 8.01 (2H, d, *J* 8.8 Hz), 7.94 (1H, d, *J* 9.2 Hz), 7.73 (1H, dd, *J* 9.2 1.8 Hz), 7.09 (2H, d, *J* 8.8 Hz), 6.85 (2H, d, *J* 9.3 Hz), 3.86 (3H, s), 3.43 (4H, q, *J* 7.0 Hz), 1.15 (6H, t, *J* 7.0 Hz)
- 25

- 30 **N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)-2-**

methoxybenzamide LCMS RT= 9.56min, MH⁺ 415.9; ¹H NMR (DMSO): 10.40 (1H, s), 8.56-8.55 (1H, m), 8.07 (2H, d, *J* 9.2 Hz), 7.93 (1H, d, *J* 9.2 Hz), 7.67 (1H, dd, *J* 7.5 1.6 Hz), 7.61 (1H, dd, *J* 9.1 1.7 Hz), 7.56-7.51 (1H, m), 7.21 (1H, d, *J* 8.6 Hz), 7.10

37

(1H, t, *J* 7.5 Hz), 6.85 (2H, d, *J* 9.3 Hz), 3.93 (3H, s), 3.43 (4H, q, *J* 7.0 Hz), 1.15 (6H, t, *J* 7.0 Hz)

4-Chloro-N-(2-(4-(diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)benzamide

5 **LCMS RT=** 9.71min, MH^+ 420.0; **¹H NMR (DMSO):** 10.56 (1H, s), 8.53-8.52 (1H, m), 8.08 (2H, d, *J* 9.2 Hz), 8.04 (2H, d, *J* 8.7 Hz), 7.96 (1H, d, *J* 9.1 Hz), 7.72 (1H, dd, *J* 9.2 1.8 Hz), 7.65 (2H, d, *J* 8.6 Hz), 6.85 (2H, d, *J* 9.2 Hz), 3.44 (4H, q, *J* 7.0 Hz), 1.15 (6H, t, *J* 7.0 Hz)

10 **N-(2-(4-(Diethylamino)phenyl)-2H-benzo[d][1,2,3]triazol-5-yl)-4-(dimethylamino)benzamide**

LCMS RT= 8.84min, MH^+ 428.9; **¹H NMR (DMSO):** 10.02 (1H, s), 8.43-8.42 (1H, m), 7.99 (2H, d, *J* 9.2 Hz), 7.85-7.82 (3H, m), 7.66 (1H, dd, *J* 9.1 1.7 Hz), 6.77 (2H, d, *J* 9.4 Hz), 6.71 (2H, d, *J* 9.1 Hz), 3.35 (4H, q, *J* 7.0 Hz), 2.94 (6H, s), 1.07 (6H, t, *J* 7.0

15 Hz)

N-(2-(4-Chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)propionamide

LCMS RT= 7.16min, MH^+ 301.0; **¹H NMR (DMSO):** 10.22 (1H, s), 8.50-8.48 (1H, m), 8.30 (2H, d, *J* 9.0 Hz), 7.97 (1H, d, *J* 9.3 Hz), 7.71 (2H, d, *J* 9.0 Hz), 7.50 (1H, dd, *J* 9.3 1.7 Hz), 1.13 (3H, t, *J* 7.1 Hz)

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N-(2-(4-Chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)butyramide

LCMS RT= 7.64min, MH^+ 314.8; **¹H NMR (DMSO):** 10.22 (1H, s), 8.49-8.48 (1H, m), 8.29 (2H, d, *J* 9.0 Hz), 7.97 (1H, d, *J* 9.3 Hz), 7.71 (2H, d, *J* 9.0 Hz), 7.51 (1H, dd, *J* 9.3 1.7 Hz), 2.38 (2H, t, *J* 7.0 Hz), 1.72-1.59 (2H, m), 0.94 (3H, t, *J* 7.4 Hz)

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N-(2-(4-Chlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide

LCMS RT= 7.59min, MH^+ 314.9; **¹H NMR (DMSO):** 10.18 (1H, s), 8.50-8.49 (1H, m), 8.30 (2H, d, *J* 9.0 Hz), 7.97 (1H, d, *J* 9.3 Hz), 7.71 (2H, d, *J* 9.0 Hz), 7.53 (1H, dd, *J* 9.3 1.7 Hz), 2.67 (1H, m), 1.15 (6H, d, *J* 6.8 Hz)

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

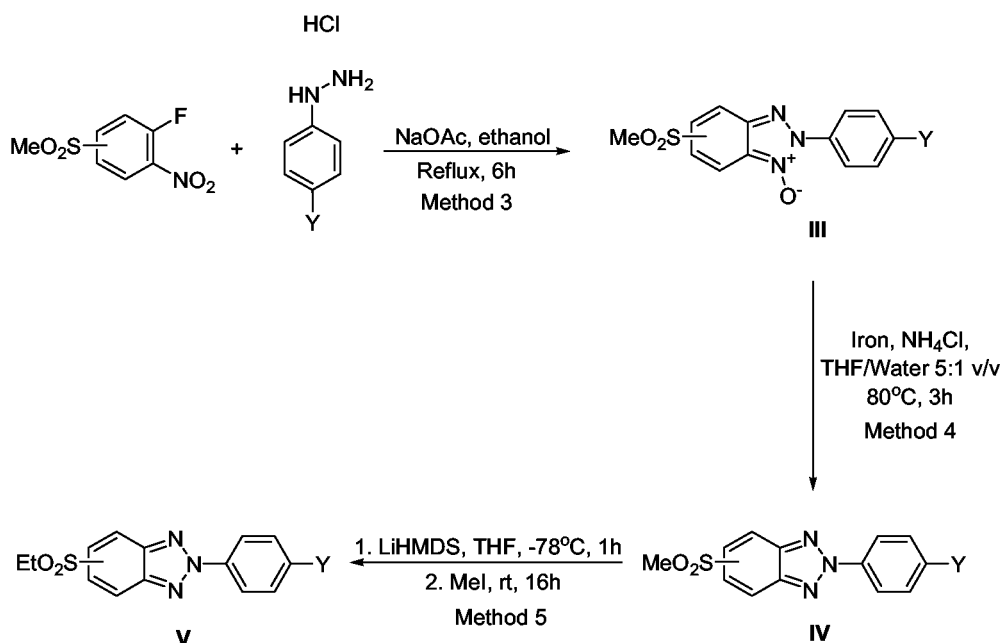
38

LCMS RT= 6.52min, MH^+ 287.0; 1H NMR (DMSO): 10.30 (1H, s), 8.47-8.45 (1H, m), 8.29 (2H, d, J 9.0 Hz), 7.98 (1H, d, J 9.3 Hz), 7.71 (2H, d, J 9.0 Hz), 7.49 (1H, dd, J 9.3 1.7 Hz), 2.13 (3H, s)

5 **N-(2-(3,4-Dichlorophenyl)-2H-benzo[d][1,2,3]triazol-5-yl)isobutyramide**

LCMS RT= 8.29min, MH^+ 349.1; 1H NMR (DMSO): 10.20 (1H, s), 8.50 (1H, dd, J 1.8 0.7 Hz), 8.48 (1H, d, J 2.5 Hz), 8.27 (1H, dd, J 8.8 2.5 Hz), 7.98 (1H, dd, J 9.2 0.7 Hz), 7.92 (1H, d, J 8.8 Hz), 7.55 (1H, dd, J 9.3 1.8 Hz), 2.71-2.62 (1H, m), 1.15 (6H, d, J 6.8 Hz)

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15 **Method 3 : Compounds III**

2-(4-Chlorophenyl)-6-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole 1-oxide

(4-Chlorophenyl)hydrazine hydrochloride (1.64g, 9.17mmol), 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (1.00g, 4.56mmol) and sodium acetate trihydrate (1.87g, 13.7mmol) were suspended in ethanol (15mL) and heated to reflux for 6h. The mixture was then cooled to room temperature and the product removed by filtration.

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The residue was washed with methanol, water and then methanol again to afford 1.13g (77%) of the title compound (LCMS RT= 5.92min, (MH⁺+MeCN) 364.9)

¹H NMR (DMSO): 8.39-8.38 (1H, m), 8.21-8.14 (3H, m), 7.98 (1H, dd, *J* 9.2 1.7 Hz), 7.80 (2H, d, *J* 9.0 Hz), 3.38 (3H, s)

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6-(Methylsulfonyl)-2-(naphthalen-2-yl)-2H-benzo[d][1,2,3]triazole 1-oxide

LCMS RT= 6.12min; ¹H NMR (DMSO): 8.84 (1H, d, *J* 1.8 Hz), 8.42-8.41 (1H, m), 8.27-8.10 (5H, m), 8.01 (1H, dd, *J* 9.2 1.7 Hz), 7.76-7.68 (2H, m), 3.39 (3H, s)

10 **Method 4 : Compounds IV**

2-(4-Chlorophenyl)-5-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole

To a suspension of 2-(4-chlorophenyl)-6-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole 1-oxide (157mg, 0.49mmol) and ammonium chloride (52mg, 0.97mmol) in tetrahydrofuran/water 5:1 v/v (6mL) at 80°C was added iron powder (136mg, 2.43mmol). The resulting mixture was stirred for 3h at 80°C. After cooling, the solution was passed through a pad of Celite[®] and washed with tetrahydrofuran. The filtrate was then concentrated *in vacuo*, suspended in water and extracted three times 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 25:75 v/v to afford 29.7mg (20%) of the title compound (LCMS RT= 6.59min)

¹H NMR (CDCl₃): 8.60-8.58 (1H, m), 8.28 (2H, d, *J* 9.0 Hz), 8.04 (1H, dd, *J* 9.0 0.9 Hz), 7.82 (1H, dd, *J* 9.0 1.6 Hz), 7.49 (2H, d, *J* 9.0 Hz), 3.06 (3H, s)

25

The compound below was prepared following the same general procedure.

2-(3,4-Dichlorophenyl)-5-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole

LCMS RT= 7.35min, MH⁺ 342.1; ¹H NMR (DMSO): 8.70-8.69 (1H, m), 8.57 (1H, d, *J* 2.5 Hz), 8.37-8.33 (2H, m), 8.04-7.97 (2H, m), 3.37 (3H, s)

30

5-(Methylsulfonyl)-2-(naphthalen-2-yl)-2H-benzo[d][1,2,3]triazole

40

LCMS RT= 6.92min; ¹H NMR (DMSO): 9.01 (1H, d, *J* 2.1 Hz), 8.73-8.72 (1H, m), 8.52 (1H, dd, *J* 8.9 2.2 Hz), 8.38 (1H, dd, *J* 9.0 0.8 Hz), 8.27 (2H, d, *J* 8.6 Hz), 8.13-8.08 (1H, m), 8.02 (1H, dd, *J* 9.0 1.7 Hz), 7.71-7.67 (2H, m), 3.38 (3H, s)

5 Method 5 : Compounds V

2-(3,4-Dichlorophenyl)-5-(ethylsulfonyl)-2H-benzo[d][1,2,3]triazole

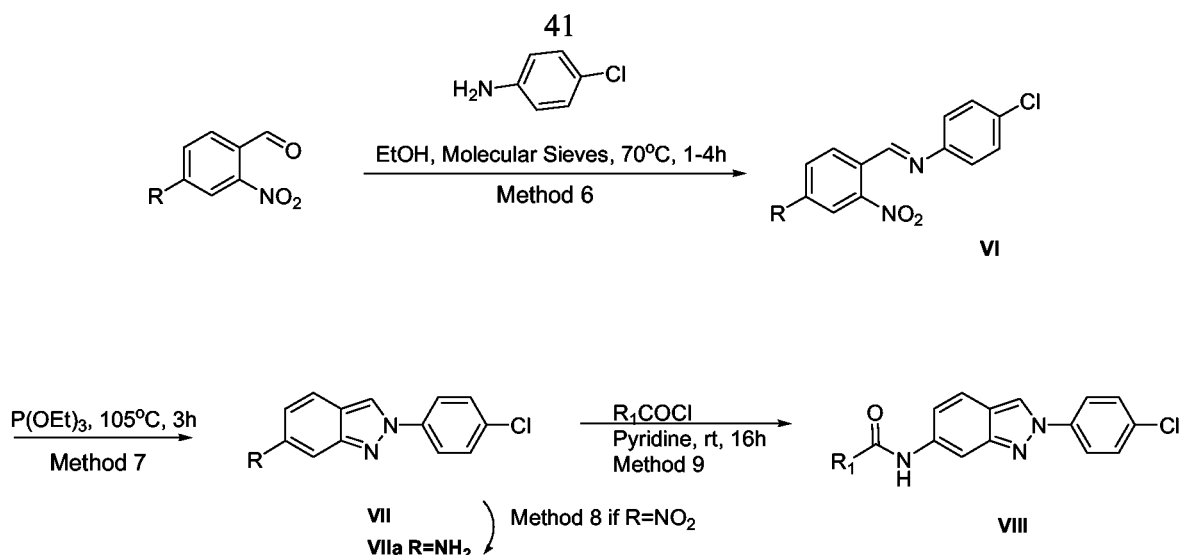
To a dry Schlenk flask under nitrogen was added 2-(3,4-dichlorophenyl)-5-(methylsulfonyl)-2H-benzo[d][1,2,3]triazole (93.5mg, 0.27mmol) and dry
10 tetrahydrofuran (5mL). The solution was then cooled down to -78°C, and lithium bis(trimethylsilyl)amide (0.30mL, 0.30mmol) was added. The reaction was left stirring at -78°C for 1h, and then methyl iodide (35μL, 0.55mmol) was added. The solution was allowed to warm up to room temperature for 16h. Aqueous saturated ammonium chloride (10mL) was added to the solution, the organic layer was separated and the
15 aqueous layer was extracted three times 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 20:80 v/v to afford 52mg (54%) of the title compound (LCMS RT= 7.65min)

¹H NMR (DMSO): 8.68-8.67 (1H, m), 8.57 (1H, d, *J* 2.5 Hz), 8.38-8.33 (2H, m), 8.01-
20 7.94 (2H, m), 3.46 (2H, q, *J* 7.5 Hz), 1.15 (3H, t, *J* 7.4 Hz)

The compound below was prepared following the same general procedure.

2-(4-Chlorophenyl)-5-(ethylsulfonyl)-2H-benzo[d][1,2,3]triazole

25 LCMS RT= 6.89min; ¹H NMR (DMSO): 8.67-8.66 (1H, m), 8.39 (2H, d, *J* 9.1 Hz), 8.34 (1H, dd, *J* 9.0 0.8 Hz), 7.95 (1H, dd, *J* 9.0 1.6 Hz), 7.79 (2H, d, *J* 9.0 Hz), 3.45 (2H, q, *J* 7.3 Hz), 1.15 (3H, t, *J* 7.4 Hz)



Method 6 : Compounds VI

5

(E)-4-Chloro-N-(4-(methylsulfonyl)-2-nitrobenzylidene)aniline

To 4-(methylsulfonyl)-2-nitrobenzaldehyde (250mg, 1.09mmol) in ethanol (5mL) with molecular sieves at room temperature was added 4-chloroaniline (139mg, 1.09mmol). The resulting mixture was stirred at room temperature for 1h, and then heated at 70°C for 1h. After cooling, the mixture was filtered off, and the filtrate concentrated *in vacuo* to afford the title compound, which was used crude in the next step.

Method 7 : Compounds VII

2-(4-Chlorophenyl)-6-(methylsulfonyl)-2H-indazole

A suspension of (E)-4-Chloro-N-(4-(methylsulfonyl)-2-nitrobenzylidene)aniline (133mg, 0.39mmol) in triethyl phosphate (2mL) was stirred at 105°C for 3h. After cooling, a solid was filtered off and washed with hexanes to afford 89mg (74%) of the title compound (LCMS RT= 6.17min, MH⁺ 307.0)

¹H NMR (DMSO): 9.36 (1H, d, *J* 0.9 Hz), 8.34 (1H, br), 8.19 (2H, d, *J* 8.9 Hz), 8.08 (1H, dd, *J* 8.9 0.8 Hz), 7.73 (2H, d, *J* 8.9 Hz), 7.58 (1H, dd, *J* 8.8 1.4 Hz), 3.30 (3H, s)

The compound below was prepared following the same general procedure.

2-(4-Chlorophenyl)-6-nitro-2H-indazole

25

42

LCMS RT= 7.27min; ¹H NMR (DMSO): 9.40 (1H, s), 8.76-8.74 (1H, m), 8.20 (2H, d, *J* 9.0 Hz), 8.08 (1H, d, *J* 9.2 Hz), 7.89 (1H, dd, *J* 9.2 2.0 Hz), 7.74 (2H, d, *J* 8.9 Hz)

2-(4-Chlorophenyl)-2H-indazole

5 LCMS RT= 7.05min, MH⁺ 229.0; ¹H NMR (DMSO): 9.14 (1H, d, *J* 0.9 Hz), 8.14 (2H, d, *J* 9.0 Hz), 7.77 (1H, dt, *J* 8.4 1.1 Hz), 7.71 (1H, dd, *J* 8.8 0.9 Hz), 7.67 (2H, d, *J* 9.0 Hz), 7.33 (1H, ddd, *J* 8.9 6.6 1.1 Hz), 7.12 (1H, ddd, *J* 8.4 6.6 0.8 Hz)

10 **Method 8 : Compounds VIIa**

2-(4-Chlorophenyl)-2H-indazol-6-amine

To 2-(4-chlorophenyl)-6-nitro-2H-indazole (103mg, 0.37mmol) in tetrahydrofuran:water 4:1 v/v (5mL) at room temperature was added ammonium chloride (40mg, 0.75mmol). The mixture was heated at 80°C and iron powder (105mg, 1.87mmol) was added. The resulting mixture was stirred at 80°C for 3h. After cooling, the solution was filtered through a pad of Celite[®] and washed with tetrahydrofuran. After evaporation of the solvent, the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous
15
20 MgSO₄ and evaporated to afford 84mg (92%) of the title compound.

Method 9 : Compounds VIII

N-(2-(4-Chlorophenyl)-2H-indazol-6-yl)isobutyramide

25 To a solution of 2-(4-chlorophenyl)-2H-indazol-6-amine (84mg, 0.34mmol) in pyridine (5mL) at room temperature was added isobutyryl chloride (43μL, 0.41mmol). The resulting mixture was stirred at room temperature for 16h. Ethyl acetate was added and the organic layer was washed twice with saturated aqueous copper sulfate, followed by brine and water. The combined organic layers were dried over anhydrous MgSO₄ and
30 evaporated. The resulting solid was purified by column chromatography eluting with ethyl acetate/hexanes 25:75 v/v to afford 11mg (10%) of the title compound (LCMS RT= 6.38min, MH⁺ 314.2)

43

¹H NMR (DMSO): 10.14 (1H, s), 9.24 (1H, d, *J* 0.8 Hz), 8.42-8.40 (1H, m), 8.31 (2H, d, *J* 9.0 Hz), 7.89 (1H, dd, *J* 9.1 0.7 Hz), 7.85 (2H, d, *J* 8.9 Hz), 7.36 (1H, dd, *J* 9.0 1.6 Hz), 2.90-2.81 (1H, m), 1.34 (6H, d, *J* 6.8 Hz)

5 **Method 10: Compounds IX**

2-(4'-Chlorophenyl)-6-(isopropylsulfonyl)-2H-indazole

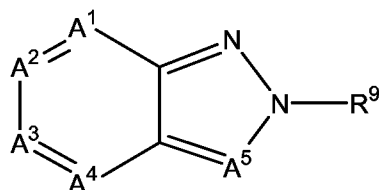
To a dry Schlenk flask under nitrogen was added 2-(4-chlorophenyl)-6-(methylsulfonyl)-2H-indazole (200mg, 0.65mmol) and dry tetrahydrofuran (9mL). The solution was then cooled down to -78°C, and lithium bis(trimethylsilyl)amide (0.72mL, 0.72mmol) was added. The reaction was left stirring at -78°C for 1h, and then methyl iodide (81μL, 1.31mmol) was added. The solution was allowed to warm up to room temperature for 16h. Aqueous saturated ammonium chloride (10mL) was added to the solution, the organic layer was separated and the aqueous layer was extracted three times 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 20mg (9%) of the title compound (LCMS RT= 6.53min, MH⁺ 335.2)

¹H NMR (DMSO): 9.37 (1H, d, *J* 0.9 Hz), 8.29-8.27 (1H, m), 8.18 (2H, d, *J* 9.0 Hz), 8.07 (1H, dd, *J* 8.8 0.8 Hz), 7.72 (2H, d, *J* 9.0 Hz), 7.49 (1H, dd, *J* 8.8 1.6 Hz), 3.58-3.48 (1H, m), 1.20 (6H, d, *J* 6.8 Hz)

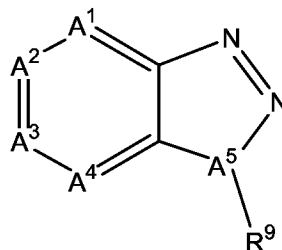
The compounds listed in Table 2, can be prepared by analogues methods to those described above, or by literature methods known or adapted by the persons skilled in the art.

Claims

1. Use of a compound of Formula (I) or (II)



I



II

5

wherein

A^1 , A^2 , A^3 , A^4 and A^5 , which may be the same or different, represent N or CR^1 ,

R_9 represents $-L-R^3$, in which L is a single bond or a linker group and R^3 represents hydrogen or a substituent and

10 in addition,

when an adjacent pair of $A^1 - A^4$ each represent CR^1 , then the adjacent carbon atoms, together with their substituents may form a ring B,

when A^5 represents CR^1 , then A^5 and $N - R^9$, together with their substituents may form a ring C,

15 or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia.

2. Use according to claim 1, wherein R^3 in the compound of formula 1 represents
20 alkyl, alkoxy or aryl, each optionally substituted by one to three substituents, R^2 , which may be the same or different.

3. Use of a compound according to:

25 formula I of claim 1 or of formula II of claim 1 in which A^5 represents N,
wherein:

L is single bond and R^3 represents:

thioalkyl optionally substituted by alkyl or optionally substituted aryl,

- O-aryl or thioaryl, in which the aryl is optionally substituted,
optionally substituted aryl,
hydroxyl,
NR¹⁰R¹¹,
5 SO₂R¹²,
NR¹³SO₂R¹⁴,
C(=W)R¹⁶,
NR¹⁵C(=W)R¹⁷,
R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁶ and R¹⁷, which may be the same or different,
10 represent hydrogen, alkyl optionally substituted by optionally substituted aryl,
optionally substituted aryl,
in addition,
R¹⁰ and R¹¹ together with the nitrogen to which they are attached may form a
ring,
15 R¹² may have the same meaning as NR¹⁰R¹¹,
R¹⁶ and R¹⁷, which may be the same or different, may each represent
alkyl substituted by one or more of halogen, alkoxy optionally substituted aryl
or optionally substituted aryl,
optionally substituted aryloxy,
20 aryl or NR¹⁰R¹¹,
and when R¹⁶ or R¹⁷ represents NR¹⁰R¹¹, one of R¹⁰ and R¹¹ may additionally
represent CO alkyl optionally substituted or COaryl optionally substituted, and
in addition to the definitions shared with R¹⁷, R¹⁶ may represent hydroxyl;
25 or a compound of formula II of claim 1 in which A⁵ represents CH, and wherein
L is single bond and R³ represents:
thioalkyl optionally substituted by alkyl or optionally substituted aryl,
thioaryl, in which the aryl is optionally substituted,
optionally substituted aryl,
30 hydroxyl,
NO₂,
CN,
NR¹⁰R¹¹,

halogen,
 SO_2R^{12} ,
 $\text{NR}^{13}\text{SO}_2\text{R}^{14}$,
 $\text{C}(=\text{W})\text{R}^{16}$,
 5 $\text{OC}(=\text{W})\text{NR}^{10}\text{R}^{11}$
 $\text{NR}^{15}\text{C}(=\text{W})\text{R}^{17}$,
 R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{17} , which may be the same or different,
 represent hydrogen, alkyl optionally substituted by optionally substituted aryl,
 optionally substituted aryl,
 10 in addition,
 R^{10} and R^{11} together with the nitrogen to which they are attached may form a
 ring,
 R^{12} may have the same meaning as $\text{NR}^{10}\text{R}^{11}$,
 R^{16} and R^{17} , which may be the same or different, may each represent
 15 alkyl substituted by one or more of halogen, alkoxy optionally substituted aryl
 or optionally substituted aryl,
 optionally substituted aryloxy,
 aryl or $\text{NR}^{10}\text{R}^{11}$,
 and when R^{16} or R^{17} represents $\text{NR}^{10}\text{R}^{11}$, one of R^{10} and R^{11} may additionally
 20 represent CO alkyl optionally substituted or COaryl optionally substituted, and
 in addition to the definitions shared with R^{17} , R^{16} may represent hydroxyl.

4. Use according to claim 2, in which R^1 and R^2 , which may be the same or
 different, may represent:
 25 alkyl optionally substituted by one or more halogen, alkoxy or optionally
 substituted aryl, thioaryl or aryloxy,
 alkoxy optionally substituted by optionally by alkyl or optionally substituted
 aryl,
 hydroxyl,
 30 $\text{OC}(=\text{W})\text{NR}^{10}\text{R}^{11}$
 aryl,
 thioalkyl optionally substituted by alkyl or optionally substituted aryl,
 thioaryl, in which the aryl is optionally substituted,

NO₂,

CN,

NR¹⁰R¹¹,

halogen,

5 SO₂R¹²,

NR¹³SO₂R¹⁴,

C(=W)R¹⁶,

NR¹⁵C(=W)R¹⁷,

P(=O)OR₄₀R₄₁,

10 R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₄₀ and R₄₁, which may be the same or different, represent hydrogen, alkyl optionally substituted by optionally substituted aryl, optionally substituted aryl,

in addition,

NR¹⁰R¹¹ together with the nitrogen to which they are attached may form a ring,

15 R¹² may have the same meaning as NR¹⁰R¹¹,

when R₁₇ represents NR¹⁰R¹¹, that NR¹⁰R¹¹ may represent hydrogen, COalkyl and CO optionally substituted aryl,

R¹⁶ may represent hydroxy, alkoxy, or NR¹⁰R¹¹,

20 and R¹⁷ may represent alkyl substituted by one or more of halogen, alkoxy, optionally substituted aryl or NR¹⁰R¹¹.

5. Use of a compound according to either:

25 formula I of claim 1 or of formula II of claim 1 in which A⁵ represents N, wherein:

L represents a linker group which is:

O, S or NR¹⁸,

30 alkylene, alkenylene, alkynylene, each of which may be optionally interrupted by one or more of O, S, NR¹⁸, or one or more C-C single, double or triple bonds, and R¹⁸ represents hydrogen, alkyl, COR¹⁶.

or a compound of formula II of claim 1 in which A⁵ represents CH, wherein:

L represents a linker group which is:

O, S, NR¹⁸,

alkylene, alkenylene, alkynylene, each of which may be optionally interrupted by one or more of O, S, NR¹⁸, or one or more C-C single, double or triple bonds,

a -N-N- single or double bond,

5 and R¹⁸ represents hydrogen, alkyl, COR¹⁶.

6. Use of a compound according to any preceding claim in which when any of the substituents represents alkyl, alkyl is saturated and has from 1 to 10 carbon atoms.

10 7. Use of a compound according to any preceding claim, in which aryl is 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.

15 8. Use of a compound according to any preceding claim, in which aryl is phenyl or naphthalene.

9. Use if a compound according to any preceding claim, in which aryl is furan, thiophene, pyrrole or pyridine.

20

10. Use of a compound according to claim 1, in which ring B or ring C is a saturated or unsaturated 3 to 10 membered carbocyclic or heterocyclic ring.

11. Use of a compound according to claim 1, in which ring B is benzene ring.

25

12. Use of a compound according to claim 1, in which ring C is a 3- 10 membered saturated or unsaturated carbocyclic ring.

13. Use of a compound according to claim 1, in which at least one R₁ represents
30 NR₁₅C(=W)R₁₇.

14. Use of a compound according to claim 1, in which at least one R₁ represents NR₁₅C(=O)R₁₇.

15. Use of a compound according to claim 1, in which at least one R_1 represents $\text{CONR}_{10}\text{R}_{11}$.
- 5 16. Use of a compound according to claim 1, in which at least one R_1 represents NHCOR_{17} , wherein R_{17} is selected from:
- alkyl $\text{C}_1 - \text{C}_6$,
 - alkyl $\text{C}_1 - \text{C}_6$ substituted by phenyl,
 - alkyl $\text{C}_1 - \text{C}_6$ substituted by alkoxy $\text{C}_1 - \text{C}_6$,
 - 10 haloalkyl $\text{C}_1 - \text{C}_6$,
 - perfluoroalkyl $\text{C}_1 - \text{C}_6$,
 - phenyl optionally substituted by one or more of halogen, alkyl $\text{C}_1 - \text{C}_6$, alkoxy $\text{C}_1 - \text{C}_6$, amino, (alkyl $\text{C}_1 - \text{C}_6$)amino, di(alkyl $\text{C}_1 - \text{C}_6$) amino or phenyl,
 - CH:CH phenyl,
 - 15 naphthyl, pyridinyl, thiophenyl and furanyl.
17. Use of a compound according to claim 1 in which one or both of R_1 and R_2 is other than $-\text{COOH}$.
- 20 18. Use of a compound according to claim 1, in which at least one of R_1 represents $\text{NR}_{15}\text{CONR}_{10}\text{R}_{11}$, wherein R_{10} and R_{11} , which may be the same or different, are selected from optionally substituted aryl, alkyl and COaryl optionally substituted.
- 25 19. Use of a compound according to claim 1, in which at least one of R_1 represents NHCONHR_{15} and R_{15} is selected from phenyl, alkyl C_1 to C_6 and COphenyl optionally substituted by one or more halogen.
- 30 20. Use of a compound according to claim 1, in which at least one of R_1 represents alkyl C_1 to C_6 , optionally substituted by phenyl or a 4 to 7- membered, preferably 5 or 6-membered saturated or unsaturated heterocycle preferably containing one to two heteroatoms selected from N, S and O.

21. Use of a compound according to claim 1 in which at least one of R_1 represents COR_{16} and R_{16} is alkoxy $C_1 - C_6$, amino, (alkyl $C_1 - C_6$)amino or di(alkyl $C_1 - C_6$) amino.
- 5 22. Use of a compound according to claim 1, in which at least one of R_1 represents:
 NO_2 ,
 halogen,
 amino or (alkyl $C_1 - C_6$)amino or di(alkyl $C_1 - C_6$) amino in which the alkyl C_1
to C_6 is optionally substituted by phenyl or a 5 or 6 membered saturated or unsaturated
10 heterocycle,
 $NHSO_2$ alkyl $C_1 - C_6$, $NHSO_2$ phenyl,
 SO_2 alkyl $C_1 - C_6$,
 phenyl optionally substituted by C_1 to C_6 alkoxy $C_1 - C_6$,
 a 5 – 10 membered, saturated or unsaturated, mono- or bi-cyclic heterocycle
15 containing from 1 – 3 heteroatoms selected from N, S and O.
23. Use of a compound according to claim 1, in which R_3 represent aryl and is optionally substituted by one to three substituents, R_2 , which may be the same or different.
- 20 24. Use of a compound according to claim 22 in which R_3 is a 5 – 10 membered aromatic mono- or bi-cyclic system.
- 25 25. Use of a compound according to claim 23, in which the aromatic system is a hydrocarbon.
26. Use of a compound according to claim 24, in which the aromatic hydrocarbon is benzene or naphthalene.
- 30 27. Use of a compound according to claim 23, in which the aromatic system is a heterocyclic system containing up to three heteroatoms, which may be the same or different, selected from N, O and S.

28. Use of a compound according to claim 27, in which the heterocyclic system is thiophene, furan, pyridine or pyrrole.

29. Use of a compound according to claim 2, in which the substituent(s) R^2 is/are selected from is:

alkyl $C_1 - C_6$, optionally substituted by thiophenyl or phenoxy, each optionally substituted by halogen,

alkoxy $C_1 - C_6$,

phenyl,

10 thioalkyl $C_1 - C_6$,

thiophenyl, optionally substituted by halogen,

NO_2 ,

CN

15 $NR_{10}R_{11}$, in which R_{10} and R_{11} , which may be the same or different represent hydrogen, alkyl $C_1 - C_6$, or together with the nitrogen to which they are attached form a 5 to 7 membered ring which may contain one or more additional heteroatoms selected from N, O and S,

halogen,

20 SO_2R_{12} , in which R_{12} represents a 5 to 7 membered ring which may contain one or more additional heteroatoms selected from N, O and S,

$NHCOR_{17}$, in which R_{17} represents

alkyl $C_1 - C_6$, optionally substituted by:

phenyl or halogen, or

phenyl optionally substituted by alkoxy $C_1 - C_6$, carboxy, or

25 halogen, or

a 5 or 6 membered saturated or unsaturated heterocycle,

phenyl or a 5 or 6 membered saturated or unsaturated heterocycle

optionally substituted by halogen, alkoxy C_1 to C_6 , carboxy or a group $SO_2NR_{10}R_{11}$.

30 30. Use of a compound according to claim 29 in which $NR_{10} R_{11}$ represents N-pyrrole, N-piperidine, $N'(C_1 - C_6)$ alkyl N piperazine or N-morpholine.

52

31. Use of a compound of formula II of claim 1 in which A⁵ represents CH, wherein L represents:

-NH.NH-,

-CH=CH-,

5

-C≡C- or

-NCOR₁₆ in which R₁₆ represents phenyl or a 5 or 6 membered saturated or unsaturated heterocycle optionally substituted by halogen, alkoxy C1 to C6, carboxy.

10 32. Use of a compound according to claim 1 in which two of A₁ – A₄ represent nitrogen.

33. Use of a compound according to claim 1 in which one of A₁ – A₄ represents nitrogen.

15

34. Use of a compound according to claim 1 in which all of A₁ – A₄ represents CR₁.

35. Use of a compound as listed in table 1 according to claim 1.

20