

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau



(10) International Publication Number

WO 2018/060704 A1

(43) International Publication Date

05 April 2018 (05.04.2018)

## (51) International Patent Classification:

*C07D 403/12* (2006.01) *A61P 13/00* (2006.01)  
*A61K 31/4196* (2006.01) *A61P 5/00* (2006.01)  
*C07D 249/08* (2006.01) *A61P 11/00* (2006.01)  
*A61P 35/00* (2006.01) *A61P 9/00* (2006.01)  
*A61P 1/00* (2006.01)

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

## (21) International Application Number:

PCT/GB2017/052898

## (22) International Filing Date:

28 September 2017 (28.09.2017)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

1616439.4 28 September 2016 (28.09.2016) GB

(71) **Applicant:** MIRONID LIMITED [GB/GB]; BioCity Scotland, Bo'nness Road, Newhouse, North Lanarkshire ML1 5UH (GB).

(72) **Inventors:** ADAM, Julia Mary; c/o Mironid Limited, BioCity Scotland, Bo'nness Road, Newhouse, North Lanarkshire ML1 5UH (GB). ADAMS, David Roger; c/o Mironid Limited, BioCity Scotland, Bo'nness Road, Newhouse, North Lanarkshire Scotland ML1 5UH (GB).

(74) **Agent:** HARRIS, Jennifer Lucy; Lacon London, 84 Theobalds Road, London London, WC1X 8NL (GB).

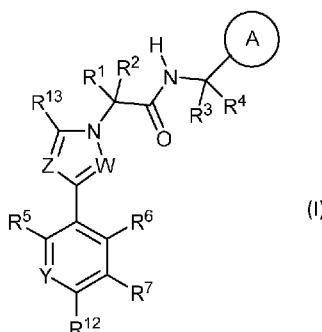
(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

## Published:

— with international search report (Art. 21(3))

## (54) Title: COMPOUNDS AND THEIR USE AS PDE4 ACTIVATORS

(57) **Abstract:** Compounds of Formula (I), which are activators of long form cyclic nucleotide phosphodiesterase-4 (PDE4) enzymes (isoforms) are provided. Methods and uses of these compounds for the treatment or prevention of disorders requiring a reduction of second messenger responses mediated by cyclic 3', 5'-adenosine monophosphate (cAMP) are also described. (Formula (I))



(I)

## **COMPOUNDS AND THEIR USE AS PDE4 ACTIVATORS**

### **Field of the Invention**

5 The present invention relates to compounds as defined herein, which are activators of long form cyclic nucleotide phosphodiesterase-4 (PDE4) enzymes (isoforms) and to therapies using these activators. In particular, the invention relates to these activator compounds for use in a method for the treatment or prevention of disorders requiring a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP).

### **10 Background to the invention**

Cyclic 3',5'-adenosine monophosphate - "cAMP" - is a critical intracellular biochemical messenger that is involved in the transduction of the cellular effects of a variety of hormones, neurotransmitters, and other extracellular biological factors in most animal and human cells.

15 The intracellular concentration of cAMP is controlled by the relative balance between its rate of production and degradation. cAMP is generated by biosynthetic enzymes of the adenylyl cyclase superfamily and degraded by members of the cyclic nucleotide phosphodiesterase (PDE) superfamily. Certain members of the PDE superfamily, such as PDE4, specifically degrade cAMP, while others either specifically degrade cyclic guanosine monophosphate 20 (cGMP) or degrade both cAMP and cGMP. PDE4 enzymes inactivate cAMP, thereby terminating its signalling, by hydrolysing cAMP to 5'-AMP (Lugnier, C. *Pharmacol Ther.* 109: 366-398, 2006).

25 Four PDE4 genes (*PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*) have been identified, each of which encodes a number of different enzyme isoforms through the use of alternative promoters and mRNA splicing. On the basis of their primary structures, the catalytically active PDE4 splice variants can be classified as "long", "short" or "super-short" forms (Houslay, M.D. *Prog Nucleic Acid Res Mol Biol.* 69: 249-315, 2001). A "dead short" form also exists, which is not catalytically active (Houslay, M.D., Baillie, G.S. and Maurice, D.H. *Circ Res.* 100: 950-66, 2007). PDE4 long forms have two regulatory regions, called upstream conserved regions 1 and 2 (UCR1 and UCR2), located between their isoform-specific N-terminal portion and the catalytic domain. The UCR1 domain is absent in short forms, whereas the super-short forms not only lack UCR1, but also have a truncated UCR2 domain (Houslay, M.D., Schafer, P. and Zhang, K. *Drug Discovery Today* 10: 1503-1519, 2005).

PDE4 long forms, but not short forms, associate into dimers within cells (Richter, W and Conti, M. *J. Biol. Chem.* 277: 40212-40221, 2002; Bolger, G. B. *et al.*, *Cell. Signal.* 27: 756-769, 2015). A proposed negative allosteric modulation of PDE4 long forms by small molecules has been reported (Burgin A. B. *et al.*, *Nat. Biotechnol.* 28: 63-70, 2010; Gurney 5 M. E. *et al.*, *Handb. Exp. Pharmacol.* 204: 167-192, 2011).

It is known in the art that PDE4 long forms may be activated by endogenous cellular mechanisms, such as phosphorylation (MacKenzie, S. J. *et al.*, *Br. J. Pharmacol.* 136: 421-433, 2002) and phosphatidic acid (Grange *et al.*, *J. Biol. Chem.* 275: 33379-33387, 2000).

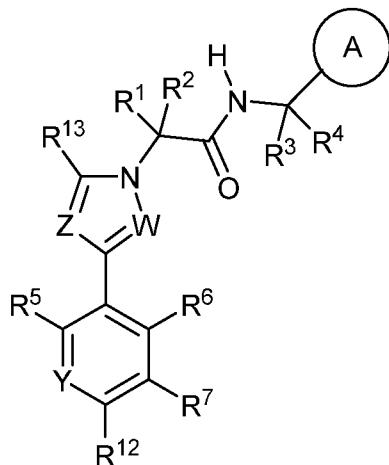
10 Activation of PDE4 long forms by ectopic expression of a 57 amino acid protein (called 'UCR1C') whose precise sequence reflects part of that of the upstream conserved region 1 of PDE4D ('UCR1C' sequence reflects that of amino acids 80-136 while UCR is amino acids 17-136: numbering based on the PDE4D3 long isoform) has recently been reported (Wang, L. *et al.*, *Cell. Signal.* 27: 908-922, 2015: "UCR1C is a novel activator of phosphodiesterase 15 4 (PDE4) long isoforms and attenuates cardiomyocyte hypertrophy"). The authors hypothesised that PDE4 activation might be used as a potential therapeutic strategy for preventing cardiac hypertrophy.

20 Small molecules that act as activators of PDE4 long forms have not previously been disclosed. Small molecule activators would be desirable for a number of reasons, including ease of manufacture and formulation and improved pharmacokinetic properties.

25 It is amongst the objects of the present invention to provide small molecule activators of at least one of the long forms of PDE4 for use in a method of therapy, as well as specific disease treatment or prevention.

### **Summary of the invention**

In a first aspect of the invention, there is provided a compound for use in therapy, wherein the compound is a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

5 R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-6)alkyl; the

10 (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy

Y is selected from N and CR<sup>11</sup>;

R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl,

15 (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, a 5-membered heteroaromatic ring that contains one to three

20 heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, and a fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N;

wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl,

25 (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

$R^{13}$  is selected from  $-C(O)X$ ,  $-CN$ ,  $H$ , (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-NR^{16}R^{17}$ ,  $C(O)-OR^{16}$ ,  $S(O)_2NR^{16}R^{17}$ , CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted

5 with one or more fluoros;

$X$  is selected from  $OR^{8a}$  and  $NR^{9a}R^{10a}$ ;

each  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$ , when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy; and

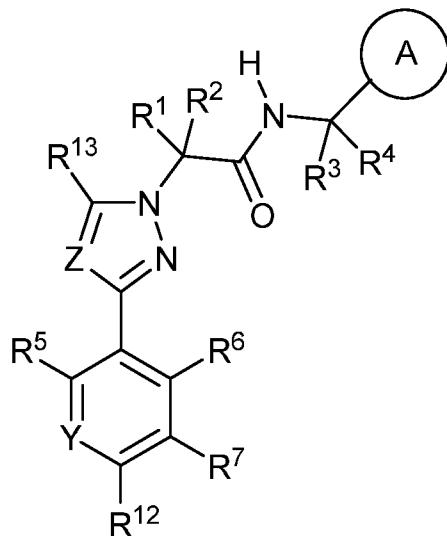
10 each  $R^{16}$  and  $R^{17}$ , when present, is independently selected from H and (C1-4)alkyl;

provided that:

when (i)  $Z$  is N,  $W$  is N,  $Y$  is  $CR^{11}$  and  $A$  is an optionally substituted 6-membered aromatic ring; or (ii)  $A$  is a optionally substituted fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, or an optionally substituted

15 fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N;  $R^{13}$  is  $-C(O)X$  or  $-CN$ .

In an embodiment of the invention, there is provided a compound for use in therapy, wherein the compound is a compound of Formula Ia:



20

Formula Ia

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are independently selected from H and (C1-4)alkyl;

$R^5$  and  $R^6$  are independently selected from H and F;

25  $R^7$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-OR^8$ ,  $C(O)-NR^9R^{10}$ ,  $S(O)_2NR^9R^{10}$ , CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

Y is selected from N and CR<sup>11</sup>;

R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

5 Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains 1 to 3 heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>,

10 S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

R<sup>13</sup> is selected from -C(O)X, -CN, H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and

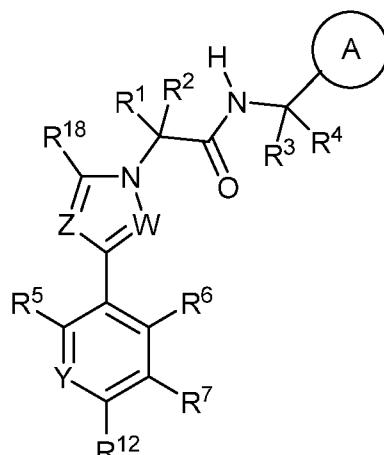
15 halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-4)alkyl;

20 each R<sup>16</sup> and R<sup>17</sup>, when present, is independently selected from H and (C1-4)alkyl; provided that when Z is N, Y is CR<sup>11</sup> and A is an optionally substituted 6-membered aromatic ring, R<sup>13</sup> is -C(O)X or -CN.

In a second aspect of the invention, there is provided a compound of Formula II:



25 Formula II

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

$R^5$  and  $R^6$  are independently selected from H and F;

$R^7$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

5 each  $R^8$ ,  $R^9$  and  $R^{10}$ , when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy;

$Y$  is selected from N and CR<sup>11</sup>;

$R^{11}$ , when present, and  $R^{12}$  are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy,

10 (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein  $R^{19}$  is H or (C1-4)alkyl;

A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that

15 contains one to three N atoms, a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, and a fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N;

20 wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

$R^{18}$  is selected from -C(O)X and -CN;

25 X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

each  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$ , when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy;

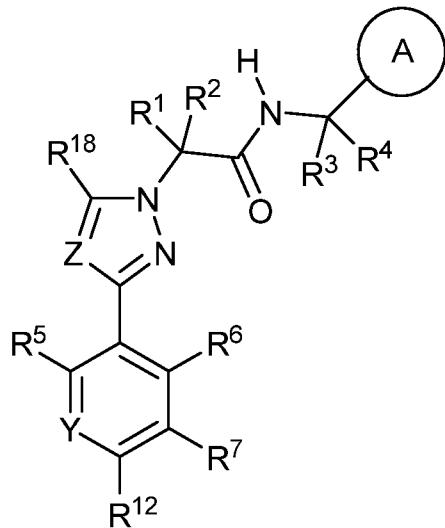
wherein when Y is N, and A is a 6-membered aromatic ring, a 6-membered heteroaromatic

30 ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted as defined above,  $R^{18}$  may additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-

35 OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros; and

each  $R^{16}$  and  $R^{17}$ , when present, is independently selected from H and (C1-4)alkyl.

In an embodiment of the invention, there is provided a compound of Formula IIa:



Formula IIa

5 or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-

10 4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

Y is selected from N and CR<sup>11</sup>;

R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

15 Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

A is a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>,

20 S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

R<sup>18</sup> is selected from -C(O)X and -CN;

X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-4)alkyl; and

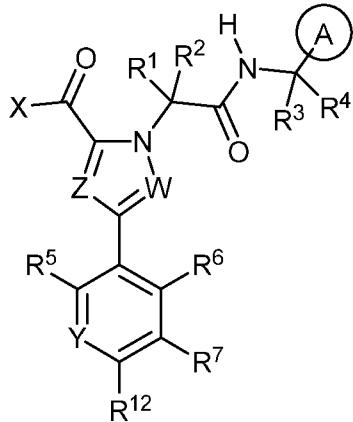
wherein when Y is N, R<sup>18</sup> may additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1

to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and each R<sup>16</sup> and R<sup>17</sup>, when present, is independently selected from H and (C1-4)alkyl.

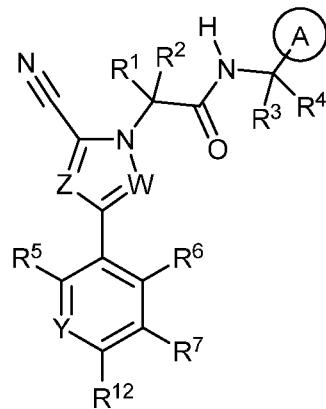
5

In any aspect or embodiment of a compound of Formula II or IIa described herein, R<sup>18</sup> may preferably be -C(O)X or -CN. Accordingly, the invention also provides a compound of Formula II wherein R<sup>18</sup> is -C(O)X or -CN and all other moieties are as defined herein. For example, the invention provides a subgenus of the compounds of formula II, wherein the

10 compound is a compound of Formula III or Formula IV:



Formula III



Formula IV

or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

15 R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

20 Y is selected from N and CR<sup>11</sup>;

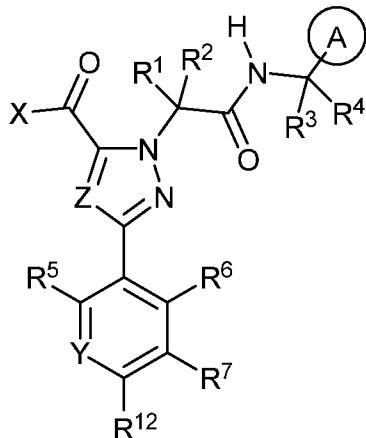
R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

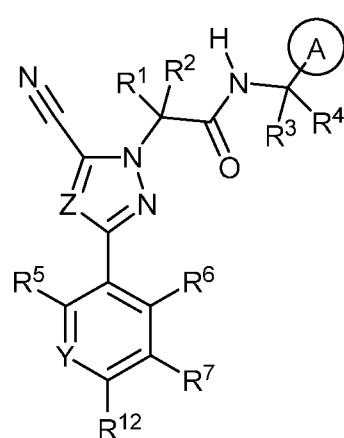
25 A is a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, or a fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from

O, S and N; wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and

5 each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-4)alkyl. For example, the invention also provides a subgenus of the compounds of formula II, wherein the compound is a compound of Formula IIIa or Formula IVa:



Formula IIIa

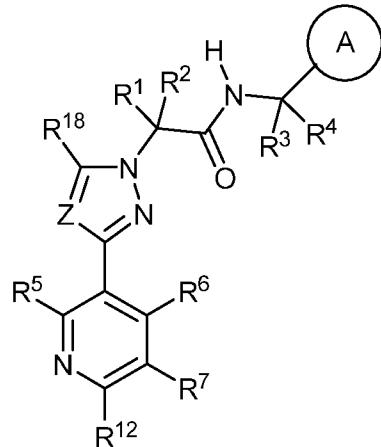


Formula IVa

10 or a pharmaceutically acceptable salt thereof, wherein  
 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;  
 R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;  
 R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;  
 15 X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;  
 Y is selected from N and CR<sup>11</sup>;  
 R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;  
 20 Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;  
 A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents  
 25 selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and

each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-4)alkyl.

In any aspect or embodiment of a compound of Formula II or IIa described herein, Y may be 5 N. For example, the invention therefore also relates to a subgenus of the compounds of Formula II, wherein the compound is a compound of Formula V:



Formula V

or a pharmaceutically acceptable salt thereof, wherein

10 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;  
 R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;  
 R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

15 R<sup>12</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;  
 Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;  
 A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to 20 three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

25 R<sup>18</sup> is -C(O)X, CN, H, (C1-6)alkyl or (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen,

the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-4)alkyl; and

each R<sup>16</sup> and R<sup>17</sup>, when present, is independently selected from H and (C1-4)alkyl.

Compounds of Formulae I to V are shown in the Examples to activate PDE4 long form enzymes.

10

In one aspect, the present invention provides a compound of any of Formulae I to V for use in therapy. In an embodiment, the therapy is the treatment or prevention of a disease or disorder mediated by excessive intracellular cAMP signalling. In these diseases, a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) should provide a therapeutic benefit. Also provided is a method of treating or preventing a disease or disorder mediated by excessive intracellular cAMP signalling, comprising the step of administering an effective amount of a compound of any of Formulae I to V to a patient in need thereof. Also provided is the use of a compound of any of Formulae I to V in the manufacture of a medicament for treating or preventing a disease or disorder mediated by excessive intracellular cAMP signalling.

A compound of any of Formulae I to V can be provided in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

25

In certain embodiments of the foregoing aspects, the compounds of the invention are provided for the treatment or prevention of a condition selected from hyperthyroidism, Jansens's metaphyseal chondrodysplasia, hyperparathyroidism, familial male-limited precocious puberty, pituitary adenomas, Cushing's disease, polycystic kidney disease, polycystic liver disease, McCune-Albright syndrome, cholera, whooping cough, anthrax, tuberculosis, HIV, AIDS, Common Variable Immunodeficiency (CVID), melanoma, pancreatic cancer, leukaemia, prostate cancer, adrenocortical tumours, testicular cancer, primary pigmented nodular adrenocortical diseases (PPNAD), Carney Complex, autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), maturity onset diabetes of young type 5 (MODY5), or cardiac hypertrophy.

#### Brief description of the Figures

Figure 1 shows (a) dose dependent activation of PDE4 long form, PDE4D5 by Example 2, and (b) a lack of activation of PDE4 short form, PDE4B2, by Example 2, using the method described in Experiment 1, Protocol A, demonstrating selectivity for activation of the PDE4 long form over the PDE4 short form.

5

Figure 2 shows a reduction in intracellular cAMP levels in MDCK cells treated with PDE4 long form activator, Example 1 (10  $\mu$ M) for 10 min prior to treatment with forskolin (F) (10  $\mu$ M) for 2 min, using the method described in Experiment 2.

10 Figure 3 shows inhibition of cyst formation in a 3D culture of MDCK cells treated with PDE4 long form activator, Example 28, using the method described in Experiment 3, Protocol D.

#### **Detailed description of the Invention**

The invention is based on the surprising identification of new compounds that are able to activate long isoforms of PDE4 enzymes. The compounds are small molecules and so are expected to be easier and cheaper to make and formulate into pharmaceuticals than large biological molecules such as polypeptides, proteins or antibodies. The compounds can be chemically synthesized, as demonstrated in the Examples.

20 The Examples demonstrate that a number of compounds of Formulae I to V are able to activate long isoforms of PDE4. The Examples go on to demonstrate that certain tested compounds of the invention do not activate a short form of PDE4, thereby demonstrating selectivity for activation of PDE4 long forms over PDE4 short forms. The Examples further demonstrate that PDE4 long form activators reduce cAMP levels in a cellular assay.

25

Various embodiments of the invention are described herein. It will be recognised that features specified in each embodiment may be combined with other specified features to provide further embodiments.

30 A first aspect of the invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, as set out above, for use in therapy.

In the compounds of Formula I, W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl. In an embodiment of the compounds of Formula I, W and Z are each, independently, selected from N and CH. In an embodiment, at least one of W and Z is N. In an embodiment of the compounds of Formula I, W and Z are both N or W is N and Z is CR<sup>19</sup>. In another embodiment, Z is N and W is CR<sup>19</sup>. The remaining moieties may

be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In an embodiment, a compound of Formula I may be a compound wherein:

5 R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

10 R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

15 R<sup>13</sup> is selected from -C(O)X, -CN, H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

20 A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

25 each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-4)alkyl; and the remaining moieties are as defined for any aspect or embodiment of Formula I described herein;

provided that:

when (i) Z is N, W is N, Y is CR<sup>11</sup> and A is an optionally substituted 6-membered aromatic ring; or (ii) A is a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, or a fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N; R<sup>13</sup> is -C(O)X or -CN..

30 In the compounds of Formula I or Ia, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl. In an embodiment of the compounds of Formula I or Ia, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

35 In the compounds of Formula I or Ia, R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F. In an embodiment of the compounds of Formula I or Ia, R<sup>5</sup> and R<sup>6</sup> are H. In a further

embodiment, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are H. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In the compounds of Formula I, R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more (preferably 1 to 3) fluoros; wherein R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined herein. In the compounds of Formula Ia, R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; wherein R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined herein. In a further embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above, R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted as defined above, e.g. with 1 to 3 fluoros. In a further embodiment, R<sup>7</sup> is H or halogen. In a further embodiment, R<sup>7</sup> is H. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In the compounds of Formula I or Ia, Y is selected from N and CR<sup>11</sup>, wherein R<sup>11</sup> is as defined herein. In a further embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above, Y is CR<sup>11</sup>. In a further embodiment, Y is CR<sup>11</sup> and R<sup>11</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, Y is CR<sup>11</sup> and R<sup>11</sup> is H or halogen. Preferably, R<sup>7</sup> is H, Y is CR<sup>11</sup> and R<sup>11</sup> is H or halogen. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In the compounds of Formula I or Ia, R<sup>19</sup>, when present, is H or (C1-4)alkyl, preferably H. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In the compounds of Formula I or Ia, Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl. In a further embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above, Z is N or CH. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In another embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above, Y is CR<sup>11</sup> and Z is N, Y is CR<sup>11</sup> and Z is CH, Y and Z are both N, or

Y is N and Z is CH, wherein R<sup>11</sup> is as defined herein. In a further embodiment, Y is CR<sup>11</sup> and Z is N or CH, preferably N, wherein R<sup>11</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, R<sup>11</sup> is H or halogen. In yet a further embodiment, Y is CH 5 and Z is CH or Y is CH and Z is N. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In the compounds of Formula I, R<sup>12</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, 10 (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more (preferably 1 to 3) fluoros. In the compounds of Formula Ia, R<sup>12</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment of a compound of Formula I or Ia, 15 including any of the embodiments thereof described above, R<sup>12</sup> is selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted as defined above, e.g. with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

20 In the compounds of Formula I, A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, a 5-membered heteroaromatic ring that contains 1 to 3 heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, and a fused 9-membered bicyclic aromatic heteroaromatic ring system that 25 contains 1 to 3 heteroatoms selected from O, S and N; wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more (preferably 1 to 3) fluoros. In the compounds of Formula Ia, A is a 6-membered aromatic ring or a 6-membered 30 heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. 35 In a further embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above, A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>,

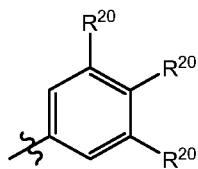
CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted as described above, e.g. with 1 to 3 fluoros. In yet a further embodiment, A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being 5 optionally substituted as described above, e.g. with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In a further embodiment of a compound of Formula I or Ia, including any of the embodiments 10 thereof described above, A is a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one or two N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, 15 C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being 20 optionally substituted with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In a further embodiment of a compound of Formula I or Ia, including any of the embodiments 25 thereof described above, A is a phenyl ring, optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. The remaining moieties 30 may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

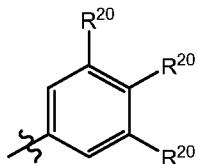
In a further embodiment A is a phenyl ring, optionally substituted with one to three 35 substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

35 In a further embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above, A is:



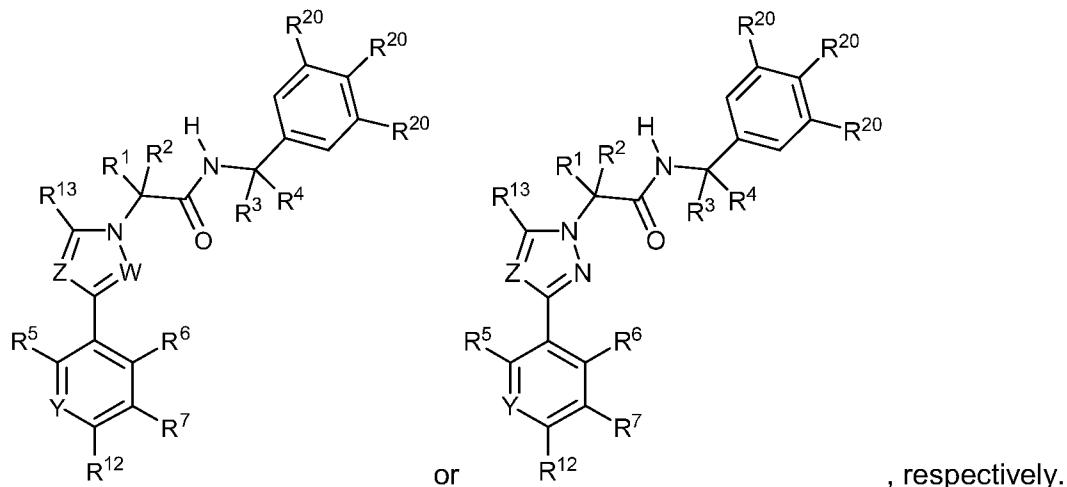
wherein each R<sup>20</sup> is independently selected from hydrogen, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

5 In a further embodiment, each R<sup>20</sup> is independently selected from hydrogen, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, at least one R<sup>20</sup> is not hydrogen. In a further embodiment, one or two instances of R<sup>20</sup> are not hydrogen. It will be appreciated that



the structure of a compound of Formula I or Ia where A is may be

10 represented as



In the compounds of Formula I, R<sup>13</sup> is selected from -C(O)X, -CN, H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 15 one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more (preferably 1 to 3) fluoros; provided that: when (i) Z is N, W is N, Y is CR<sup>11</sup> and A is an optionally substituted 6-membered aromatic ring; or (ii) A is an optionally substituted fused 10-membered bicyclic 20 aromatic ring system or heteroaromatic ring system that contains one to three N atoms, or an optionally substituted fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N; R<sup>13</sup> is -C(O)X or -CN. In the

compounds of Formula Ia,  $R^{13}$  is selected from  $-C(O)X$ ,  $-CN$ ,  $H$ , (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-NR^{16}R^{17}$ ,  $C(O)-OR^{16}$ ,  $S(O)_2-NR^{16}R^{17}$ , CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; wherein X,  $R^{16}$  and  $R^{17}$ , are as defined herein, provided that when Z is N, Y is  $CR^{11}$  and A is an optionally substituted 6-membered aromatic ring,  $R^{13}$  is  $-C(O)X$  or  $-CN$ . In a further embodiment of a compound of Formula I or Ia, including any of the embodiments thereof described above,  $R^{13}$  is selected from  $-C(O)X$ ,  $-CN$ ,  $H$ , methyl, ethyl or methoxymethyl. In a further embodiment,  $R^{13}$  is not H. In a further embodiment,  $R^{13}$  is  $-C(O)X$  or CN. In a further embodiment,  $R^{13}$  is  $-C(O)X$  and X is  $OR^{8a}$  or  $NR^{9a}R^{10a}$ , wherein  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$  are independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy, preferably wherein  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$  are independently selected from H and (C1-4)alkyl or from H and (C1-2)alkyl. In a further embodiment,  $R^{13}$  is  $-C(O)X$  and X is  $NR^{9a}R^{10a}$ , wherein  $R^{9a}$  and  $R^{10a}$  are as defined above. In a further embodiment,  $R^{13}$  is  $-C(O)X$ , wherein X is  $NH_2$ ,  $NH(C1-6alkyl)$ ,  $NH(C1-2alkyloxyC1-2alkyl)$ ,  $N(C1-2alkyl)_2$  or  $O(C1-2alkyl)$ , for example  $R^{13}$  is  $-C(O)NH_2$ ,  $-C(O)NHMe$ ,  $-C(O)NMe_2$ ,  $-C(O)OMe$ ,  $-C(O)OEt$ ,  $-C(O)NH(CH(CH_3)_2)$ ,  $-C(O)NHEt$ ,  $-C(O)NH(CH_2CH_2OCH_3)$ ,  $-C(O)NHcyclohexyl$ . In a further embodiment,  $R^{13}$  is  $-C(O)X$ , wherein X is  $NH_2$ ,  $NH(C1-2alkyl)$ ,  $N(C1-2alkyl)_2$  or  $O(C1-2alkyl)$ , for example  $R^{13}$  is  $-C(O)NH_2$ ,  $-C(O)NHMe$ ,  $-C(O)NMe_2$ ,  $-C(O)OMe$  or  $-C(O)OEt$ . The remaining moieties may be as defined for any aspect or embodiment of Formula I or Ia described herein, *mutatis mutandis*.

In an embodiment, the compound of Formula I is selected from:

25 Methyl 3-(4-chloro-3-fluorophenyl)-1- $\{[(3\text{-fluorobenzyl})carbamoyl]methyl\}$ -1H-1,2,4-triazole-5-carboxylate;  
Ethyl 1- $\{[(benzylcarbamoyl)methyl]\}$ -3-(4-chloro-3-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate;  
Methyl 1- $\{[(benzylcarbamoyl)methyl]\}$ -3-(4-chloro-3-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate;  
30 Ethyl 3-(4-chloro-3-fluorophenyl)-1- $\{[(3\text{-fluorobenzyl})carbamoyl]methyl\}$ -1H-1,2,4-triazole-5-carboxylate;  
Ethyl 3-(4-chloro-3-fluorophenyl)-1- $\{[(3\text{-methoxybenzyl})carbamoyl]methyl\}$ -1H-1,2,4-triazole-5-carboxylate;  
35 3-(4-chloro-3-fluorophenyl)-1- $\{[(3\text{-fluorobenzyl})carbamoyl]methyl\}$ -1H-1,2,4-triazole-5-carboxylic acid;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylic acid;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxamide;

5 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

10 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-fluorobenzyl)acetamide;

*N*-(3-fluorobenzyl)-2-[5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl]acetamide;

15 *N*-benzyl-2-[3-(4-chlorophenyl)-1*H*-pyrazol-1-yl]acetamide;

2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-methoxybenzyl)acetamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N*-isopropyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

20 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N*-ethyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N*-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

25 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N*-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N*-cyclohexyl-1*H*-1,2,4-triazole-5-carboxamide;

Ethyl 3-(4-chlorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-pyrazole-5-carboxylate;

30 Methyl 1-[(3-fluorobenzyl)carbamoyl]methyl]-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N*-methyl-1*H*-pyrazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N*-methyl-1*H*-pyrazole-5-carboxamide;

35 Ethyl 3-(4-chlorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-{[(1*H*-indazol-5-yl)methyl]carbamoyl}methyl)-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

*N*-[(1*H*-imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetamide;

5 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl)acetamide;  
Methyl 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate;  
3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

10 and pharmaceutically acceptable salts thereof.

A second aspect of the invention provides a compound of Formula II, Formula IIa, Formula III, Formula IIIa, Formula IV, Formula IVa, or Formula V, or a pharmaceutically acceptable salt thereof, as set out above.

15

In the compounds of Formula II to V, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl. In an embodiment of the compounds of Formula II to V, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H. The remaining moieties may be as defined for any aspect or embodiment of Formula II to IV described herein, *mutatis mutandis*.

20

In the compounds of Formula II, W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl. In an embodiment of the compounds of Formula II, W and Z are each, independently, selected from N and CH. In an embodiment, at least one of W and Z is N. In an embodiment of the compounds of Formula II, W and Z are both N or W is N and Z is CR<sup>19</sup>. In another embodiment, Z is N and W is CR<sup>19</sup>. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

In an embodiment, a compound of Formula II may be a compound wherein:

30 R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;  
each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-4)alkyl;  
R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

5 wherein when Y is N, and A is a 6-membered aromatic ring, or a 5-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted as defined above, R<sup>18</sup> may additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and the remaining moieties are as defined for any aspect or embodiment of Formula II described herein.

10

15

In the compounds of Formula II to V, R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F. In an embodiment of the compounds of Formula II to V, R<sup>5</sup> and R<sup>6</sup> are H. In a further embodiment, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are H. The remaining moieties may be as defined for any aspect or embodiment of Formula II to IV described herein, *mutatis mutandis*.

20

In the compounds of Formula II, R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros; wherein R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, are as defined herein. In the compounds of Formula IIa, III, IIIa, IV, IVa, or V, R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; wherein R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined herein. In a further embodiment of a compound of Formula II to V, including any of the embodiments thereof described above, R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, R<sup>7</sup> is H or halogen. In a further embodiment, R<sup>7</sup> is H. The remaining moieties may be as defined for any aspect or embodiment of Formula II to IV described herein, *mutatis mutandis*.

25

30

35 In the compounds of Formula II to IV, Y is selected from N and CR<sup>11</sup>, wherein R<sup>11</sup> is as defined herein. In a further embodiment of a compound of Formula II to IV, including any of the embodiments thereof described above, Y is CR<sup>11</sup>. In a further embodiment, Y is CR<sup>11</sup>

and R<sup>11</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, Y is CR<sup>11</sup> and R<sup>11</sup> is H or halogen. Preferably, R<sup>7</sup> is H, Y is CR<sup>11</sup> and R<sup>11</sup> is H or halogen. The remaining moieties may be as defined for any aspect or embodiment of

5 Formula II to V described herein, *mutatis mutandis*.

In the compounds of Formula II to V, R<sup>19</sup>, when present, is H or (C1-4)alkyl, preferably H. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

10

In the compounds of Formula II to V, Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl. In a further embodiment of a compound of Formula II to V, including any of the embodiments thereof described above, Z is N or CH. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

15

In another embodiment of a compound of Formula II to IV, including any of the embodiments thereof described above, Y is CR<sup>11</sup> and Z is N, Y is CR<sup>11</sup> and Z is CH, Y and Z are both N, or Y is N and Z is CH, wherein R<sup>11</sup> is as defined herein. In a further embodiment, Y is CR<sup>11</sup> and Z is N or CH, preferably N, wherein R<sup>11</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN 20 and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, R<sup>11</sup> is H or halogen. In yet a further embodiment, Y is CH and Z is CH or Y is CH and Z is N. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

25

In the compounds of Formula II, R<sup>12</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more (preferably 1 to 3) fluoros. In the compounds of Formula IIa, III, IIIa, IV, IVa or V, R<sup>12</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>,

30

S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment of a compound of Formula II to V, including any of the embodiments thereof described above, R<sup>12</sup> is selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted as defined above, e.g. with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

In the compounds of Formula II, III or IV, A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that 5 contains one to three N atoms, and a fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N; wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more 10 fluoros. In the compounds of Formula IIa, IIIa, IVa, or V, A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment of a 15 compound of Formula II to V, including any of the embodiments thereof described above, A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted as 20 described herein, e.g. with 1 to 3 fluoros. In yet a further embodiment, A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted as described herein, e.g. with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or 25 embodiment of Formula II to V described herein, *mutatis mutandis*.

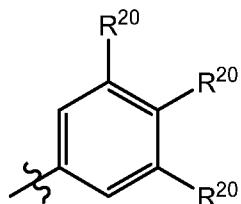
In a further embodiment of a compound of Formula II to V, including any of the embodiments thereof described above, A is a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one or two N atoms, or a 5-membered heteroaromatic ring that contains 30 one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being 35 optionally substituted with 1 to 3 fluoros. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

In a further embodiment of a compound of Formula II to V, including any of the embodiments thereof described above, A is a phenyl ring, optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-

5 NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment A is a phenyl ring, optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros. The remaining moieties may be as defined for

10 any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

In a further embodiment of a compound of Formula II to V, including any of the embodiments thereof described above, A is:



15 wherein each R<sup>20</sup> is independently selected from hydrogen, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros. In a further embodiment, each R<sup>20</sup> is independently selected from hydrogen, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally 20 substituted with 1 to 3 fluoros. In a further embodiment, at least one R<sup>20</sup> is not hydrogen. In a further embodiment, one or two instances of R<sup>20</sup> are not hydrogen. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

25 In the compounds of Formula II, R<sup>18</sup> is -C(O)X or -CN, wherein when Y is N, and A is a 6-membered aromatic ring, or a 5-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted as defined above, R<sup>18</sup> may 30 additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more (preferably 1 to 3) substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more (preferably 1 to 3) fluoros; wherein X, R<sup>16</sup> and

$R^{17}$ , are as defined herein. In the compounds of Formula IIa,  $R^{18}$  is  $-C(O)X$  or  $-CN$ ; wherein when Y is N,  $R^{18}$  may additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-NR^{16}R^{17}$ ,  $C(O)-OR^{16}$ ,  $S(O)_2-$

5  $NR^{16}R^{17}$ , CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; wherein X,  $R^{16}$  and  $R^{17}$ , are as defined herein. In the compounds of Formula V,  $R^{18}$  is  $-C(O)X$ , CN, H, (C1-6)alkyl or (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-NR^{16}R^{17}$ ,  $C(O)-OR^{16}$ ,  $S(O)_2-$

10  $NR^{16}R^{17}$ , CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; wherein X,  $R^{16}$  and  $R^{17}$ , are as defined herein. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

15 In a further embodiment of a compound of Formula II wherein Y is N, or a compound of Formula V, including any of the embodiments thereof described above,  $R^{18}$  is H, methyl, ethyl or methoxymethyl. The remaining moieties may be as defined for any aspect or embodiment of Formula II to V described herein, *mutatis mutandis*.

20 In a further embodiment of a compound of Formula II, IIa or V, including any of the embodiments thereof described above,  $R^{18}$  is not H. In a further embodiment of a compound of Formula II, IIa or V, including any of the embodiments thereof described above,  $R^{18}$  is selected from  $-C(O)X$  and  $-CN$ , wherein X is as defined herein. In a further embodiment,  $R^{18}$  is  $-C(O)X$  and X is  $NR^{9a}R^{10a}$ . The remaining moieties may be as defined for any aspect or

25 embodiment of Formula II to V described herein, *mutatis mutandis*.

In a compound of Formula II, IIa or V wherein  $R^{18}$  is  $-C(O)X$ , or a compound of Formula III or IIIa, including any of the embodiments thereof described above, X is selected from  $OR^{8a}$  and  $NR^{9a}R^{10a}$  and each  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$  is as defined herein. In a further embodiment, X is  $OR^{8a}$

30 or  $NR^{9a}R^{10a}$ , wherein  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$  are independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy, preferably wherein  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$  are independently selected from H and (C1-4)alkyl or from H and (C1-2)alkyl. In a further embodiment,  $R^{18}$  is  $-C(O)X$  and X is  $NR^{9a}R^{10a}$ , wherein  $R^{9a}$  and  $R^{10a}$  are as defined above. In a further embodiment of Formula II, IIa or V wherein  $R^{18}$  is  $-C(O)X$ , or a compound of Formula III or IIIa, X is  $NH_2$ ,  $NH(C1-6alkyl)$ ,  $NH(C1-2alkyloxyC1-2alkyl)$ ,  $N(C1-2alkyl)_2$  or  $O(C1-2alkyl)$ , for example  $R^{18}$  is  $-C(O)NH_2$ ,  $-C(O)NHMe$ ,  $-C(O)NMe_2$ ,  $-C(O)OMe$ ,  $-C(O)OEt$ ,  $-$

$\text{C}(\text{O})\text{NH}(\text{CH}(\text{CH}_3)_2)$ ,  $-\text{C}(\text{O})\text{NHEt}$ ,  $-\text{C}(\text{O})\text{NH}(\text{CH}_2\text{CH}_2\text{OCH}_3)$ ,  $-\text{C}(\text{O})\text{NHcyclohexyl}$ . In a further embodiment,  $\text{R}^{18}$  is  $-\text{C}(\text{O})\text{X}$ , wherein  $\text{X}$  is  $\text{NH}_2$ ,  $\text{NH}(\text{C}1\text{-}2\text{alkyl})$ ,  $\text{N}(\text{C}1\text{-}2\text{alkyl})_2$  or  $\text{O}(\text{C}1\text{-}2\text{alkyl})$ , for example  $\text{R}^{18}$  is  $-\text{C}(\text{O})\text{NH}_2$ ,  $-\text{C}(\text{O})\text{NHMe}$ ,  $-\text{C}(\text{O})\text{NMe}_2$ ,  $-\text{C}(\text{O})\text{OMe}$  or  $-\text{C}(\text{O})\text{OEt}$ .

5 In an embodiment of the compound of Formula II, the compound is selected from:  
Methyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate;  
Ethyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate;

10 Methyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate;  
Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate;  
Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate;

15 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylic acid;  
3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylic acid;

20 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxamide;  
3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxamide;

25 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;  
3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

30 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;  
2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-fluorobenzyl)acetamide;  
2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]acetamide;

35 2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-methoxybenzyl)acetamide;  
3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N*-isopropyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-N-ethyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-N-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

5 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-N-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-N-cyclohexyl-1*H*-1,2,4-triazole-5-carboxamide;

Ethyl 3-(4-chlorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylate;

10 Methyl 1-{[(3-fluorobenzyl) carbamoyl]methyl}-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-N-methyl-1*H*-pyrazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-N-methyl-1*H*-pyrazole-5-carboxamide;

15 Ethyl 3-(4-chlorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-{[(1*H*-indazol-5-yl)methyl]carbamoyl}methyl)-N-methyl-1*H*-1,2,4-triazole-5-carboxamide;

20 *N*-[(1*H*-imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetamide;

2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl)acetamide;

Methyl 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate;

25 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-N-methyl-1*H*-1,2,4-triazole-5-carboxamide;

and pharmaceutically acceptable salts thereof.

#### Definitions

30 The term “aromatic ring” refers to an aromatic carbocyclic ring system. The term “heteraromatic ring” refers to an aromatic ring system wherein one or more of the ring-forming atoms is a heteroatom such as O, S or N. In the definition of Formula I to V, A may be an optionally substituted 6-membered aromatic ring. This aromatic ring is an optionally substituted phenyl ring. Alternatively, A may be a 6-membered heteroaromatic ring that

35 contains one to three N atoms or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N. Examples of such 6- or 5-membered heteroaromatic rings include pyridine, pyridazine, pyrazine, pyrimidine, thiophene, furan,

thiazole, thiadiazole, oxazole, oxadiazole, imidazole, triazole and their isomers including isothiazole, isothiadiazole, isoxazole and isoxadiazole. Alternatively, in some embodiments A may be a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, or a fused 9-membered bicyclic aromatic heteroaromatic 5 ring system that contains 1 to 3 heteroatoms selected from O, S and N. Examples of such fused bicyclic ring systems include indazole, indole, naphthalene, quinoline, isoquinoline and benzimidazole.

The term "(C1-6)alkyl" as used herein means a branched or unbranched alkyl group having 10 1-6 carbon atoms, optionally containing a ring. Examples of (C1-4)alkyl include hexyl, cyclohexyl, pentyl, cyclopentyl, butyl, isobutyl, cyclobutyl, tertiary butyl, propyl, isopropyl, cyclopropyl, ethyl and methyl. The term "(C1-4)alkyl" as used herein means a branched or unbranched alkyl group having 1-4 carbon atoms, optionally containing a ring. Examples of (C1-4)alkyl include butyl, isobutyl, cyclobutyl, tertiary butyl, propyl, isopropyl, cyclopropyl, 15 ethyl and methyl. A (C1-4)alkyl as referenced herein may preferably be a (C1-2)alkyl. Where specified in the formulae above, (C1-4)alkyl may be substituted, for example with 1 to 3 fluoros. A particularly preferred example of a substituted (C1-4)alkyl is trifluoromethyl. Alternatively (C1-4)alkyl may be unsubstituted.

20 The term "(C1-4)alkyloxy" means -O-(C1-4)alkyl wherein (C1-4)alkyl has the meaning as defined above. Examples of (C1-4)alkyloxy include methoxy, ethoxy, propoxy, isopropoxy, butyloxy, isobutoxy and tertiary butoxy. A (C1-4)alkyloxy as referenced herein may preferably be a (C1-2)alkyloxy. Where specified in the formulae above, (C1-4)alkyloxy may be substituted, for example with 1 to 3 fluoros. A particularly preferred example of a substituted 25 (C1-4)alkyloxy is trifluoromethoxy. Alternatively, (C1-4)alkyloxy may be unsubstituted. In the present invention, alkyloxy is attached to the rest of the molecule by the "oxy" moiety.

The term "(C1-4)alkylsulfonyl" means -S(O)<sub>2</sub>-(C1-4)alkyl wherein (C1-4)alkyl has the meaning as defined above.

30 The term "halogen" means F, Cl, Br or I. F and Cl are particularly preferred.

The compounds of Formulae I to V may be prepared by methods known in the art of organic chemistry in general. For example, suitable methods for constructing pyrazole and 1,2,4-35 triazole rings are described in the general reference Katritzky, A.R.: Comprehensive heterocyclic chemistry (First Edition, Pergamon Press, 1984, see especially Volume 5, Part 4A, Five-membered rings with two or more nitrogen atoms). Suitable protecting groups for

functional groups which are to be temporarily protected during syntheses are known in the art, for example from Wuts, P.G.M. and Greene, T.W.: *Protective Groups in Organic Synthesis*, Fourth Edition, Wiley, New York, 2006.

5 Activation of long PDE4 Isoforms

PDE4 long isoforms have two regulatory regions, upstream conserved region 1 (UCR1) and upstream conserved region 2 (UCR2). These are between the isoform-specific N-terminal portion and the catalytic domain. The UCR1 domain is missing in the short forms, whereas the super-short forms not only lack UCR1, but also have a N-terminal truncated UCR2 10 domain (Houslay, M. D., Schafer, P. and Zhang, K. *Drug Discovery Today* 10: 1503-1519, 2005).

There are four PDE4 families, PDE4A, PDE4B, PDE4C and PDE4D. The present invention concerns compounds that are capable of activating one or more of the long isoforms from 15 one or more of these four families. The long isoform PDE4 may therefore be long isoform PDE4A, long isoform PDE4B, long isoform PDE4C or long isoform PDE4D. For the avoidance of doubt, a long isoform PDE4 comprises a UCR1 region. Typically, the long isoform PDE4 is human. UCR1 is conserved within mammalian species (Houslay, MD, Sullivan, M and Bolger GB *Adv. Pharmacol.* 44: 225-342, 1998), so in other embodiments, 20 the long isoform PDE4 can be from a non-human mammal.

Without wishing to be bound by theory, PDE4 long form activators of Formulae I to V of the present invention are small molecules that are believed to bind directly to PDE4 long forms and induce structural changes that increase, stabilise, uncover and/or maintain the catalytic 25 activity of these enzymes. In the field of pharmacology, and as used herein, a small molecule is defined as a low molecular weight organic compound that may serve as a regulator of biological processes. A small molecule activator according to the present invention has a molecular weight of less than or equal to 700 Daltons. This allows for the possibility to rapidly diffuse across cell membranes and reach intracellular sites of action 30 (Veber, D. F. et al., *J. Med. Chem.* 45: 2615–2623, 2002). The preferred molecular weight for a small molecule activator according to the present invention is greater than or equal to 200 Daltons and less than or equal to 600 Daltons. Especially preferred small molecule activators according to the present invention have molecular weights of greater than or equal to 250 Daltons and less than or equal to 500 Daltons (Lipinski, C. A. *Drug Discovery Today: Technologies* 1: 337–341, 2004).

One suitable method of detecting whether or not a compound is capable of serving as an activator of a PDE4 long form is using a two-step radio-assay procedure described in Experiment 1. In summary, the method involves incubating a PDE4 long form with a test small molecule activator, together with [<sup>3</sup>H]-labelled cAMP to assess alterations in the 5 breakdown of cAMP to the 5'-adenosine monophosphate (5'-AMP) product. A sample of the reaction mixture from such an incubation is subsequently treated with snake venom 5'-nucleotidase to allow conversion of the nucleotide [<sup>3</sup>H]-labelled 5'-AMP to the uncharged nucleoside [<sup>3</sup>H]-labelled adenosine, which can be separated and quantified to assess PDE4 10 activity and the effect of the test compound (Thompson, W. J. and Appleman, M. M. 15 *Biochemistry* 10: 311-316, 1971, with some modifications as described in: Marchmont, R. J. and Houslay, M. D. *Biochem J.* 187: 381-92, 1980).

Using the above assay procedure, as described in detail in Experiment 1, preferred small 20 molecule activators according to the present invention produce an increase in the background activity of one or more PDE4 long forms of more than 50% at a test compound concentration of 100 micromolar or less. Especially preferred small molecule activators according to the present invention produce an increase in the background activity of one or more PDE4 long forms of more than 50% at a test compound concentration of 10 15 micromolar, or less, for example 3 micromolar.

25 The compounds of the present invention may be selective for the long form of the PDE4 enzyme and, as such, do not act or act to a lesser extent as activators of the short or super-short isoforms of the PDE4 enzyme. The short or super-short isoform PDE4 may therefore be short or super-short isoform PDE4A, short or super-short isoform PDE4B, short or super- 30 short isoform PDE4C, or short or super-short isoform PDE4D. For the avoidance of doubt, short and super-short isoforms of PDE4 lack a UCR1 domain. Super-short isoforms comprise a truncated UCR2 domain. Typically, the short or super-short isoform PDE4 is human, but may also be from other mammalian species (where UCR2 is conserved, see Houslay, MD, Sullivan, M and Bolger GB *Adv. Pharmacol.* 44: 225-342, 1998).

35 Under the same assay conditions, as described in Experiment 1, the small molecule activators according to the present invention may produce a less than 50% increase in the background activity of the short or super-short forms of the PDE4A, PDE4B, PDE4C or PDE4D enzymes at a test compound concentration of 100 micromolar, or less.

Compounds of the invention may therefore provide a positive result in an assay for activation of a long form PDE4 and a negative result in an assay for activation of a short form (or super-short form) of PDE4.

5 PDE4 long isoforms include those now known as PDE4A4, PDE4A4/5, PDE4A5, PDE4A8, PDE4A10, PDE4A11, PDE4B1, PDE4B3, PDE4B4, PDE4C1, PDE4C2, PDE4C3, PDE4D3, PDE4D4, PDE4D5, PDE4D7, PDE4D8, PDE4D9 and PDE4D11. Further long isoforms may be or have already been identified or called by different nomenclature from any of the four PDE4 sub-families.

10 PDE4 short isoforms include PDE4A1, PDE4B2, PDE4D1 and PDE4D2. Further short isoforms may be or have already been identified or called by different nomenclature from any of the four PDE4 sub-families.

15 PDE4 super-short isoforms include PDE4B5, PDE4D6 and PDE4D10. Further super-short isoforms may be or have already been identified or called by different nomenclature from any of the four PDE4 sub-families.

20 The Examples below exemplify activity of compounds in human PDE4D5 and PDE4B1 long isoforms and a lack of activity in the human PDE4B2 short isoform. Details of these isoforms and a number of the other known isoforms, including GenBank accession numbers, are provided in Tables A to D immediately below.

<u>PDE4A</u>				
Isoform	accession	calculated size	SDS-PAGE (kDa)	Type
A1 (human)	U97583		83	S
A1 (rodent)	M26715, L27062		76	S
A4* (humanA5)	L20965		125	L
A5 (rodentA4)	L27057		107	L
A7** (human)	U18088		37	DS
A8 (rodent)	L36467	88 kDa	98	L
A10 (human)	AF110461	91 kDa	121	L
A11 (human)	AY618547	95 kDa	126	L

L = Long; S = short; SS = Super-short; D = Dead short

\* Note that the PDE4A4B clone is correct while PDE4A4A has a cloning artefact and PDE4A4C is a truncation artefact.

\*\* Note that this species is C- as well as N-terminally truncated and so will NOT be detected by pan PDE4A antisera that detect all active forms.

**Table A** – Examples of known PDE4A isoforms

<b><u>PDE4B</u></b>			
<b>Isoform</b>	<b>accession</b>	<b>SDS-PAGE (kDa)</b>	<b>Type</b>
B1	L20966	104	L
B2	M97515, L20971	68	S
B3	U85048	103	L
B4	AF202733	84	L
B5	EF595686	58	SS

L = Long; S = short; SS = Super-short; D = Dead short

**Table B** – Examples of known PDE4B Isoforms

<b>PDE4C</b>		
<b>Isoform Name</b>	<b>GenBank</b>	<b>Size (aa)</b>
PDE4C1 (partial clone)	L20968	251*(partial)
PDE4C1	Z46632	712* (Long)
PDE4C2	U88712	606 (Long)
PDE4C3	U88713	700* (Long)
PDE4C4	U66346	791* (Long)
PDE4C5	U66347	426*
PDE4C6	U66348	518*
PDE4C7	U66349	427*

5 **Table C** – Examples of known PDE4C Isoforms

<u>PDE4D</u>				
Isoform	accession	calculated	SDS-PAGE (kDa)	Type
D1	U50157, U79571	66 kDa	68	S
D2	U50158, AFO12074	66 kDa	68	S
D3	L20970, U50159	77 kDa	95	L
D4	L20969	91 kDa	119	L
D5	AFO12073	84 kDa	105	L
D6 (m)	AF536975	59 kDa	59	SS
D7	AF536976	85 kDa	103	L
D8*	AF536977	78 kDa	96	L
D9	AY245867	77 kDa	95	L
D10	DQ665896	58 kDa	58	SS
D11	EU489880	79 kDa	95	L

L = Long; S = short; SS = Super-short; D = Dead short

\* nb D8 was originally called PDE4D6 in the literature

(m) Memory clones are (AY245867, AF536977, AF536976)

**Table D** – Examples of known PDE4D IsoformsReduction of cAMP levels

5 Without wishing to be bound by theory, the compounds of the present invention may function by reducing cAMP levels in one or more intracellular compartments. The PDE4 long form

activators of the present invention may thus provide a means to regulate certain cellular processes that are dependent upon cAMP. Excessive intracellular cAMP signalling mediates a number of diseases and disorders. Therefore, the compounds of the invention are expected to be of utility for the treatment of diseases associated with abnormally

5 elevated cAMP levels, increased cAMP-mediated signalling and/or reduced cAMP elimination, enzymatic or otherwise (e.g. *via* efflux). The treatment is typically of a human, but may also be of a non-human animal, such as a non-human mammal (e.g. veterinary treatment).

10 In one aspect, the present invention provides a small molecule activator of a PDE4 long form of Formulae I to V, for use in a method for the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required.

15 For example, gain-of-function gene mutations in proteins involved in driving cAMP signalling upstream of adenylyl cyclase, such as GPCRs and G $\alpha$ , can lead to abnormal excessive cAMP activity with pathological consequences (Lania A, Mantovani G, Spada A. *Ann Endocrinol (Paris)*. 73: 73-75, 2012.; Thompson, M. D. *et al.*, *Methods Mol. Biol.* 448: 109-137, 2008; Weinstein LS, Liu J, Sakamoto A, Xie T, Chen M. *Endocrinology*. 145: 5459-20 5464, 2004; Lania A, Mantovani G, Spada A. *Eur J Endocrinol*. 145: 543-559, 2001). PDE4 long form activators of the present invention, possessing the ability to accelerate the termination of cAMP action, would therefore be expected to be effective in the treatment, prevention or partial control of diseases characterised by undesirably high cAMP levels, or activity, as detailed below.

25

#### Diseases characterised by elevated cAMP levels

##### ***Hyperthyroidism***

Stimulation of the thyroid-stimulating hormone (TSH) receptor (TSHR) leads to increased 30 generation and release of thyroid hormones, thyroxine and triiodothyronine, through a cAMP-dependent signalling mechanism involving G $\alpha$ -mediated activation of adenylyl cyclase. Gain-of-function mutations in the TSHR have been reported to be involved in the development of hyperthyroidism (Duprez, L. *et al.*, *Nat. Genet.* 7: 396-401, 1994; Biebermann, H. *et al.*, *J. Clin. Endocrinol. Metab.* 86: 4429-4433, 2001; Karges, B. *et al.*, *J. Endocrinol.* 186: 377-385, 2005). Activating mutations of both TSHR and G $\alpha$  have also 35 been found in goitre and thyroid adenomas (Arturi, F. *et al.*, *Exp. Clin. Endocrinol. Diabetes* 106: 234-236, 1998). The increased cAMP activity in thyroid adenomas, as a result of the

activating TSHR or G<sub>α</sub> mutations, has been reported to produce a protective adaptive increase in PDE4 activity to counteract abnormal rise in cAMP levels and signal transduction (Persani, L. *et al.*, *J. Clin. Endocrinol. Metab.* 85: 2872-2878, 2000).

5 The most common cause of hyperthyroidism is Graves' disease, an autoimmune disorder in which antibodies mimic TSH action at the TSHR, leading to excessive cAMP activity in thyroid follicle cells and consequently a state of hyperthyroidism.

10 PDE4 long form activators of the present invention are therefore expected to be effective in the treatment, prevention or partial control of hyperthyroidism. In one embodiment, the hyperthyroidism is associated with Graves' disease.

***Jansens's Metaphyseal Chondrodysplasia and Hyperparathyroidism***

15 Jansens's Metaphyseal Chondrodysplasia (JMC) is a very rare disease resulting from gain-of-function mutations of the parathyroid hormone (PTH) receptor 1 (PTHR1) (Thompson, M. D. *et al.*, *Methods Mol. Biol.* 448: 109-137, 2008). The constitutive activation of the PTHR1 which couples to adenylyl cyclase as effector is associated with excessive cAMP signalling primarily in bone and kidney, leading to dysregulation of ion homeostasis characterised by 20 hypercalcemia and hypophosphatemia (Calvi, L.M. and Schipani, E. *J. Endocrinol. Invest.* 23: 545-554, 2000) and developmental (e.g. short stature) and physical (e.g. protruding eyes) abnormalities.

25 Primary hyperparathyroidism results from excessive release of PTH from the parathyroid gland due to tissue enlargement or non-cancerous adenoma. The resulting excessive stimulation of the PTHR1 receptor causes disruption of plasma ion homeostasis with patients showing hypercalcemia and hypophosphatemia. PDE4 long form activators of the present invention are therefore expected to be effective in the treatment, prevention or partial control of JMC and hyperparathyroidism.

30 ***Familial Male Precocious Puberty (Testotoxicosis)***

Familial male-limited precocious puberty (FMPP), also known as familial sexual precocity or gonadotropin-independent testotoxicosis, is a disorder in which boys generally develop signs of precocious puberty in early childhood.

35 The spinal length in boys may be short due to a rapid advance in epiphyseal maturation. FMPP is an autosomal dominant condition with constitutively activating mutations in the luteinizing hormone (LH) receptor, which leads to increased cAMP production, associated

with Leydig cell hyperplasia and low sperm cell count (Latronico, A.C. *et al.*, *J Clin. Endocrinol. Metab.* 80: 2490-2494, 1995; Kosugi, S. *et al.*, *Hum. Mol. Genet.* 4: 183-188, 1995). PDE4 long form activators of the present invention are therefore expected to be effective in the treatment, prevention or partial control of FMPP.

5

#### ***Pituitary Adenomas and Cushing's Disease***

Non-cancerous tumours of the pituitary gland are collectively referred to as pituitary adenomas and can lead to hypersecretion of adenohypophyseal hormones (e.g. growth hormone, thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone and 10 adrenocorticotropic hormone), which exert their action through GPCRs coupled to Gs and cAMP generation. Thus pituitary adenomas can lead to a state of enhanced cAMP mediated signalling in a variety of endocrine tissues which can precipitate a number of hormonal disorders such as acromegly (mainly due to excess growth hormone secretion), Cushing's disease (due to overproduction of adrenocorticotropic hormone (ACTH) and the 15 subsequent hypercortisolemia) and/or general hyperpituitarism (associated with excess release of multiple anterior pituitary hormones). Current treatment options for pituitary adenomas include treatment with dopamine receptor agonists, which reduce tumour size and lower pituitary hormonal output through a mechanism involving lowering of intracellular cAMP levels. PDE4 long form activators of the present invention may also be expected to 20 attenuate the pathological effects of pituitary hormones in their target tissues, such as the adrenal glands.

In Cushing's disease, pituitary adenoma related overproduction of ACTH can lead to hypercortisolemia through an overactivation of melanocortin 2 receptor (MC2) and 25 subsequent cAMP mediated stimulation of steroidogenesis and release of cortisol from the adrenal cortex (Tritos, N. A. and Biller, B. M. *Discov. Med.* 13: 171-179, 2012). PDE4 long form activators of the present invention are therefore expected to be effective in the treatment, prevention or partial control of Cushing's disease.

30 ***Polycystic kidney disease***

Polycystic kidney disease (PKD) is a genetic disorder of the kidneys characterised by development of pathological cysts, which damage renal structure and compromise kidney function (Takiar, V. and Caplan, M. J. *Biochim. Biophys. Acta.* 1812: 1337-1343, 2011; 35 Masoumi, A. *et al.*, *Drugs* 67: 2495-2510, 2007). There are two types of PKD: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). ADPKD affects between 0.1% and 0.2% of the population worldwide and is characterized by progressive cyst development and enlarged kidneys. Approximately 50%

of people with this disease will develop end stage kidney disease, usually between 40 and 70 years of age and require dialysis or kidney transplantation. ARPKD affects around 1:20,000 live births and is typically identified in the first few weeks after birth. Pulmonary hypoplasia results in a 30-50% death rate in neonates with ARPKD.

5

Defects in two genes are thought to be responsible for ADPKD. In around 85% of patients, development of ADPKD can be linked to mutations in the gene PKD1, encoding polycystin-1 (PC-1); in around 15% of patients mutations in PKD2, encoding polycystin-2 (PC-2) are implicated. Cyclic AMP has been identified as an important stimulus for proliferation and cyst expansion in polycystic kidney cells but not in normal human kidney cells (Yamaguchi, T. et al., *Kidney Int.* 57: 1460-1471, 2000). A considerable body of evidence has now developed to implicate cAMP as an important facilitator of renal cystogenesis (Masoumi, A. et al., *Drugs* 67: 2495-2510, 2007; Wallace, D. P. *Biochim. Biophys. Acta.* 1812: 1291-1300, 2011). Consistent with the role of cAMP in cyst formation, agents that lower cAMP levels (e.g. 10 vasopressin V2 receptor antagonists and the somatostatin receptor agonist octreotide) showed efficacy in rodent models of PKD (Torres, V. E. et al., *Nat. Med.* 10: 363-364, 2004; Gattone, V. H. 2<sup>nd</sup> et al., *Nat. Med.* 9: 1323-1326, 2003; Belibi, F. A. and Edelstein, C. L. *Expert Opin. Investig. Drugs.* 19: 315-328, 2010). In zebrafish embryos, depletion of a cAMP-hydrolysing PDE enzyme subtype, PDE1A, resulted in development of a cystic 15 phenotype, while PDE1A over-expression partially rescued cystic phenotypes resulting from PC2 depletion (Sussman, C. R., Ward, C. J., Leightner, A. C., Smith, J. L., Agarwal, R., Harris, P. C., Torres, V. E. *J. Am. Soc. Nephrol.* 25: 2222-2230, 2014). Phosphodiesterase activation has been suggested as a therapeutic strategy for PKD treatment (Sun, Y., Zhou, 20 H. and Yang, B-X. *Acta Pharmacologica Sinica* 32: 805-816, 2011).

25

PDE4 long form activators of the present invention are therefore expected to be effective in the treatment, prevention or partial control of polycystic kidney disease.

### ***Polycystic Liver Disease***

30 Polycystic liver disease (PLD) is a rare inherited condition associated with hepatic cystogenesis (usually defined when number of cysts exceeds 20), which often occurs in association with ADPKD (Strazzabosco, M. and Somlo, S. *Gastroenterology* 140: 1855-1859, 2011; Gevers, T. J. and Drenth, J. P. *Curr. Opin. Gastroenterol.* 27: 294-300, 2010). PLD may have a different genetic pathology when compared to ADPKD, driven by mutated 35 proteins associated with the endoplasmic reticulum and the cilium. Increased cholangiocyte proliferation, neovascularisation and elevated fluid secretion act to drive liver cyst formation through dysregulation of multiple signal transduction pathways, including cAMP-mediated

signalling. Elevation of hepatic cAMP levels stimulates cAMP-dependent chloride and fluid secretion in biliary epithelial cells and increases cholangiocyte proliferation (Janssen, M. J. *et al.*, *J. Hepatol.* 52: 432-440, 2010). Somatostatin, which acts through a Gi-coupled mechanism to lower cAMP levels, reduced cholangiocyte proliferation and fluid secretion 5 (Gong, A.Y. *et al.*, *Am. J. Physiol. Cell. Physiol.* 284: C1205-1214, 2003). Furthermore, the synthetic somatostatin analogue, octreotide, showed efficacy in an animal model of PLD through a mechanism involving reduction in cAMP signalling (Masyuk, T.V. *et al.*, *Gastroenterology* 132: 1104-1116, 2007). PDE4 long form activators of the present invention may therefore be effective in the treatment, prevention or partial control of polycystic liver 10 disease due at least in part to cAMP.

#### ***Maturity onset diabetes of young type 5 (MODY5)***

MODY5 is a form of non-insulin-dependent diabetes mellitus associated with renal cysts. It is an autosomal dominant disorder caused by mutations in the gene encoding hepatocyte 15 nuclear factor-1 $\beta$  (HNF-1 $\beta$ ). The predominant clinical feature of patients affected by MODY5 is renal dysfunction, frequently diagnosed before the onset of diabetes. In some patients, HNF-1 $\beta$  mutations can result in additional phenotypic features, such as pancreatic atrophy, abnormal liver function and genital tract abnormalities. Studies in mice suggest that the mechanism responsible for renal cyst formation, associated with mutations of HNF-1 $\beta$ , 20 involves a severe defect of the transcriptional activation of PKD2, in addition to effects on uromodulin (UMOD) and PKD1 genes. Down-regulation of PKD1 and PKD2 is associated with cAMP-driven formation of renal cysts (Mancusi, S. *et al.*, *J. Nephrol.* 26: 207-12, 2013). HNF-1 $\beta$  also binds to the PDE4C promoter and regulates the expression of PDE4C (Ma *et al.*, *PNAS* 104: 20386, 2007).

25

PDE4 long form activators of the present invention are therefore expected to be effective in the treatment, prevention or partial control of the symptoms of MODY5.

#### ***Cardiac hypertrophy, heart failure and arrhythmia***

30 Localized regulation and integration of cAMP signalling are important for proper cardiac function and perturbation of this signalling can lead to heart failure. Upon chronic  $\beta$ -adrenergic receptor stimulation, cardiomyocyte hypertrophy is induced via elevated cAMP and activation of its downstream effectors, including PKA and Epac (Wang, L. *et al.*, *Cell. Signal.* 27: 908-922, 2015 and references therein). Cardiomyocyte hypertrophy increases 35 the risk of heart failure and arrhythmia.

PDE4 long form activators of the present invention may therefore be effective in the treatment, prevention or partial control of cardiac hypertrophy, heart failure and/or arrhythmia.

5 Diseases associated with increased cAMP-mediated signalling

***Disorders associated with activating mutations of the alpha subunit of the G protein (GNAS1)***

The G-protein Gs acts as a transducer for GPCRs that stimulate adenylyl cyclase activity and exert their biological effects by increasing intracellular cAMP levels. Gs is a 10 heterotrimeric protein composed of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits. Activating mutations in the gene, GNAS1, for the  $\alpha$ -subunit have been identified which lead to exaggerated abnormal cAMP signalling in a variety of tissues and give rise to a range of disorders.

***McCune-Albright syndrome***

15 McCune-Albright syndrome (MAS) is a rare genetic disorder typically characterised by three dominating features of precocious puberty, fibrous dysplasia of bone and café au lait lesions. The underlying molecular pathology for MAS involves an activating mutation of the GNAS1 gene (Diaz, A. Danon, M. and Crawford, J. *J. Pediatr. Endocrinol. Metab.* 20: 853-880, 2007). PDE4 long form activators of the present invention would therefore be expected to be 20 effective in the treatment, prevention or partial control of disorders associated with activating mutations of GNAS1, including McCune-Albright syndrome.

Amelioration of toxin-induced increases in adenylyl cyclase activity in infectious diseases.

25 Adenylyl cyclase, the enzyme responsible for production of cAMP, is a key biological target thought to be involved in mediating the effects of many bacterial toxins (Ahuja et al., *Critical Reviews in Microbiology*, 30: 187-196, 2004). These toxins produce their effects by raising cAMP levels through enhancement of host immune cell and/or pathogen related adenylyl cyclase activity. PDE4 long form activators of the present invention, by reducing cAMP levels, would therefore be expected to be of utility in the treatment or partial control of 30 symptoms of infectious diseases that are associated with elevated cAMP activity. The following are some examples of such infectious diseases:

***Cholera***

35 *Vibrio cholerae* produces cholera toxin, which through adenosine disphosphate ribosylation of the  $\alpha$  subunit of Gs leads to host cell adenylyl cyclase activation and cAMP production. Diarrhoea caused by cholera toxin is believed to be a result of excessive cAMP accumulation in the cells of the gastrointestinal tract.

***Whooping Cough***

*Bordetella pertussis* is the pathogen responsible for the childhood disease whooping cough.

5 *Bordetella pertussis* toxin stimulates adenosine disphosphate ribosylation of the  $\alpha$  subunit of Gi and indirectly augments cAMP levels in target cells. The bacterium also secretes an invasive adenylyl cyclase, which produces toxic cAMP levels and impairs host immune defence.

***Anthrax***

10 Anthrax is caused by *Bacillus anthracis* and whilst it is primarily an animal disease it can be transmitted to humans through contact. Anthrax infections are associated with widespread oedema, the development of which is thought to be driven by oedema toxin. The latter is an adenylyl cyclase and is activated by host calmodulin to produce abnormally high levels of cAMP that have a toxic effect on host immune cells.

15

***Tuberculosis***

20 *Mycobactrium tuberculosis* expresses a large and diverse range of adenylyl cyclases, which may play a role in virulence and generation of disease pathology. One adenylyl cyclase subtype, RV0386, has been demonstrated to enter host macrophages and elevate intracellular cAMP to cause toxicity (Agarwal et al., *Nature*, 460: 98-102, 2009).

PDE4 long form activators of the present invention may therefore be effective in the treatment, prevention or partial control of infectious diseases such as cholera, whooping cough, anthrax and tuberculosis.

25

**Diseases dependent upon activation of PKA by elevated cAMP.**

30 In eukaryotes, cAMP activates protein kinase A (PKA), which is also known as cAMP-dependent protein kinase. PKA is normally inactive as a tetrameric holoenzyme, consisting of two catalytic and two regulatory units, with the regulatory units blocking the catalytic centres of the catalytic units. cAMP binds to specific locations on the regulatory units of PKA and causes dissociation between the regulatory and catalytic units, thus activating the catalytic units. The active catalytic units catalyse the transfer of phosphate from ATP to specific residues of protein substrates, which may modulate the function of those protein substrates.

35

PDE4 long form activation reduces cAMP levels and cAMP mediated activation of PKA. PDE4 long form activators of the present invention would therefore be expected to be of

utility in the treatment or partial control of disorders where inhibitors of PKA show evidence of therapeutic effects.

Disorders that are dependent upon activation of PKA by cAMP may be identified by their 5 response to PKA inhibitors such as Rp-8-Br-cAMPS. Rp-8-Br-cAMPS is an analogue of cAMP that occupies the cAMP binding sites of PKA, preventing its dissociation and activation.

#### ***HIV infection and AIDS***

10 T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by Rp-8-Br-cAMPS than are normal T cells. Excessive activation of PKA by cAMP has been associated with the progressive T cell dysfunction in HIV infection (Aandahl, E. M. et al., *FASEB J.* 12: 855–862, 1998). Furthermore, *in vivo* administration of Rp-8-Br-cAMPS has been shown to restore T cell responses in retrovirus-infected mice (Nayjib, B. et al., *The 15 Open Immunology Journal*, 1: 20-24, 2008). PDE4 long form activators of the present invention are therefore expected to be of utility in the treatment, prevention or partial control of HIV infection and AIDS.

#### ***Common Variable Immunodeficiency (CVID)***

20 *In vitro* administration of Rp-8-Br-cAMPS has been shown to correct impaired secretion of the cytokine IL-10 by T cells from patients with Common Variable Immunodeficiency (CVID) (Holm, A. M. et al., *J. Immunol.* 170: 5772-5777, 2003). PDE4 long form activators of the present invention are therefore expected to be of utility in the treatment, prevention or partial control of CVID.

25 Diseases dependent upon activation of either or both of Epac1 and Epac2 by elevated cAMP.

In addition to PKA, cAMP activates another intracellular receptor, known as exchange protein directly activated by cAMP (Epac). There are two isoforms of Epac, Epac1 and 30 Epac2, both consisting of a regulatory region that binds cAMP and a catalytic region that promotes the exchange of GDP for GTP on the small G proteins, Rap1 and Rap2 of the Ras family. In addition, Epac proteins exert their functions through interactions with a number of other cellular partners at specific cellular loci. Pathophysiological changes in Epac signalling have been associated with a wide range of diseases (Breckler, M. et al., *Cell. Signal.* 23: 35 1257-1266, 2011).

Relevant disorders that are dependent upon activation of Epac proteins by cAMP may be identified by their response to Epac inhibitors, such as ESI-09, a novel non-cyclic nucleotide Epac1 and Epac2 antagonist that is capable of specifically blocking intracellular Epac-mediated Rap1 activation and Akt phosphorylation, as well as Epac-mediated insulin secretion in pancreatic beta cells (Almahariq, M. et al., *Mol. Pharmacol.* 83: 122-128, 2013).

### ***Melanoma***

Epac1 has been implicated in promoting migration and metastasis in melanoma (Baljinnyam, E. et al., *Pigment Cell Melanoma Res.* 24: 680-687, 2011 and references cited therein).

10 PDE4 long form activators of the present invention are therefore expected to be of utility in the treatment, prevention or partial control of melanoma.

### ***Pancreatic cancer***

It has recently been shown that Epac1 is markedly elevated in human pancreatic cancer cells as compared with normal pancreas or surrounding tissue (Lorenz, R. et al., *Pancreas* 37: 102-103, 2008).

20 Pancreatic cancer is often resistant to treatments that are usually effective for other types of cancer. Using the Epac inhibitor ESI-09, a functional role of Epac1 overexpression in pancreatic cancer cell migration and invasion was demonstrated (Almahariq, M. et al., *Mol. Pharmacol.* 83: 122-128, 2013). These findings are consistent with results based on RNAi silencing techniques and suggest that inhibition of Epac1 signalling could be an effective therapeutic strategy for pancreatic cancer.

25 PDE4 long form activators of the present invention would therefore be expected to be of utility in the treatment, prevention or partial control of pancreatic cancer.

### Diseases dependent upon modulation of cAMP-gated ion channels by elevated cAMP.

30 In addition to activation of PKA and Epac, another effector pathway for elevated cAMP is the activation of cAMP-gated ion channels. PDE4 long form activators of the present invention would therefore be expected to be of utility in the treatment of disorders where inhibitors of cAMP-gated ion channels show evidence of therapeutic effects.

### Diseases associated with increased activity of cAMP response element binding protein.

35 The cAMP response element binding protein (CREB) is an important transcription factor involved in the regulation of a variety of cellular functions such as cell proliferation, differentiation, survival, and apoptosis (Cho et al., *Crit Rev Oncog*, 16: 37-46, 2011). CREB

activity is regulated by kinase dependant phosphorylation through a range of extracellular signals, such as stress, growth factors and neurotransmitters. Phosphorylation leads to dimerisation of CREB, and together with other co-activator partner proteins, enables it to bind to promoter regions of target genes containing the cAMP response element (CRE sites) 5 and initiate transcriptional activity. The cAMP pathway (e.g. through cAMP-dependant protein kinase mediated phosphorylation) is an important positive modulator of CREB mediated biological activity. PDE4 long form activators of the present invention are therefore expected to be of utility in the treatment, prevention or partial control of disorders associated with elevated CREB activity.

10

### ***Leukaemia***

Bone marrow cells from acute lymphoid and myeloid leukaemia patients have been reported to overexpress CREB protein and mRNA (Crans-Vargas et al., *Blood*, 99: 2617-9, 2002; Cho et al., *Crit Rev Oncog*, 16: 37-46, 2011). Furthermore, the increased CREB level correlates 15 with poor clinical response in subjects with acute myeloid leukaemia (Crans-Vargas et al., *Blood*, 99: 2617-9, 2002; Shankar et al., *Cancer Cell*, 7:351-62, 2005). Upregulation of CREB is associated with stimulation of human leukaemia cell growth whilst downregulation inhibits myeloid cell proliferation and survival. PDE4 long form activators of the present 20 invention would be expected to reduce CREB activity and function through attenuation of cAMP mediated stimulation of CREB and therefore expected to have utility in the treatment, prevention or partial control of acute lymphoid and myeloid leukaemia.

### ***Prostate Cancer***

Abnormal excessive androgen activity is an important driver in the development of prostate 25 cancer as it stimulates the development of intraepithelial neoplasias (Merkle et al., *Cellular Signalling*, 23: 507-515, 2011). This is strongly supported by the use of androgen ablation approaches, involving chemical or surgical castration, in the treatment of prostate cancer. Cyclic AMP elevating agents such as forskolin can enhance androgen receptor activity through multiple intracellular mechanisms including androgen receptor activation through 30 phosphorylation and/or interaction with CREB. Epac1 activation has also been implicated in promoting cellular proliferation in prostate cancer (Misra, U. K. and Pizzo, S. V. *J. Cell. Biochem.* 108: 998-1011, 2009; Misra, U. K. and Pizzo, S. V. *J. Cell. Biochem.* 113: 1488-1500, 2012). PDE4 long form activators of the present invention are therefore expected to have utility in the treatment, prevention or partial control of prostate cancer.

35

### **Diseases associated with reduced activity of cAMP-hydrolysing PDE enzymes**

Loss-of-function mutations in gene(s) for cAMP-hydrolysing PDE isoforms other than PDE4, such as PDE8 and PDE11, have been detected in a number of diseases (Vezzosi, D. and Bertherat, J., *Eur. J. Endocrinol.* 165: 177-188, 2011; Levy, I. et al., *Curr. Opin. Pharmacol.* 11: 689-697, 2011; Azevedo, M. F. and Stratakis, C. A. *Endocr. Pract.* 17 Suppl 3: 2-7, 5 2011). These mutations can lead to abnormally high cAMP levels and/or duration of cAMP action with pathological consequences as detailed below. PDE4 long form activators of the present invention are therefore expected to be of utility in the treatment, prevention or partial control of these diseases, such as adrenocortical tumours, testicular cancer, PPNAD and Carney Complex.

10

### ***Adrenocortical tumours***

Adrenocortical tumours associated with an inactivating point mutation in the gene encoding PDE11A4 have decreased expression of PDE11A4 and increased cAMP levels (Horvath, A. et al., *Nat Genet.* 38: 794-800, 2006; Horvath, A. et al., *Cancer Res.* 66: 11571-11575, 2006; 15 Libé, R., et al., *Clin. Cancer Res.* 14: 4016-4024, 2008).

20

### ***Testicular Cancer***

Mutations that reduce PDE11A activity and increase cAMP levels have been observed in some forms of testicular cancer (Horvath, A. et al., *Cancer Res.* 69: 5301-5306, 2009).

25

### ***Primary pigmented nodular adrenocortical diseases (PPNAD)***

Mutations in the *PDE8B* gene have also been identified as a predisposing factor for PPNAD and the mutant protein shows reduced ability to degrade cAMP (Horvath, A., Mericq, V. and Stratakis, C. A. *N. Engl. J. Med.* 358: 750-752, 2008; Horvath, A. et al., *Eur. J. Hum. Genet.* 16: 1245-1253, 2008).

30

### ***Carney Complex***

In Carney Complex (CNC) caused by *PRKAR1A* mutations, some patients also have defects in PDE11A that may exert a synergistic effect to enhance abnormal activation of the cAMP signal transduction pathway, leading to adrenal and testicular cancer (Libé, R. et al., *J. Clin. Endocrinol. Metab.* 96: E208-214, 2011).

### **Treatment and posology**

By "treatment" herein is meant the treatment by therapy, whether of a human or a non-human animal (e.g., in veterinary applications) typically a non-human mammal, in which some desired therapeutic effect on the condition is achieved; for example, the inhibition of the progress of the disorder, including a reduction in the rate of progress, a halt in the rate of

progress, amelioration of the disorder or cure of the condition. Treatment as a prophylactic measure is also included. References herein to prevention or prophylaxis do not indicate or require complete prevention of a condition; its manifestation may instead be reduced or delayed via prophylaxis or prevention according to the present invention.

5

By a "therapeutically effective amount" herein is meant an amount of the one or more compounds of the invention or a pharmaceutical formulation comprising such one or more compounds, which is effective for producing such a therapeutic effect, commensurate with a reasonable benefit/risk ratio.

10

It will be appreciated that appropriate dosages of the compounds of the invention may vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination and the age, sex, weight, condition, general health and prior medical history of the patient. The amount of compound(s) and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action so as to achieve the desired effect. Administration *in vivo* can be effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to a person skilled in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician. In general, a suitable dose of the one or more compounds of the invention may be in the range of about 0.001 to 50 mg/kg body weight of the subject per day, preferably in a dosage of 0.01-25 mg per kg body weight per day, e.g., 0.01, 0.05, 0.10, 0.25, 0.50, 1.0, 2.5, 10 or 25 mg/kg per day. Where the compound(s) is a salt, solvate, prodrug or the like, the amount administered may be calculated on the basis of the parent compound and so the actual weight to be used may be increased proportionately.

#### Combination therapies

35 The compounds of the invention may also find application in mimicking or enhancing the effects of drugs known to produce their therapeutic effect through lowering of intracellular cAMP levels.

A number of therapeutically beneficial drugs have a primary mode of action involving lowering intracellular cAMP levels and/or cAMP-mediated activity, as summarised below. Since PDE4 long form activators of the present invention will also act to lower cAMP levels it

5 is expected that these agents will mimic and / or augment the pharmacological properties and therapeutic utility of drugs operating through a down-regulation of cAMP-mediated signalling. In certain embodiments, a compound of the invention is therefore provided as part of a combination therapy with another agent that lowers intracellular cAMP levels and/or cAMP-mediated activity. The combination therapy may be administered simultaneously, 10 contemporaneously, sequentially or separately. In one embodiment, the compound of the invention and the separate cAMP lowering agent are provided in a single composition, as described in more detail below. The combination therapy may comprise a compound of the invention and one or more of:

15 (i) a presynaptic  $\alpha$ -2 adrenergic receptor agonist, optionally clonidine, dexmedetomidine, or guanfacine;

(ii) a  $\beta$ -1 Adrenergic receptor antagonist ("beta-blocker"), optionally Atenolol, Metoprolol, Bisoprolol, Acebutolol, or Betaxolol.

#### ***Combination with $\alpha$ -2 Adrenergic receptor agonist***

20  $\alpha$ -2 Adrenergic receptor stimulation is known to reduce cAMP levels through a  $G_i$  protein-mediated inhibition of adenylyl cyclase activity in a broad range of tissues. In noradrenergic neurones in the brain and peripheral sympathetic nervous system, presynaptic  $\alpha$ -2 adrenergic receptor activation inhibits noradrenaline release and noradrenergic activity. Drugs (e.g. clonidine, dexmedetomidine, guanfacine) that act as agonists at these receptors 25 are effective in the treatment of a variety of clinical conditions. Clonidine, the prototypic agent, has shown therapeutic utility in the treatment of hypertension, neuropathic pain, opioid detoxification, insomnia, ADHD, Tourette syndrome, sleep hyperhidrosis, addiction (narcotic, alcohol and nicotine withdrawal symptoms), migraine, hyperarousal, anxiety and also as a veterinary anaesthetic. Lowering of cAMP levels by PDE4 long form activation may 30 be expected to yield similar effects to drugs acting through  $\alpha$ -2 adrenergic receptor stimulation. Furthermore, PDE4 long form activators of the present invention may be expected to potentiate the pharmacodynamic effects of  $\alpha$ -2 adrenergic receptor agonists when used in combination.

#### ***Combination with $\beta$ -1 Adrenergic receptor antagonist***

$\beta$ -1 Adrenergic receptor antagonists are used in the treatment a range of cardiovascular indications including hypertension, cardiac arrhythmias and cardioprotection following

myocardial infarction. Their primary mechanism of action involves reducing the effects of excessive circulating adrenaline and sympathetic activity, mediated by noradrenaline, particularly at cardiac  $\beta$ -1 adrenergic receptors. Endogenous and synthetic  $\beta$ -1 adrenergic receptor agonists stimulate adenylyl cyclase activity through  $G_s$  activation and raise 5 intracellular cAMP levels in a variety of tissues such as heart and kidney. Consequently, drugs that block  $\beta$ -1 adrenergic receptor mediated activity exert their pharmacological effects by attenuating the increase in cAMP mediated signalling. Given that PDE4 long form activation will also lower cAMP concentration and transduction in cardiac tissue, PDE4 long form activators of the present invention may be expected to find utility in the treatment or 10 partial control of hypertension, cardiac arrhythmias, congestive heart failure and cardioprotection. Additional non-cardiovascular therapeutic utility may be expected in disorders such as post-traumatic stress related disorder, anxiety, essential tremor and glaucoma, which also respond to  $\beta$ -1 adrenergic antagonist treatment. Furthermore, PDE4 long form activators of the present invention may be expected to potentiate the 15 pharmacodynamic effects of  $\beta$ -1 adrenergic receptor antagonists when used in combination.

#### Methods of treatment

In a further aspect, the present invention provides a small molecule activator of a PDE4 long form of Formulae I to V for use in a method for the treatment or prevention of a disease or 20 disorder in a patient in need of such therapy. The invention also provides a method of treating or preventing a disease or disorder in a patient in need thereof, comprising administering to a patient in need thereof an effective amount of a compound if the invention. The disease or disorder may be any disease or disorder described herein, including: a 25 disease associated with increased cAMP production and signalling (such as hyperthyroidism, Jansens's metaphyseal chondrodysplasia, hyperparathyroidism, familial male-limited precocious puberty, pituitary adenomas, Cushing's disease, polycystic kidney disease, polycystic liver disease, MODY5 and cardiac hypertrophy); diseases known to be associated with increased cAMP-mediated signalling, including disorders associated with activating mutations of the alpha subunit of the G protein (GNAS1) (such as McCune- 30 Albright syndrome); amelioration of toxin-induced increases in adenylyl cyclase activity in infectious diseases (such as cholera, whooping cough, anthrax, and tuberculosis); treatment of diseases known to be dependent upon activation of PKA by elevated cAMP (such as HIV infection and AIDS, and Common Variable Immunodeficiency (CVID)); treatment of diseases known to be dependent upon activation of either or both of Epac1 and Epac2 by elevated 35 cAMP (such as melanoma and pancreatic cancer); treatment of diseases dependent upon modulation of cAMP-gated ion channels by elevated cAMP; treatment of diseases known to be associated with increased activity of cAMP response element binding protein (such as

leukaemia and prostate cancer); treatment of diseases known to be associated with reduced activity of cAMP-hydrolysing PDE enzymes (such as adrenocortical tumours, testicular cancer, primary pigmented nodular adrenocortical diseases (PPNAD) and Carney Complex); and mimicking or enhancing the effects of drugs known to produce their therapeutic effect  
5 through lowering of intracellular cAMP levels.

As used herein, the terms “compound of the invention”, “compound of Formula I”, “compound of Formula Ia”, “compound of Formula II”, “compound of Formula IIa”, “compound of Formula III”, “compound of Formula IIIa”, “compound of Formula IV”,  
10 “compound of Formula Va”, “compound of Formula V” etc. include pharmaceutically acceptable derivatives thereof and polymorphs, isomers and isotopically labelled variants thereof. For example, reference to compounds of Formulae I to V includes pharmaceutically acceptable salts thereof. Furthermore, these terms include all the sub-embodiments of those compounds disclosed herein. Moreover, reference to compounds of Formulae I to V refers to  
15 all of Formulae I, II, IIa, III, IIIa, IV, IVa and V and, likewise, reference to compounds of Formulae II to V refers to all of Formulae II, IIa, III, IIIa, IV, IVa and V

#### Pharmaceutically acceptable derivatives

Pharmaceutically acceptable derivatives of a compound of the invention include  
20 pharmaceutically acceptable salts, solvates, esters, hydrates or amides thereof. The present invention further provides pharmaceutical compositions comprising a compound of the invention, including a pharmaceutically acceptable salt, solvate, ester, hydrate or amide thereof, in admixture with a pharmaceutically acceptable excipient(s), and optionally other therapeutic agents. The term “acceptable” means being compatible with the other  
25 ingredients of the composition and not deleterious to the recipient thereof. Compositions include e.g. those suitable for oral, sublingual, subcutaneous, intravenous, epidural, intrathecal, intramuscular, transdermal, intranasal, pulmonary, topical, local, or rectal administration, and the like, typically in unit dosage forms for administration.

30 The term “pharmaceutically acceptable salt” includes a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic or organic acids and bases. Compounds of the invention which contain basic, e.g. amino, groups are capable of forming pharmaceutically acceptable salts with acids. Examples of pharmaceutically acceptable acid addition salts of the compounds according to the invention include acid addition salts formed  
35 with organic carboxylic acids such as acetic, lactic, tartaric, maleic, citric, pyruvic, oxalic, fumaric, oxaloacetic, isethionic, lactobionic and succinic acids; organic sulfonic acids such

as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids.

Compounds of the invention which contain acidic, e.g. carboxyl, groups are capable of forming pharmaceutically acceptable salts with bases. Pharmaceutically acceptable basic salts of the compounds of the invention include, but are not limited to, metal salts such as alkali metal or alkaline earth metal salts (e.g. sodium, potassium, magnesium or calcium salts) and zinc or aluminium salts and salts formed with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines (e.g. diethanolamine), benzylamines, N-methyl-glucamine, amino acids (e.g. lysine) or pyridine.

Hemisalts of acids and bases may also be formed, e.g. hemisulphate salts.

Pharmaceutically acceptable salts of compounds of the compounds of the invention may be prepared by methods well-known in the art. For a review of pharmaceutically acceptable salts, see Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection and Use* (Wiley-VCH, Weinheim, Germany, 2002).

### Prodrugs

The invention includes prodrugs of the compounds of Formulae I to V. Prodrugs are derivatives of compounds of Formulae I to V (which may have little or no pharmacological activity themselves), which can, when administered *in vivo*, be converted into compounds of Formulae I to V.

Prodrugs can, for example, be produced by replacing functionalities present in the compounds of Formulae I to V with appropriate moieties which are metabolized *in vivo* to form a compound of Formulae I to V. The design of prodrugs is well-known in the art, as discussed in Bundgaard, *Design of Prodrugs 1985* (Elsevier), *The Practice of Medicinal Chemistry 2003*, 2<sup>nd</sup> Ed, 561-585 and Leinweber, *Drug Metab. Res.* **1987**, 18: 379.

Examples of prodrugs of compounds of Formulae I to V are amides and esters of those compounds. For example, where the compound of Formulae I to V contains a carboxylic acid group (-COOH), the hydrogen atom of the carboxylic acid group may be replaced in order to form an ester (e.g. the hydrogen atom may be replaced by C<sub>1-6</sub>alkyl). Where a compound contains an alcohol group (-OH), the hydrogen atom of the alcohol group may be replaced in order to form an ester (e.g. the hydrogen atom may be replaced by -C(O)C<sub>1-6</sub>alkyl).

### Solvates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compounds described herein, which may be used in the any one of the uses/methods described. The term solvate is used herein to refer to a complex of solute, such as a 5 compound or salt of the compound, and a solvent. If the solvent is water, the solvate may be termed a hydrate, for example a mono-hydrate, di- hydrate, tri-hydrate etc, depending on the number of water molecules present per molecule of substrate.

### Stereoisomers

10 It will be appreciated that the compounds of the present invention may exist in various stereoisomeric forms and the compounds of the present invention as hereinbefore defined include all stereoisomeric forms and mixtures thereof, including enantiomers and racemic mixtures. The present invention includes within its scope the use of any such stereoisomeric form or mixture of stereoisomers, including the individual enantiomers of the compounds of 15 Formulae I to V as well as wholly or partially racemic mixtures of such enantiomers. Where appropriate, isomers can be separated from their mixtures by the application or adaptation of known methods (e.g. chromatographic techniques and recrystallisation techniques). Where appropriate, isomers can be prepared by the application or adaptation of known methods (e.g. asymmetric synthesis).

20

### Isotopes

The invention includes pharmaceutically acceptable isotopically-labelled compounds of Formulae I to V wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass 25 number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as  $^2\text{H}$  and  $^3\text{H}$ , carbon, such as  $^{11}\text{C}$ ,  $^{13}\text{C}$  and  $^{14}\text{C}$ , chlorine, such as  $^{36}\text{Cl}$ , fluorine, such as  $^{18}\text{F}$ , iodine, such as  $^{123}\text{I}$  and  $^{125}\text{I}$ , nitrogen, such as  $^{13}\text{N}$  and  $^{15}\text{N}$ , 30 oxygen, such as  $^{15}\text{O}$ ,  $^{17}\text{O}$  and  $^{18}\text{O}$ , and sulphur, such as  $^{35}\text{S}$ . Certain isotopically-labelled compounds of Formulae I to V, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes  $^3\text{H}$  and  $^{14}\text{C}$  are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with positron emitting isotopes, such as  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{15}\text{O}$  and  $^{13}\text{N}$ , can be useful in Positron Emission Topography (PET) studies for examining substrate 35 receptor occupancy. Isotopically-labelled compounds of Formulae I to V can generally be prepared by conventional techniques known to those skilled in the art or by processes

analogous to those described herein using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

Pharmaceutical compositions

5 For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

Formulations suitable for oral administration may also be designed to deliver the compounds of the invention in an immediate release manner or in a rate-sustaining manner, wherein the 10 release profile can be delayed, pulsed, controlled, sustained, or delayed and sustained or modified in such a manner which optimises the therapeutic efficacy of the said compounds. Means to deliver compounds in a rate-sustaining manner are known in the art and include slow release polymers that can be formulated with the said compounds to control their release.

15

Examples of rate-sustaining polymers include degradable and non-degradable polymers that can be used to release the said compounds by diffusion or a combination of diffusion and polymer erosion. Examples of rate-sustaining polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, sodium 20 carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthum gum, polymethacrylates, polyethylene oxide and polyethylene glycol.

Liquid (including multiple phases and dispersed systems) formulations include emulsions, suspensions, solutions, syrups and elixirs. Such formulations may be presented as fillers in 25 soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

30

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, *Expert Opinion in Therapeutic Patents* 2001, 11(6): 981-986.

35 The formulation of tablets is discussed in H. Lieberman and L. Lachman, *Pharmaceutical Dosage Forms: Tablets* 1980, vol. 1 (Marcel Dekker, New York).

For administration intranasally or by inhalation, the active ingredient may be presented in the form of a dry powder from a dry powder inhaler or in the form of an aerosol spray of a solution or suspension from a pressurised container, pump, spray, atomiser or nebuliser.

5 For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

10

For parenteral administration, the compounds of the invention may be administered directly into the blood stream, into subcutaneous tissue, into muscle, or into an internal organ. Suitable means for administration include intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and

15 subcutaneous. Suitable devices for administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous or oily solutions. Where the solution is aqueous, excipients such as sugars (including but not restricted to glucose, mannitol,

20 sorbitol, etc.) salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9) may be used. For some applications, the compounds of the invention may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water (WFI).

25 Parenteral formulations may include implants derived from degradable polymers such as polyesters (e.g. polylactic acid, polylactide, polylactide-co-glycolide, polycapro-lactone, polyhydroxybutyrate), polyorthoesters and polyanhydrides. These formulations may be administered *via* surgical incision into the subcutaneous tissue, muscular tissue or directly into specific organs.

30

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

35 The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the

incorporation of co-solvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

Mixed with such pharmaceutically acceptable excipients, e.g. as described in the standard

5 reference, Gennaro, A.R. et al, Remington: The Science and Practice of Pharmacy (21st Edition, Lippincott Williams & Wilkins, 2005, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules, suppositories or patches. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, 10 e.g. as an injection preparation or as an aerosol spray, in the form of a solution, suspension, or emulsion.

For making solid dosage units, the use of conventional additives such as fillers, colorants,

polymeric binders and the like is contemplated. In general any pharmaceutically acceptable

15 additive that does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically 20 acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

The invention further includes a pharmaceutical composition, as hereinbefore described, in

combination with packaging material suitable for said composition, said packaging material

25 including instructions for the use of the composition for the use as hereinbefore described.

In some embodiments, the one or more compounds of the present invention may be used in

combination therapies for the treatment of the described conditions i.e., in conjunction with

other therapeutic agents. For the case of active compounds combined with other therapies

the two or more treatments may be given in individually varying dose schedules and *via*

30 different routes.

The combination of the agents listed above with a compound of the present invention would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

35

Where a compound of the invention is administered in combination therapy with one, two, three, four or more, preferably one or two, preferably one other therapeutic agents, the

compounds can be administered simultaneously or sequentially. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer period apart where required), the precise dosage regimen being commensurate with  
5 the properties of the therapeutic agent(s).

In one embodiment, the invention provides a product comprising a compound of the invention and another therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment or  
10 prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required. Products provided as a combined preparation include a composition comprising a compound of the invention and the other therapeutic agent together in the same pharmaceutical composition, or the compound of the invention and the other therapeutic agent in separate form, e.g. in the form of a kit.

15

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of the invention and another therapeutic agent. Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, as described above.

20 In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

25

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

30

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to  
35 physicians (e.g. in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician)

shortly before administration; (iii) in the patient themselves, e.g. during sequential administration of the compound of the invention and the other therapeutic agent.

Method of manufacture & method of treatment

5 The invention also provides the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent in the manufacture

10 of medicament for treating a disease or condition mediated by cAMP for the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required, wherein the medicament is prepared for administration with a compound of the invention.

15 The invention also provides a compound of the invention for use in the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required, wherein the compound of the invention is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in the treatment or prevention of disorders where

20 a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required, wherein the other therapeutic agent is prepared for administration with a compound of the invention. The invention also provides a compound of the invention for use in for the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is

25 required, wherein the compound of the invention is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required, wherein the other therapeutic agent is administered with a compound of the invention.

30 The invention also provides the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP) is required, wherein the patient has previously (e.g. within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent in the manufacture of a medicament for the treatment or prevention of disorders where a reduction of second messenger responses mediated by cyclic 3',5'-adenosine monophosphate (cAMP)

is required, wherein the patient has previously (e.g. within 24 hours) been treated with a compound of the invention.

In one embodiment, the other therapeutic agent is:

5 (i) a presynaptic  $\alpha$ -2 adrenergic receptor agonist, optionally clonidine, dexmedetomidine, or guanfacine;  
(ii) a  $\beta$ -1 Adrenergic receptor antagonist ("beta-blocker"), optionally Atenolol, Metoprolol, Bisoprolol, Acebutolol, or Betaxolol.

10 **Examples**

The present invention will now be further described by way of the following non-limiting examples and with reference to the Tables and Figures:

15 Table 1 shows the structures of small molecule PDE4 long form activators, Examples 1 to 32, according to the present invention.

Table 2 shows enzyme assay data for PDE4D5, a long form of PDE4.

20 Table 3 shows enzyme assay data for PDE4B1, another long form of PDE4.

Table 4 shows enzyme assay data for PDE4B2, a short form of PDE4.

25 Figure 1 shows activation of PDE4 long form, PDE4D5, and a lack of activation of PDE4 short form, PDE4B2, by Example 2, demonstrating selectivity for activation of the PDE4 long form over the PDE4 short form.

Figure 2 shows a reduction in intracellular cAMP levels in Madin-Darby canine kidney (MDCK) cells treated with Example 1 (10  $\mu$ M) for 10 min prior to treatment with forskolin (F) (10  $\mu$ M) for 2 min.

30 Figure 3 shows inhibition of PGE2-stimulated cyst formation in a 3D culture of MDCK cells treated with PDE4 long form activator, Example 28.

**Experimental details**

35 **Preparation of PDE4 long form activators (Examples 1 to 32)**

Reactions were monitored by thin layer chromatography (Merck Millipore TLC Silica Gel 60 F<sub>254</sub>). Flash column chromatography was performed on Phenomenex Strata® or Biotage

Isolera® pre-packed silica gel columns. NMR spectra were recorded using a Bruker AV300 or a Bruker 400 MHz spectrometer at 25 °C. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dd (doublet of doublet), dt (doublet of triplet).

5

Example 1: Methyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate

Step 1: *N*-(3-Fluorobenzyl)-2-chloroacetamide

10 To a stirred solution of 3-fluorobenzylamine (3.32g, 26.6 mmol) and triethylamine (3.87 mL, 27.9 mmol) in dry dichloromethane (80 mL) at -5°C (salt / ice bath) under argon was added chloroacetyl chloride (2.22 mL, 27.9 mmol), dropwise over 10 minutes. The reaction mixture was stirred at -5°C for a further 30 minutes, then stirred at room temperature for 2 hours. The mixture was then diluted with chloroform (50 mL), washed with saturated aqueous 15 sodium bicarbonate solution (3 x 20 mL) and then brine (3 x 20 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered through a 2cm silica gel pad, washing with 2% methanol in chloroform, and the filtrate concentrated under reduced pressure to afford *N*-(3-fluorobenzyl)-2-chloroacetamide as a white solid (5.15 g, 25.5 mmol).

20 Step 2: *N*-(3-Fluorobenzyl)-2-iodoacetamide

To a stirred solution of *N*-(3-fluorobenzyl)-2-chloroacetamide (5.13 g, 25.4 mmol) in acetonitrile (50 mL) was added sodium iodide (4.00g, 26.7 mmol). The mixture was refluxed at 90°C (oil bath) for 3h and then allowed to cool to room temperature. The precipitate was filtered off using a short pad of Celite®, washing with dichloromethane. The filtrate was 25 concentrated under reduced pressure to afford crude product as a light brown solid. The crude product was purified by flash column chromatography, eluting with 5% to 35% ethyl acetate in petroleum ether, to afford *N*-(3-fluorobenzyl)-2-iodoacetamide as a pale yellow powder (7.11 g, 24.3 mmol).

30 Step 3: 4-Chloro-3-fluorobenzene carboximidic acid methyl ester, hydrochloride salt

Hydrochloric acid solution in methanol (3N; 3 mL), chlorotrimethylsilane (3.26 g, 30.0 mmol) and 4-chloro-3-fluorobenzonitrile (2.33 g, 15 mmol) were added sequentially to a dry reaction tube, with stirring under argon at room temperature. The mixture was heated to 50°C with stirring for 1h, during which time a thick white precipitate formed in the mixture. Cyclopentyl 35 methyl ether (5 mL) was added and the mixture was heated to 50°C for a further 1h, with periodic shaking to loosen the precipitate. The mixture was then allowed to cool to room temperature and the solid filtered off, washing with cyclopentyl methyl ether (2 x 5 mL) to

afford 4-chloro-3-fluorobenzene carboximidic acid methyl ester, hydrochloride salt (1.43 g, 6.9 mmol).

Step 4: Methyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate

5 A mixture of 4-chloro-3-fluorobenzene carboximidic acid methyl ester, hydrochloride salt (374 mg, 1.8 mmol), hydrazine hydrate (1.75 mL, 36.0 mmol) and aluminium chloride (240 mg, 1.8 mmol) in toluene (25 mL) was heated to reflux for 3h. The mixture was concentrated under reduced pressure, taken up in toluene and concentrated under reduced pressure twice more. The residue was suspended in a toluene / acetonitrile mixture (12:1, 26 mL),  
10 methyl chlorooxacetate (0.83 mL, 9.0 mmol) was added and the mixture was heated to reflux for 2h. The mixture was concentrated under reduced pressure and purified by flash column chromatography, eluting with 20% to 25% ethyl acetate in petroleum ether, to afford methyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate (43 mg, 0.17 mmol).

15 Step 5: Methyl 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate

To a stirred solution of methyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate (21.5 mg, 0.084 mmol) in dimethyl formamide (2 mL) under argon at 0°C was added sodium hydride (60% dispersion in mineral oil, 4.0 mg, 0.10 mmol). After 10 minutes, a solution of *N*-  
20 (3-fluorobenzyl)-2-iodoacetamide (30 mg, 0.10 mmol) in dimethylformamide (3 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 72h. The mixture was concentrated under reduced pressure and then partitioned between ethyl acetate (20 mL) and water (10 mL). The organic layer was separated, washed with brine (2 x 10 mL), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced  
25 pressure. The crude product was purified by flash column chromatography, eluting with 40% ethyl acetate in petroleum ether to afford methyl 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate as a white solid (4.0 mg, 0.010 mmol).

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.92 (1H, dd, *J* 9.7, 1.9), 7.87 (1H, ddd, *J* 8.3, 1.9, 0.8), 7.47 (1H, dd, *J* 8.3, 7.3), 7.27–7.34 (1H, m), 6.94–7.06 (3H, m), 6.12 (1H, broad t, *J* 5.0), 5.38 (2H, s), 4.50 (2H, d, *J* 6.0), 4.04 (3H, s).

Example 2: Ethyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate

The title compound was prepared according to the method of Example 1, using benzylamine instead of 3-fluorobenzylamine in Step 1 and ethyl chlorooxoacetate instead of methyl chlorooxoacetate in Step 4.

5  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.92 (1H, dd,  $J$  9.9, 1.9), 7.87 (1H, ddd,  $J$  8.3, 1.9, 0.8), 7.46 (1H, dd,  $J$  8.2, 7.6), 7.24–7.36 (5H, m), 6.10 (1H, broad s), 5.36 (2H, s), 4.50 (2H, q,  $J$  7.1), 4.49 (2H, d,  $J$  5.6), 1.45 (3H, t,  $J$  7.1).

Example 3: Methyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate

10

The title compound was prepared according to the method of Example 1, using benzylamine instead of 3-fluorobenzylamine in Step 1.

15  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.91 (1H, dd,  $J$  9.8, 1.9), 7.86 (1H, ddd,  $J$  8.3, 1.9, 0.8), 7.46 (1H, dd,  $J$  8.2, 7.5), 7.25–7.37 (5H, m), 6.10 (1H, broad s), 5.37 (2H, s), 4.50 (2H, d,  $J$  5.7), 4.03 (3H, s).

Example 4: Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1*H*-1,2,4-triazole-5-carboxylate

20 Step 1: Ethyl 4-chloro-3-fluorobenzimidate hydrochloride salt

Anhydrous HCl gas was bubbled through ice-cold absolute ethanol (150 mL) for 30 min. To this, a solution of 4-chloro-3-fluorobenzonitrile (25 g, 160 mmol) in chloroform (70 mL) was added and HCl was further purged for 2 h. The resulting mixture was allowed to warm to room temperature, and the flask was capped with a glass stopper. The resulting solution was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and the residue was diluted with ether (150 mL). The resulting white precipitate was filtered and washed with ether (3 x 50 mL) to obtain ethyl 4-chloro-3-fluorobenzimidate hydrochloride (22 g) as a white solid.

30 Step 2: *t*-Butyl 2-[(4-chloro-3-fluorophenyl)(imino)methyl]hydrazine-1-carboxylate

To a stirred solution of ethyl 4-chloro-3-fluorobenzimidate hydrochloride (10 g, 42 mmol) in absolute ethanol (100 mL) under nitrogen was added trimethylamine (17.5 mL, 126 mmol). After 10 min at room temperature, *t*-butyl carbazate (11.1 g, 84 mmol) was added portion wise. The resulting mixture was heated to 50°C for 16 h, then cooled to room temperature.

35 Volatiles were removed using a rotary evaporator and the residue obtained was diluted with water. The resultant white precipitate was filtered, washed with water, and excess of ether. The white solid obtained was dried under vacuum at 50°C for 4 h to afford *t*-butyl 2-[(4-

chloro-3-fluorophenyl)(imino)methyl]hydrazine-1-carboxylate (20 g), which was used without further purification.

Step 3: 4-Chloro-3-fluorobenzimidohydrazide hydrochloride

5 To an ice-cold solution of *t*-butyl 2-[(4-chloro-3-fluorophenyl)(imino)methyl]hydrazine-1-carboxylate (20 g, 69.7 mmol) in  $\text{CH}_2\text{Cl}_2$ / methanol (200 mL, 9:1) was added 4 M HCl in dioxane (87 mL, 348.5 mmol). The resulting mixture was stirred at room temperature for 20 h. Then all solvent was removed on rotary evaporator and the residue was diluted with ether (100 mL). The solid obtained was filtered and washed with ether (3 X 50 mL) to afford 4-10 chloro-3-fluorobenzimidohydrazide, hydrochloride salt (14 g) as a white solid.

Step 4: Ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate

In a sealed-tube, 4-chloro-3-fluorobenzimidohydrazide, hydrochloride salt (8 g, 35.7 mmol) was added to acetonitrile/ toluene (100 mL, 3:1) under nitrogen. The suspension was cooled 15 to 0°C and diisopropylethylamine (18.6 mL, 107.1 mmol) was added, followed by ethyl 2-chloro-2-oxoacetate (7.3 g, 53.6 mmol). The resulting solution was heated to 90°C for 4 h. The reaction was cooled to room temperature and all volatiles were removed under reduced pressure. The residue obtained was purified by flash column chromatography, eluting with 15% to 35% ethyl acetate in petroleum ether, to afford ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-20 1,2,4-triazole-5-carboxylate (5.0 g) as a white solid.

Step 5: Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate

Alkylation of ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate with *N*-(3-fluorobenzyl)-2-iodoacetamide was carried out according to the procedure of Example 1, Step 5, to afford the title compound as an off white solid.

$^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz,  $\text{DMSO}-d_6$ ) 8.87 (1H, t, *J* 5.6), 7.93 – 7.88 (2H, m), 7.75 (1H, t, *J* 8.0), 7.40 – 7.35 (1H, m), 7.14 – 7.06 (3H, m), 5.37 (2H, s), 4.40 – 4.35 (4H, m), 1.32 (3H, t, *J* 7.2).

30

Example 5: Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate

The title compound was prepared according to the method of Example 4, using *N*-(3-methoxybenzyl)-2-iodoacetamide instead of *N*-(3-fluorobenzyl)-2-iodoacetamide in Step 5. *N*-(3-methoxybenzyl)-2-iodoacetamide was prepared according to the method of Example 1, Steps 1 and 2, using 3-methoxybenzylamine instead of 3-fluorobenzylamine.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.80 (1H, t, *J* 5.6), 7.93 – 7.88 (2H, m), 7.74 (1H, t, *J* 8.0), 7.28 (1H, t, *J* 8.0), 6.87 – 6.82 (3H, m), 5.35 (2H, s), 4.37 (2H, q, *J* 7.0), 4.30 (2H, d, *J* 5.6), 3.75 (3H, s), 1.32 (3H, t, *J* 7.0).

5 General procedure 1: Ester hydrolysis

The following procedure was used to prepare carboxylic acid derivatives, Examples 6 and 7, from ethyl ester derivatives, Examples 4 and 5, respectively: To an ice-cold solution of ethyl ester derivative (1 equi.) in THF/ methanol (10 mL, 1:1) was added 1.5 equi of LiOH·H<sub>2</sub>O in water (5 mL). The resulting solution was stirred at room temperature for 4 h. Volatiles were 10 evaporated under vacuum and the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and neutralized with dilute HCl. The organic layer was washed with saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried over anhydrous sodium sulphate, filtered and 15 concentrated under reduced pressure. The crude solid was purified by flash column chromatography, eluting with 30% to 60% ethyl acetate in petroleum ether to afford the required carboxylic acid.

Example 6: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylic acid

20 The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate (Example 4) according to General Procedure 1.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 13.45 (1H, bs), 9.65 (1H, t, *J* 6.0), 7.96 – 7.91 (2H, m), 7.77 (1H, t, *J* 8.0), 7.40 – 7.37 (1H, m), 7.19 – 7.01 (3H, m), 5.36 (2H, s), 4.48 (2H, d, *J* 6.0).

25

Example 7: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylic acid

30 The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate (Example 5) according to General Procedure 1.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 13.40 (1H, bs), 9.56 (1H, t, *J* 5.9), 7.96 – 7.88 (2H, m), 7.77 (1H, t, *J* 8.0), 7.25 (1H, t, *J* 8.0), 6.91 (2H, bs), 6.83 (1H, d, *J* 8.0), 5.37 (2H, s), 4.43 (2H, d, *J* 5.9), 3.74 (3H, s).

General procedure 2: Synthesis of unsubstituted amides from esters

The following procedure was used to prepare unsubstituted amides, Examples 8 and 9, from ethyl ester derivatives, Examples 4 and 5, respectively: The ethyl ester derivative was added to a stirred saturated solution of ammonia in ethanol (2 mL/ 100 mg of ester). The resulting solution was heated in a steel bomb at 100°C for 4 h. The reaction was cooled to room  
5 temperature. Solvent was evaporated on rotary evaporator and the crude product obtained was purified by flash column chromatography, eluting with 30% to 60% ethyl acetate in petroleum ether, to afford the required amide.

10 Example 8: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate (Example 4) according to General Procedure 2.

15 <sup>1</sup>H NMR:  $\delta_H$  (400 MHz, DMSO-*d*6) 8.78 (1H, t, *J* 5.6), 8.32 (1H, bs), 8.07 (1H, bs), 7.94 – 7.87 (2H, m), 7.77 (1H, t, *J* 8.0), 7.40 – 7.35 (1H, m), 7.15 – 7.06 (3H, m), 5.40 (2H, s), 4.34 (2H, d, *J* 5.6).

20 Example 9: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate (Example 5) according to General Procedure 2.

25 <sup>1</sup>H NMR:  $\delta_H$  (400 MHz, DMSO-*d*6) 8.72 (1H, t, *J* 4.8), 8.31 (1H, s), 8.05 (1H, s), 7.94 – 7.87 (2H, m), 7.76 (1H, t, *J* 7.9), 7.24 (1H, t, *J* 7.8), 6.86 – 6.81 (3H, m), 5.39 (2H, s), 4.29 (2H, d, *J* 5.6), 3.75 (3H, s).

General procedure 3: Synthesis of substituted amides from esters

30 The following procedure was used to prepare substituted amides, Examples 10, 11 and 12, from ethyl ester derivatives, Examples 4 and 5: To a solution of the ethyl ester derivative (1 equiv.) in toluene was added DABAL-Me<sub>3</sub> (1.5 equiv.) and a THF solution of methyl amine or dimethyl amine (1M; 1.5 equiv.). The resulting mixture was heated to 80°C for 4 to 8 h (monitored by TLC). The reaction was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with dilute HCl and brine. The organic layer was then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure.

The crude solid was purified by flash column chromatography, eluting with 25% to 50% ethyl acetate in petroleum ether to afford the required amide.

Example 10: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-N-methyl-1*H*-

5 1,2,4-triazole-5-carboxamide

The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1*H*-1,2,4-triazole-5-carboxylate (Example 4) and methyl amine according to General Procedure 3.

10  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.96 – 8.94 (1H, m), 8.80 (1H, t, *J* 6.0), 7.94 – 7.87 (2H, m), 7.77 (1H, t, *J* 8.0), 7.40 – 7.34 (1H, m), 7.16 – 7.12 (2H, m), 7.10 – 7.06 (1H, m), 5.41 (2H, s), 4.34 (2H, d, *J* 6.0), 2.81 (3H, d, *J* 5.0).

Example 11: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-N,N-

15 dimethyl-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1*H*-1,2,4-triazole-5-carboxylate (Example 4) and dimethyl amine according to General Procedure 3.

20  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.85 (1H, t, *J* 5.8), 7.92 – 7.85 (2H, m), 7.74 (1H, t, *J* 8.0), 7.40 – 7.35 (1H, m), 7.14 – 7.06 (3H, m), 5.20 (2H, s), 4.35 (2H, d, *J* 5.8), 3.25 (3H, s), 3.02 (3H, s).

Example 12: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-N-methyl-

25 1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared from ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-1*H*-1,2,4-triazole-5-carboxylate (Example 5) and methyl amine according to General Procedure 3.

30  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.95 (1H, q, *J* 4.8), 8.74 (1H, t, *J* 5.6), 7.94 – 7.87 (2H, m), 7.79 – 7.75 (1H, m), 7.24 (1H, t, *J* 7.8), 6.87 – 6.81 (3H, m), 5.40 (2H, s), 4.29 7.75 (2H, d, *J* 5.6), 3.75 (3H, s), 2.80 (3H, d, *J* 4.8).

Example 13: 2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-N-(3-

35 fluorobenzyl)acetamide

Step 1: 3-(4-Chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxamide

Ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate (prepared as described in Example 4; 800 mg, 2.97 mmol) was added to a stirred saturated solution of ammonia in ethanol (16 mL). The resulting solution was heated in a steel bomb at 100°C for 4 h. The reaction was cooled to room temperature. Solvent was evaporated under reduced pressure 5 and the crude product obtained was purified by flash column chromatography, eluting with 40% to 60% ethyl acetate in petroleum ether, to give 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxamide (600 mg) as a pale yellow solid.

Step 2: 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carbonitrile

10 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxamide (600 mg, 2.5 mmol) was added portion wise to phosphorous oxychloride (10 mL) and the resulting mixture was heated at 90°C for 3 h. Excess of phosphorous oxychloride was removed under reduced pressure and the residual mass was diluted with ice water (50 mL), CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and separated. The organic layer was washed with saturated sodium bicarbonate (20 mL) and brine (20 mL).  
15 The organic layer was then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography, eluting with 40% to 70% ethyl acetate in petroleum ether to give 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carbonitrile (400 mg) as a white solid.

20 Step 3: 2-(3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl)-*N*-(3-fluorobenzyl)acetamide  
To a degassed solution, in a microwave tube, of 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carbonitrile (80 mg, 0.36 mmol) in dry acetone (5 mL) was added anhydrous potassium carbonate (150 mg, 1.8 mmol). *N*-(3-fluorobenzyl)-2-iodoacetamide (70 mg, 0.4 mmol) was added and the resulting mixture was heated in a microwave at 70°C for 2 h. All 25 solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (25 mL) and water (25 mL). The organic layer was washed with water (20 mL) and brine (20 mL). The organic layer was then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography, eluting with 40% to 70% ethyl acetate in petroleum ether to afford 2-(3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl)-*N*-(3-fluorobenzyl)acetamide (12 mg)  
30 as a white solid.  
35 <sup>1</sup>H NMR: δ<sub>H</sub> (400 MHz, DMSO-*d*6) 8.99 (1H, t, *J* 5.6), 7.86 – 7.79 (2H, m), 7.64 – 7.61 (1H, m), 7.38 – 7.33 (1H, m), 7.11 – 7.09 (1H, m), 7.09 – 7.01 (2H, m), 5.26 (2H, s), 4.31 (2H, d, *J* 5.6).

Example 14: *N*-(3-fluorobenzyl)-2-[5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl]acetamide

Step 1: 5-Methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazole

To a solution of sodium methoxide in dry methanol (0.5M; 4 mL) was added 3-pyridinecarbonitrile (1.04 g, 10 mmol). The resulting solution was stirred at room temperature under argon for 2.5h. A solution of acethydrazide (0.74 g, 10 mmol) in dry methanol (10 mL) was added and the mixture was heated to reflux for 3h. The mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography, eluting with 1% to 8% methanol in dichloromethane, to afford 5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazole (78 mg, 0.49 mmol).

10

Step 2: *N*-(3-Fluorobenzyl)-2-[5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl]acetamide

To a stirred solution of 5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazole (78 mg, 0.49 mmol) in dimethyl formamide (3 mL) under argon at 0°C was added sodium hydride (60% dispersion in mineral oil, 25.5 mg, 0.64 mmol). After 10 minutes, *N*-(3-fluorobenzyl)-2-iodoacetamide (187 mg, 0.64 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 20h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography, eluting with 1% to 5% methanol in dichloromethane and the product recrystallized from chloroform / hexane to afford *N*-(3-fluorobenzyl)-2-[5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl]acetamide (17 mg, 0.052 mmol).

<sup>1</sup>H NMR:  $\delta$ <sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 9.25 (1H, d, *J* 1.4), 8.58 (1H, dd, *J* 4.9, 1.6), 8.27 (1H, dt, *J* 7.9, 2.0), 7.34 (1H, ddd, *J* 8.0, 4.9, 0.8), 7.23–7.31 (1H, m), 6.92–7.02 (3H, m), 6.91 (1H, broad s), 4.86 (2H, s), 4.47 (2H, d, *J* 5.9), 2.55 (3H, s).

25 Example 15: *N*-benzyl-2-[3-(4-chlorophenyl)-1*H*-pyrazol-1-yl]acetamide

3-(4-Chlorophenyl)-1*H*-pyrazole (100 mg, 0.56 mmol) was dissolved in acetonitrile (3 mL) and DMF (5 drops). Anhydrous sodium carbonate (71 mg, 0.67 mmol) was added. The mixture was stirred at room temperature for 30 minutes, after which *N*-benzyl-2-iodoacetamide (prepared as for Example 3; 184 mg, 0.67 mmol) was added. The reaction was heated to reflux for 22 hours. The mixture was cooled to room temperature and partitioned between water and ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with 25% to 50% ethyl acetate in petroleum ether to afford *N*-benzyl-2-[3-(4-chlorophenyl)-1*H*-pyrazol-1-yl]acetamide (45.6 mg, 0.14 mmol).

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.66–7.70 (2H, m), 7.50 (1H, d, *J* 2.4), 7.33–7.38 (2H, m), 7.19–7.31 (5H, m), 6.76 (1H, broad s), 6.60 (1H, d, *J* 2.4), 4.88 (2H, s), 4.46 (2H, d, *J* 5.8).

Example 16: 2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-methoxybenzyl)acetamide

The title compound was prepared according to the method of Example 13, using *N*-(3-methoxybenzyl)-2-iodoacetamide instead of *N*-(3-fluorobenzyl)-2-iodoacetamide in Step 3.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.94 (1H, t, *J* 5.6), 7.87–7.79 (2H, m), 7.64–7.62 (1H, m), 7.22 (1H, t, *J* 7.6), 6.83–6.79 (2H, m), 6.74 (1H, d, *J* 7.6), 5.22 (2H, s), 4.27 (2H, d, *J* 5.6),

3.74 (3H, s).

General Procedure 4: Synthesis of alkylated 1*H*-1,2,4-triazole-5-carboxamides from ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate

15 Step 1: 5-Carboxamide formation

To a degassed solution of ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate (1 equiv.) and triethylamine (3 equiv.) in dry toluene was added DABAL-Me<sub>3</sub> (1.5 equiv.), followed by the corresponding amine (1.2 equiv.). The resulting mixture was heated in a sealed-tube at 110 °C for 1 to 3 h (monitored by TLC). The reaction was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with dilute aqueous hydrochloric acid and brine. The organic layer was then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography, eluting with 50% to 80% ethyl acetate in petroleum ether to afford the required amide.

25

Step 2: Alkylation

To a stirred solution of the amide from Step 1 (1 equiv.) in dry acetone at room temperature under nitrogen was added potassium carbonate (2 equiv.). After 15 minutes, *N*-(3-fluorobenzyl)-2-iodoacetamide or *N*-(3-methoxybenzyl)-2-iodoacetamide (1.5 equiv.) in dry acetone was added dropwise. The reaction was heated to reflux for 1 h to 6 h (monitored by TLC). The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate. The resulting suspension was filtered through Celite and the residue was washed with ethyl acetate. The filtrate was evaporated. This crude solid obtained was further purified by flash column chromatography, eluting with 50% to 60% ethyl acetate in petroleum ether to afford the desired carboxamide as a white solid.

Example 17: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-N-isopropyl-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared according to General Procedure 4, using isopropylamine in Step 1 and *N*-(3-methoxybenzyl)-2-iodoacetamide in Step 2.

5  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.75–8.71 (2H, m), 7.97–7.89 (2H, m), 7.75 (1H, t, *J* 8.0), 7.23 (1H, t, *J* 7.6), 6.87–6.80 (3H, m), 5.38 (2H, s), 4.29 (2H, d, *J* 6.0), 4.12–4.07 (1H, m), 3.75 (3H, s), 1.19 (6H, d, *J* 6.4).

Example 18: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-N,N-dimethyl-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared according to General Procedure 4, using dimethylamine in Step 1 and *N*-(3-methoxybenzyl)-2-iodoacetamide in Step 2.

10  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.79 (1H, t, *J* 5.9), 7.92–7.92 (2H, m), 7.74 (1H, t, *J* 8.0), 7.25 (1H, t, *J* 8.0), 6.86–6.85 (3H, m), 5.18 (2H, s), 4.30 (2H, d, *J* 5.9), 3.75 (3H, s), 3.25 (15 3H, s), 3.02 (3H, s).

Example 19: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-N-ethyl-1*H*-1,2,4-triazole-5-carboxamide

20 The title compound was prepared according to General Procedure 4, using ethylamine in Step 1 and *N*-(3-fluorobenzyl)-2-iodoacetamide in Step 2.

$^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 9.03 (1H, t, *J* 6.0), 8.81 (1H, t, *J* 6.0), 8.79–7.95 (2H, m), 7.77 (1H, t, *J* 7.6), 7.40–7.38 (1H, m), 7.15 (2H, t, *J* 6.4), 7.10–7.08 (1H, m), 5.41 (2H, s), 4.35 (2H, d, *J* 5.6), 3.34–3.33 (2H, m), 1.14 (3H, t, *J* 7.20).

25 Example 20: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-N-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared according to General Procedure 4, using 2-methoxyethylamine in Step 1 and *N*-(3-fluorobenzyl)-2-iodoacetamide in Step 2.

30  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.93 (1H, t, *J* 5.6), 8.80 (1H, t, *J* 6.0), 7.96–7.88 (2H, m), 7.77 (1H, t, *J* 8.0), 7.40–7.34 (1H, m), 7.15–7.10 (2H, m), 7.07 (1H, t, *J* 2.4), 5.41 (2H, s), 4.35 (2H, t, *J* 6.0), 3.49–3.45 (4H, m), 3.27 (3H, s).

Example 21: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-N-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide

35 The title compound was prepared according to General Procedure 4, using 2-methoxyethylamine in Step 1 and *N*-(3-methoxybenzyl)-2-iodoacetamide in Step 2.

<sup>1</sup>H NMR:  $\delta$ <sub>H</sub> (400 MHz, CD<sub>3</sub>OD) 7.99–7.93 (2H, m), 7.60 (1H, t, *J* 8.0), 7.24 (1H, t, *J* 8.0), 6.93–6.90 (2H, m), 6.84–6.81 (1H, m), 5.47 (2H, s), 4.42 (2H, s), 3.81 (3H, s), 3.58 (4H, s), 3.40 (3H, s).

5 Example 22: 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-N-cyclohexyl-1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared according to General Procedure 4, using cyclohexylamine in Step 1 and *N*-(3-fluorobenzyl)-2-iodoacetamide in Step 2.

10 <sup>1</sup>H NMR:  $\delta$ <sub>H</sub> (400 MHz, DMSO-*d*6) 8.77 (1H, t, *J* 5.8), 8.72 (1H, d, *J* 8.4), 7.95 (1H, dd, *J* 10.2, 1.5), 7.89 (1H, dd, *J* 8.4, 1.5), 7.74 (1H, t, *J* 8.0), 7.37–7.32 (1H, m), 7.15–7.04 (3H, m), 5.37 (2H, s), 4.33 (2H, d, *J* 5.8), 3.75–3.73 (1H, m), 1.77–1.72 (4H, m), 1.62–1.59 (1H, m), 1.46–1.37 (2H, m), 1.33–1.24 (2H, m), 1.12–1.09 (1H, m).

15 Example 23: Ethyl 3-(4-chlorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1*H*-pyrazole-5-carboxylate

A mixture of finely powdered K<sub>2</sub>CO<sub>3</sub> (452 mg, 3.27 mmol), *N*-(3-fluorobenzyl)-2-iodoacetamide (491 mg, 1.68 mmol) and ethyl 3-(4-chlorophenyl)-1*H*-pyrazole-5-carboxylate (400 mg, 1.60 mmol; commercially sourced from Fluorochem) in acetone (16 mL) was stirred at ambient temperature for 18 h. The reaction mixture was then partitioned between 2 M 20 hydrochloric acid (15 mL) and ethyl acetate (20 mL). The organic layer was separated and the aqueous phase further extracted with ethyl acetate (20 mL). The combined organic phase was washed with brine (15 mL), dried (MgSO<sub>4</sub>) and evaporated to give a crude product mixture as a solid (678 mg). This was processed by flash column chromatography, eluting with 10% to 20% ethyl acetate in chloroform, to afford two isomeric product 25 components. Fractions containing the faster running product component were combined and evaporated to afford ethyl 3-(4-chlorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1*H*-pyrazole-5-carboxylate (478 mg) as a white powder.

30 <sup>1</sup>H NMR:  $\delta$ <sub>H</sub> (400 MHz, DMSO-*d*6) 8.71 (1H, broad t, *J* 6.0), 7.89–7.91 (2H, AA'BB' m), 7.47–7.50 (2H, AA'BB' m), 7.45 (1H, s), 7.36 (1H, td, *J* 8.0, 6.1), 7.04–7.13 (3H, m), 5.28 (2H, s), 4.34 (2H, d, *J* 6.0), 4.30 (2H, q, *J* 7.1), 1.29 (3H, t, *J* 7.1).

Example 24: Methyl 1-[(3-fluorobenzyl)carbamoyl]methyl-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate

35 Step 1: Methyl 3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate

A stirred solution of 1-(3-methoxyphenyl)ethanone (1.00 g, 6.66 mmol) in anhydrous THF (50 mL) was cooled under argon to -78°C. A solution of lithium hexamethyldisilazide (1M in

THF; 7.0 mL, 7.0 mmol) was then added over 2 min. The resulting pale yellow solution was stirred for 45 min at -78 °C prior to addition of a solution of dimethyl oxalate (0.826 g, 7.00 mmol) in THF (25 mL) over 5 min. The mixture was allowed to come to ambient temperature. After 18 h the mixture was decanted into saturated NH<sub>4</sub>Cl solution (100 mL) and extracted 5 with ethyl acetate (2 × 60 mL). The combined organic phase was washed with brine (30 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to afford a pale yellow solid that was triturated with 0.3 M hydrochloric acid (60 mL) and then collected by filtration. The filter cake was dried *in vacuo* (50 °C, 1 mmHg) to afford pale yellow powder (1.38 g). This was processed by flash 10 column chromatography, eluting with 10% to 40% ethyl acetate in light petroleum to afford a pale yellow powder (476 mg). <sup>1</sup>H NMR analysis of this indicated that it contained a 1:3 mixture of 1-(3-methoxyphenyl)ethanone starting material and methyl 4-(3-methoxyphenyl)-2,4-dioxobutanoate. This mixture (476 mg) was dissolved in acetic acid (10 mL). Hydrazine 15 hydrate (1.30 mL, 20 mmol) was added with stirring, resulting in a mild exotherm. The mixture was cooled to ambient temperature. After 18 h the mixture was decanted into water (40 mL). The resulting precipitate was collected by filtration and dried *in vacuo* to afford the crude product (395 mg) as a pale yellow powder. This was processed by flash column chromatography, eluting with 20% to 40% ethyl acetate in light petroleum followed by 10% methanol in dichloromethane to afford methyl 3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (345 mg) as a white solid.

20 <sup>1</sup>H NMR:  $\delta$ <sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 10.85 (1H, broad s), 7.30–7.38 (3H, m), 7.10 (1H, s), 6.92 (1H, ddd, *J* 7.3, 2.7, 2.0), 3.94 (3H, s), 3.86 (3H, s).

Step 2: Methyl 1-[(3-fluorobenzyl)carbamoyl]methyl]-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate

25 A mixture of finely powdered K<sub>2</sub>CO<sub>3</sub> (122 mg, 0.883 mmol), *N*-(3-fluorobenzyl)-2-iodoacetamide (133 mg, 0.454 mmol) and methyl 3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (100 mg, 0.431 mmol) in acetone (4 mL) was stirred at ambient temperature. After 18 h, the reaction mixture was diluted with water (25 mL) and adjusted to pH 3 by addition of 2 M hydrochloric acid. It was then extracted with ethyl acetate (2 × 30 mL). The 30 combined organic phase was washed with brine (15 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to afford the crude product mixture as an oil (206 mg). This was processed by flash column chromatography, eluting with 30% to 100% ethyl acetate in light petroleum followed by 1% methanol in ethyl acetate to afford two isomeric product components. Fractions containing the faster running product component were combined and evaporated 35 to afford methyl 1-[(3-fluorobenzyl)carbamoyl]methyl]-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (88 mg) as a white powder.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.21–7.39 (4H, m), 7.20 (1H, s), 6.88–7.02 (4H, m), 6.08 (1H, broad t, *J* 5.8), 5.36 (2H, s), 4.46 (2H, d, *J* 6.0), 3.92 (3H, s), 3.86 (3H, s).

Example 25: 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-N-methyl-

5 1H-pyrazole-5-carboxamide

Step 1: Methyl 3-(4-chloro-3-fluorophenyl)-1*H*-pyrazole-5-carboxylate

A stirred solution of 1-(4-chloro-3-fluorophenyl)ethanone (1.50 g, 8.69 mmol) in anhydrous THF (90 mL) was cooled under argon to –78°C. A solution of lithium hexamethyldisilazide (1 10 M in THF; 9.6 mL, 9.6 mmol) was then added over 3 min. The resulting pale yellow solution was stirred for 45 min at –78 °C prior to addition of dimethyl oxalate (1.13 g, 9.57 mmol) over 5 min. The mixture was then allowed to warm to ambient temperature, stirring for 1 h, before decanting into water (150 mL) and adjusting to pH 3 by addition of 2 M hydrochloric acid. The resulting pale yellow precipitate was collected by filtration to afford methyl 4-(4-chloro-3- 15 fluorophenyl)-2,4-dioxobutanoate as a damp solid (3.59 g). A proportion of this solid (1.52 g) was dissolved in acetic acid (50 mL) with gentle warming. The solution was then ice-cooled and hydrazine hydrate (3.6 mL) added with stirring. After 5 min, the coolant bath was removed and the mixture stirred at ambient temperature for 18 h. The mixture was poured into water (150 mL) and the resulting precipitate collected by filtration and dried *in vacuo* to 20 afford methyl 3-(4-chloro-3-fluorophenyl)-1*H*-pyrazole-5-carboxylate (878 mg) as a cream-coloured powder.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (300 MHz, DMSO-*d*6) 13.99 (1H, broad s), 7.91 (1H, dd, *J* 10.8, 1.9), 7.73–7.76 (1H, m), 7.66 (1H, t, *J* 8.0), 7.42 (1H, s), 3.85 (3H, s).

25 Step 2: Methyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-1*H*-pyrazole-5-carboxylate

A mixture of finely powdered K<sub>2</sub>CO<sub>3</sub> (445 mg, 3.22 mmol), *N*-(3-methoxybenzyl)-2-iodoacetamide (503 mg, 1.65 mmol) and methyl 3-(4-chloro-3-fluorophenyl)-1*H*-pyrazole-5-carboxylate (400 mg, 1.57 mmol) in acetone (16 mL) was stirred at ambient temperature for 30 18 h. The reaction mixture was then diluted with water (60 mL) and the resulting precipitate collected by filtration, drying *in vacuo* over P<sub>2</sub>O<sub>5</sub>, to afford a white solid (627 mg). The solid was processed by flash chromatography, eluting with 20% to 50% ethyl acetate in light petroleum followed by 10% methanol in ethyl acetate to afford two isomeric product components. Fractions containing the separated faster running component were combined 35 and evaporated to afford methyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-1*H*-pyrazole-5-carboxylate (462 mg) as a cream-coloured powder.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.67 (1H, broad t, *J* 6.0), 7.89 (1H, dd, *J* 10.7, 1.9), 7.74–7.77 (1H, m), 7.64 (1H, t, *J* 8.1), 7.56 (1H, s), 7.24 (1H, t, *J* 8.1), 6.80–6.86 (3H, m), 5.27 (2H, s), 4.29 (2H, d, *J* 5.9), 3.83 (3H, s), 3.75 (3H, s).

5 Step 3: 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide

To a stirred suspension of methyl 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylate (250 mg, 0.579 mmol) in a 2:2:1 mixture of THF/MeOH/water (8 mL) was added 1 M LiOH (aq) (1.22 mL). After 3.5 h, the mixture was 10 poured into 2 M hydrochloric acid (20 mL) and extracted with ethyl acetate (2 × 40 mL). The combined organic phase was washed with brine (15 mL), dried ( $\text{MgSO}_4$ ) and evaporated to afford 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylic acid (244 mg) as a white solid. A portion of this solid (80 mg, ca. 0.19 mmol) was dissolved under argon in anhydrous DMF (3 mL), cooled in an ice bath and treated with 15 triethylamine (56  $\mu$ L, 0.40 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (40 mg, 0.21 mmol) followed after 5 min by 1-hydroxybenzotriazole (32 mg, 0.21 mmol). The mixture was stirred for 1 h prior to addition of methylamine (2 M solution in THF; 105  $\mu$ L, 0.21 mmol). It was then allowed to warm to ambient temperature. After stirring 20 for a further 18 h the mixture was diluted with 2 M hydrochloric acid (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with brine (10 mL), dried ( $\text{MgSO}_4$ ) and evaporated to afford a solid (86 mg). This was processed by flash chromatography, eluting with 2% to 4% methanol in chloroform, to afford a residue that was 25 triturated with  $\text{Et}_2\text{O}$  and then dried *in vacuo*, affording 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide (45 mg) as a white powder.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (300 MHz, DMSO-*d*6) 9.11 (1H, broad t, *J* 6.0), 7.99 (1H, broad q, *J* 4.5), 7.59–7.73 (3H, m), 7.40 (1H, s), 7.24 (1H, t, *J* 8.1), 6.88–6.90 (2H, m), 6.82 (1H, ddd, *J* 8.2, 2.5, 0.9), 5.21 (2H, s), 4.42 (2H, d, *J* 5.9), 3.74 (3H, s), 2.60 (3H, d, *J* 4.6).

30 Example 26: 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide

The title compound was prepared according to the method of Example 25, using *N*-(3-fluorobenzyl)-2-iodoacetamide instead of *N*-(3-methoxybenzyl)-2-iodoacetamide in Step 2.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (300 MHz, DMSO-*d*6) 9.17 (1H, broad t, *J* 6.0), 7.99 (1H, broad q, *J* 4.5), 7.72

35 (1H, dd, *J* 10.6, 1.6), 7.67 (1H, app. t, *J* 7.7), 7.62 (1H, dd, *J* 8.4 and 1.8), 7.39 (1H, s), 7.32–7.41 (1H, m), 7.04–7.18 (3H, m), 5.20 (2H, s), 4.46 (2H, d, *J* 6.0), 2.60 (3H, d, *J* 4.6).

Example 27: Ethyl 3-(4-chlorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-1*H*-pyrazole-5-carboxylate

The title compound was prepared according to the method of Example 23, using *N*-(3-methoxybenzyl)-2-iodoacetamide instead of *N*-(3-fluorobenzyl)-2-iodoacetamide.

5  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.64 (1H, broad t, *J* 5.9), 7.88–7.91 (2H, AA'BB' m), 7.46–7.50 (2H, AA'BB' m), 7.44 (1H, s), 7.23 (1H, t, *J* 8.1), 6.80–6.86 (3H, m), 5.26 (2H, s), 4.26–4.32 (4H, m), 3.74 (3H, s), 1.29 (3H, t, *J* 7.1).

General Procedure 5: Amide coupling with substituted triazol-1-yl acetic acids

10 To an ice-cold solution of carboxylic acid (1 equiv.), amine (1.2 equiv.) and propylphosphonic anhydride solution (T3P) (50 wt. % in ethyl acetate; 2 equiv.) in dry dichloromethane was added triethylamine (7 equiv.). The resulting reaction mixture was stirred at room temperature for 4 to 16 h (monitored by TLC). The reaction was diluted with ice water and extracted with dichloromethane (2-3 times). The combined organic layer was washed with 15 water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography, to afford the desired product as a white solid.

Example 28: 3-(4-chloro-3-fluorophenyl)-1-[(1*H*-indazol-5-yl)methyl]carbamoyl)methyl-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide

Step 1: 3-(4-chloro-3-fluorophenyl)-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide

To a stirred solution, in sealed-tube, of ethyl 3-(4-chloro-3-fluorophenyl)-1*H*-1,2,4-triazole-5-carboxylate (100 mg, 0.35 mmol) in dry toluene (5 mL), was added triethylamine (0.25 mL, 2.52 mmol), DABAL- $\text{Me}_3$  (90 mg, 0.35 mmol) and methyl amine (2.0 M in THF, 0.35 mL). The reaction mixture was stirred at 110°C for 1 h. The reaction mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed brine (25 mL), then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography, eluting with 70% to 90% ethyl acetate in petroleum ether to afford 3-(4-chloro-3-fluorophenyl)-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide (70 mg) as an off-white solid.

Step 2: Methyl 2-[3-(4-chloro-3-fluorophenyl)-5-(methylcarbamoyl)-1*H*-1,2,4-triazol-1-yl]acetate

To a stirred solution of 3-(4-chloro-3-fluorophenyl)-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide (140 mg, 0.56 mmol) in dry acetone (10 mL) was added potassium carbonate (128 mg, 0.17

mmol) and methyl bromoacetate (140 mg, 1.0 mmol). The resulting mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and filtered through Celite. The residue was washed with ethyl acetate and the filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude solid was purified by flash 5 column chromatography, eluting with 40% to 70% ethyl acetate in petroleum ether to afford methyl 2-(3-(4-chloro-3-fluorophenyl)-5-(methylcarbamoyl)-1*H*-1,2,4-triazol-1-yl)acetate (80 mg) as a colourless liquid.  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 9.01 (1H, broad s), 7.92–7.88 (2H, m), 7.76 (1H, t, *J* 7.8), 5.50 (2H, s), 3.70 (3H, s), 2.78 (3H, d, *J* 4.8).

10 Step 3: 2-[3-(4-Chloro-3-fluorophenyl)-5-(methylcarbamoyl)-1*H*-1,2,4-triazol-1-yl]acetic acid  
To an ice-cold solution of methyl 2-(3-(4-chloro-3-fluorophenyl)-5-(methylcarbamoyl)-1*H*-1,2,4-triazol-1-yl)acetate (80 mg, 0.26 mmol) in THF / water (10 mL, 1:1) was added lithium 15 hydroxide monohydrate (22 mg, 0.52 mmol) in water (2 mL). The resulting solution was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and the residue was diluted with water (20 mL) and neutralized with citric acid. The resulting solid was filtered off and dried to afford 2-(3-(4-chloro-3-fluorophenyl)-5-(methylcarbamoyl)-1*H*-1,2,4-triazol-1-yl)acetic acid (75 mg), which was used without further purification.

20 Step 4: 3-(4-chloro-3-fluorophenyl)-1-({[(1*H*-indazol-5-yl)methyl]carbamoyl}methyl)-*N*-methyl-  
1*H*-1,2,4-triazole-5-carboxamide

The title compound was prepared according to General Procedure 5, using 2-(3-(4-chloro-3-fluorophenyl)-5-(methylcarbamoyl)-1*H*-1,2,4-triazol-1-yl)acetic acid and (1*H*-indazol-5-yl)methanamine.

25  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 13.00 (1H, broad s), 8.94 (1H, q, *J* 5.0), 8.76 (1H, t, *J* 5.6), 8.16 (1H, s), 7.94–7.87 (2H, m), 7.78 – 7.74 (1H, m), 7.69–7.64 (1H, m), 7.50 (1H, d, *J* 8.4), 7.29–7.27 (1H, m), 5.39 (2H, s), 4.40 (2H, d, *J* 5.6), 2.80 (3H, d, *J* 5.0).

Example 29: *N*-(1*H*-imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetamide

30 Step 1: Ethyl 4-chloro-3-fluorobenzimidate hydrochloride salt  
Anhydrous HCl gas was bubbled through ice-cold absolute ethanol (150 mL) for 30 min. To this solution, 4-chloro-3-fluorobenzonitrile (25 g, 160 mmol) in chloroform (70 mL) was added and HCl gas was bubbled through the mixture for 2 h. The mixture was then allowed to warm 35 to room temperature, and the flask was capped with a glass stopper. The resulting solution was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and the residue was diluted with diethyl ether (150 mL). The resulting white solid

was filtered off and washed with diethyl ether (3 x 50 mL) to obtain ethyl 4-chloro-3-fluorobenzimidate hydrochloride (22 g) as a white solid.

Step 2: 3-(4-Chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazole

5 To a suspension of ethyl 4-chloro-3-fluorobenzimidate hydrochloride (10 g, 42 mmol) in absolute ethanol (80 mL) under nitrogen, in a sealed-tube, was added diisopropylethylamine (20.1 mL, 210 mmol) and propionohydrazide (4.44 g, 50.4 mmol). The resulting mixture was heated to 100°C for 20 h. The reaction was cooled to room temperature and volatiles were removed on rotary evaporator. The crude residue obtained was purified by flash column chromatography, eluting with 20% to 40% ethyl acetate in petroleum ether, to afford 3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazole (3.9 g) as an off-white solid. <sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 13.86 (1H, s), 7.87–7.82 (2H, m), 7.68–7.62 (1H, m), 2.77 (2H, q, *J* 7.5), 1.28 (3H, t, *J* 7.5).

15 Step 3: Ethyl 2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetate  
To a stirred solution of 3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazole (2.4 g, 10.6 mmol) in acetone (30 mL), potassium carbonate (2.2 g, 15.9 mmol) and ethyl 2-bromoacetate (4.1 g, 26.5 mmol) were added. The resulting mixture was heated to reflux for 16 h. The resulting mixture was cooled and concentrated under reduced pressure. The 20 crude solid was purified by flash column chromatography, using 10% – 20% ethyl acetate in petroleum ether as eluent, to afford ethyl 2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetate (2.0 g) as a yellow solid.

Step 4: 2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetic acid

25 To an ice-cold solution of ethyl 2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetate (500 mg, 1.6 mmol) in dry THF/ H<sub>2</sub>O (10 mL, 1:1) was added lithium hydroxide monohydrate (100 mg, 2.4 mmol) in water (5 mL). The resulting solution was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and the residue was diluted with water (20 mL) and neutralized with citric acid. The resulting solid was 30 filtered off and dried to afford 2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetic acid (470 mg) as a white solid. <sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 13.36 (1H, s), 7.85–7.80 (2H, m), 7.69–7.66 (1H, m), 5.10 (2H, s), 2.76 (2H, q, *J* 7.4), 1.26 (3H, t, *J* 7.4).

Step 5: *N*-[(1*H*-imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-

35 yl]acetamide

The title compound was prepared according to General Procedure 5, using 2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetic acid and (1*H*-imidazol-5-yl)methanamine,  
1*H* NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 12.09 (1H, broad s), 8.6 (1H, t, *J* 5.2), 7.84–7.80 (2H, m),  
7.69–7.62 (2H, m), 6.98 (1H, s), 4.94 (2H, s), 4.22 (2H, s), 2.75 (2H, q, *J* 7.6), 1.27 (3H, t, *J*  
5 7.6).

Example 30: 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl)acetamide

10 Step 1: 2-Bromo-1-(4-chloro-3-fluorophenyl) ethan-1-one

To a stirred solution of 1-(4-chloro-3-fluorophenyl) ethan-1-one (10 g, 56 mmol) in glacial acetic acid (200 mL) at 0°C was added bromine (2.6 mL, 52 mmol) in acetic acid (50 mL), dropwise over 30 minutes. The resulting mixture was stirred at room temperature for 5 h. The reaction was quenched by adding ice-cold water, and the solid obtained was filtered and 15 the residue dried under reduced pressure. The crude solid obtained was purified by flash column chromatography, eluting with 1% to 3% ethyl acetate in petroleum ether to afford 2-bromo-1-(4-chloro-3-fluorophenyl) ethan-1-one (8 g) as an off white solid. <sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.80–7.73 (2H, m), 7.58–7.55 (1H, m), 4.40 (2H, s).

20 Step 2: 4-(4-Chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazole

To a stirred solution of propionimidamide (2.58 g, 34 mmol) in THF (150 mL) and water (50 mL), was added potassium bicarbonate (4.76 g, 47 mmol). The resulting mixture was heated at 65°C for 30 minutes. Then 2-bromo-1-(4-chloro-3-fluorophenyl) ethan-1-one (8.0 g, 38 mmol) in THF (50 mL) was added drop wise over 15 minutes and further refluxed for 16 h. 25 Then reaction mixture was cooled and partitioned between ethyl acetate (200 mL) and water (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, using 70% to 80% ethyl acetate in petroleum ether as eluent to afford 4-(4-chloro-3-fluorophenyl)-30 2-ethyl-1*H*-imidazole (1.20 g) as a brown solid. <sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.54–7.51 (1H, m), 7.50–7.44 (1H, m), 7.40–7.36 (1H, m), 7.22 (1H, s), 2.87 (2H, q, *J* 7.6), 1.37 (3H, t, *J* 7.6).

Step 3: Methyl 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]acetate

35 To a stirred solution of 4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazole (1.0 g, 44 mmol) in DMF (20 mL) was added potassium carbonate (1.82 g, 132 mmol). Then methyl 2-bromoacetate (0.74 mL, 66 mmol) was added dropwise and the mixture stirred at room

temperature for 16 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL) and brine (25 mL). The organic layer was then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography,

5 using 30% to 40% ethyl acetate in petroleum ether as eluent to afford methyl 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]acetate (1.20 g) as an off-white solid. <sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 7.95–7.83 (1H, m), 7.67–7.51 (3H, m), 4.97 (2H, s), 3.75 (3H, s), 2.62 (2H, q, *J* 7.6), 1.21 (3H, t, *J* 7.6).

10 Step 4: 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]acetic acid

To a stirred solution of methyl 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]acetate (1.20 g, 4 mmol) in THF (12 mL) and water (12 mL) was added lithium hydroxide monohydrate (340 mg, 8 mmol). The reaction mixture was further stirred at room temperature for 3 h and then concentrated under reduced pressure. The crude residue was

15 acidified to pH 2 using dilute HCl and extracted with dichloromethane (150 mL). The organic layer was washed with water (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure afford 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]acetic acid (800 mg) as a brown solid.

<sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 7.85–7.50 (4H, m), 4.77 (2H, s), 2.62 (2H, q, *J* 7.5), 1.21 (3H, t, *J* 7.5).

20 Step 5: 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl) acetamide

To a stirred solution of 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]acetic acid

25 (100 mg, 0.35 mmol) in dry dichloromethane (10 mL) was added triethylamine (179 mg, 1.77 mmol). Then (3,5-dichlorophenyl)methanamine (75 mg, 0.42 mmol) was added followed by propylphosphonic anhydride solution (50 wt. % in ethyl acetate) (225 mg, 0.70 mmol). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (25 mL) and water (25 mL). The organic layer was separated and

30 washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography, eluting with 60% to 70% ethyl acetate in petroleum ether to afford 2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl)acetamide (8 mg) as an off-white solid. <sup>1</sup>H NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.77 (1H, t, *J* 5.8), 7.81–7.64

35 (2H, m), 7.58–7.51 (3H, m), 7.34 (2H, s), 4.74 (2H, s), 4.32 (2H, d, *J* 5.8), 2.57 (2H, q, *J* 7.6), 1.21 (3H, t, *J* 7.6).

Example 31: Methyl 3-(4-cyanophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate

Step 1: Methyl 3-iodo-1*H*-1,2,4-triazole-5-carboxylate

5 To an ice-cold solution of methyl 3-amino-1*H*-1,2,4-triazole-5-carboxylate (2.0 g, 14.1 mmol) in 1 N aqueous sulphuric acid (60 mL), was added dropwise aqueous sodium nitrite solution (1.45 g, 21.1 mmol in 10 mL water). The resulting reaction mixture was stirred in an ice bath for 1 h. A mixture of copper (I) iodide (0.8 g, 4.2 mmol) and potassium iodide (4.7 g, 28.1 mmol) was then added to the reaction. The resulting mixture was stirred at room

10 temperature for 6 h, then diluted with ethyl acetate (50 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 X 25 mL) and the combined organic layer was washed with water (35 mL), 10% aqueous sodium thiosulphate solution (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid obtained was washed with ether (2 x

15 25 mL) and dried to obtain methyl 3-iodo-1*H*-1,2,4-triazole-5-carboxylate as a pale yellow solid (1.2 g).

Step 2: Methyl 3-iodo-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate

20 To a stirred solution of methyl 3-iodo-1*H*-1,2,4-triazole-5-carboxylate (1.2 g, 4.7 mmol) in dry acetone (12 mL) at room temperature, under nitrogen, was added potassium carbonate (1.3 g, 9.5 mmol). After 15 minutes, *N*-(3-methoxybenzyl)-2-iodoacetamide (2.1 g, 7.1 mmol) in dry acetone (5 mL) was added dropwise. The reaction was stirred at room temperature for 4 h and diluted with ethyl acetate (30 mL). The resulting suspension was filtered through Celite

25 and the residue was washed with ethyl acetate (2 X 10 mL). The filtrate was evaporated to afford crude solid. The crude solid was further purified by flash column chromatography, eluting with 60% to 80% ethyl acetate in petroleum ether, to afford methyl 3-iodo-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate (600 mg) as a white solid.

30 <sup>1</sup>H NMR:  $\delta$ <sub>H</sub> (400 MHz, DMSO-*d*6) 8.82 (1H, t, *J* 5.6), 7.25 (1H, t, *J* 8.0), 6.89–6.82 (3H, m), 5.05 (2H, s), 4.30 (2H, d, *J* 5.6), 3.85 (3H, s), 3.75 (3H, s).

Step 3: Methyl 3-(4-cyanophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate

To a degassed solution, in a sealed-tube, of methyl 3-iodo-1-[(3-methoxybenzyl)carbamoyl]methyl]-1*H*-1,2,4-triazole-5-carboxylate (600 mg, 1.4 mmol), cesium carbonate (908 mg, 2.8 mmol) and 4-cyanophenylboronic acid (244 mg, 1.6 mmol) in 1,4-dioxane/ water (10 mL, 9.9 : 0.1) was added [1,1'-bis(diphenylphosphino)ferrocene]

dichloropalladium(II) (50 mg, 10 mol %). The resulting mixture was heated at 120°C for 2 h. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (20 mL) and filtered through Celite. The residue was washed with ethyl acetate (2 x 10 mL). The combined filtrate was concentrated under reduced pressure. The crude product was 5 purified by flash column chromatography, eluting with 50% ethyl acetate in hexane, to afford the title compound (100 mg) as an off-white solid.  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.93 (1H, t, *J* 5.6), 8.02 (2H, d, *J* 8.8), 7.98 (2H, d, *J* 8.8), 7.24 (1H, t, *J* 8.0), 6.85–6.76 (3H, m), 5.18 (2H, s), 4.28 (2H, d, *J* 5.6), 3.90 (3H, s). 3.75 (3H, s).

10 **Example 32: 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide**

To a stirred solution, in sealed-tube, of methyl 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate (80 mg, 0.2 mmol) in dry toluene (5 mL), was added triethylamine (0.4 mL, 0.6 mmol), DABAL-Me<sub>3</sub> (50 mg, 0.2 mmol) 15 and methyl amine hydrochloride (12 mg, 0.4 mmol). Then the reaction mixture was stirred at 110°C for 1 h. The reaction mixture was quenched with ice-water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine (15 mL), then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography, by eluting with 70% to 90% 20 ethyl acetate in petroleum ether, to afford 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide (10 mg) as an off-white solid.  $^1\text{H}$  NMR:  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*6) 8.92 (1H, t, *J* 5.1), 8.57–8.56 (1H, m), 8.03 (2H, d, *J* 8.2), 7.97 (2H, d, *J* 8.2), 7.24 (1H, t, *J* 7.5), 6.85–6.77 (3H, m), 5.12 (2H, s), 4.27 (2H, d, *J* 5.1), 3.75 (3H, s), 2.78 (3H, d, *J* 4.1).

25

**Biological Assays**

*Cell culture*

HEK 293 and MDCK cells (Public Health England, Cell Culture Collections) were maintained in DMEM supplemented with 10% (v/v) fetal bovine serum (Seralab), 2 mM L-glutamine, 30 1,000 U penicillin and 1,000 µg streptomycin (Life Technologies); termed complete media. Clonal HEK 293 cell lines were maintained in complete media supplemented with 0.6 mg/mL G418 (Enzo Life Sciences).

35 **Experiment 1: Identification of PDE4 long form activators of the present invention using full-length human PDE4 isoforms PDE4D5, PDE4A4, PDE4B1 and PDE4B2**  
(Marchmont, R. J. and Houslay, M. D. *Biochem. J.* 187: 381-92, 1980)

*Cell line generation*

HEK 293 cells were transfected with pDEST™ PDE4 expression vectors using Lipofectamine LTX/Plus reagent (Invitrogen) as outlined by the manufacturer and clonal isolates expanded to obtain cell lines that stably expressed the full-length human PDE4D5,  
5 PDE4A4 and PDE4B1 long isoforms and the full length human PDE4B2 short isoform. These were called the HEK-PDE4D5, HEK-PDE4A4, HEK-PDE4B1 and HEK-PDE4B2 cell lines, respectively.

*Lysate preparation (using PDE4D5 as a typical example)*

10 HEK-PDE4D5 cells were seeded out in 100mm plates and incubated at 37°C in an atmosphere of 5% CO<sub>2</sub>, 95% air. Cell lysates were prepared using KHEM buffer [50mM KCl, 10mM EGTA, 50mM HEPES (pH 7.2), 1.92mM MgCl<sub>2</sub>].

15 To prepare the cell lysates, the 100mm plates containing the cells were placed on ice and washed with ice-cold PBS (phosphate buffered saline, pH 7.4). KHEM buffer (500µl) was added to the cells. Cells were then scraped off the plate and triturated using a needle (BD Microlance™ 0.8, 40mm). The lysed cells were then centrifuged at 2000rpm for 10 minutes to remove cell debris and the supernatant (cell lysate containing recombinant PDE4D5) was transferred to a fresh tube and kept on ice.

20

*Cytosol fraction preparation (using PDE4D5 as a typical example)*

25 The cell lysate containing recombinant PDE4D5 was transferred into a centrifuge tube and placed into an ultracentrifuge (BECKMAN COULTER) and spun at high speed (100,000g) for 30 minutes at 4°C. The cytosol fraction was then collected and its protein amount determined using a BCA protein assay.

*PDE Assay – Protocol A (using PDE4D5 as a typical example)*

30 PDE assays were performed using a final concentration of 10 mM Tris/5 mM MgCl<sub>2</sub> and 1 µM [<sup>3</sup>H]-cAMP (Perkin Elmer) plus PDE4D5 cell lysate cytosol fraction, containing over-expressed PDE4D5, with and without test compound. Incubations were performed at 30°C for 5 minutes. The samples were then placed in a boiling water bath for 2 minutes to denature the PDE enzyme, and returned to ice. Samples were allowed to cool for 10 min after which snake venom 5'-nucleotidase (25µl, 1mg/ml; Sigma) was added. The tubes were vortexed and incubated in a water bath at 30°C for 10 minutes, to attain conversion of [<sup>3</sup>H]-5'-AMP to [<sup>3</sup>H]-adenosine, and then placed on ice. Dowex ion exchange resin (Sigma) prepared as a 1:1 Dowex: water stock was thoroughly re-suspended and diluted 2:1 with ethanol. The resulting Dowex suspension (0.4 ml) was added to each tube. Tubes were

vortexed to mix and then incubated on ice for at least 15 minutes before a final vortex. The Dowex resin was pelleted by centrifugation at 13,000g at 4°C for 3 minutes and 150 µl of the supernatant was removed to an Eppendorf tube containing 1 ml of ScintiSafe3 scintillation fluid (Fisher). Tubes were vortexed thoroughly to mix and the recovered [<sup>3</sup>H]-adenosine was 5 quantified by measuring counts over 1 minute in a scintillation counter.

The % increase in counts in the presence of test compound at a particular concentration indicates the % increase in enzyme activity at that concentration.

10 Compounds of the present invention activated the PDE4 long forms, PDE4D5 and PDE4B1. Under the same assay conditions, compounds of the present invention did not activate or activated to a lesser extent the PDE4 short form, PDE4B2. Data are shown in Tables 2 to 4 and Figure 1.

15 *PDE Assay – Protocol B (using PDE4D5 as a typical example)*

PDE assays were performed in thin walled V-bottomed 96-well plates. The assays were performed at a final concentration of 10 mM Tris/5 mM MgCl<sub>2</sub> plus PDE4D5 cell lysate cytosol fraction, containing over-expressed PDE4D5, with and without test compound. The lysate/compound mix were incubated together for 15 min at room temperature on an orbital 20 shaker prior to addition of [<sup>3</sup>H] cAMP (final concentration 1 µM [<sup>3</sup>H] cAMP; Perkin Elmer) to a final volume of 50 µl per reaction. The reactions were then incubated for 10 minutes at 30°C, terminated by heating for 2 min at 95°C and allowed to cool. Snake venom (12.5µl of 1mg/ml; *Crotalus atrox*, Sigma) was then added and the plates were agitated and incubated for a further 15 minutes at 30°C. Dowex ion exchange resin (Sigma, chloride form, 200-400 25 mesh; 200µl; prepared as a 1:1 Dowex: water stock, thoroughly re-suspended and diluted 2:1 with ethanol) was then added to each well and the plates incubated for 15 min at room temperature on an orbital shaker ensuring sufficient agitation for resin suspension (550RPM). The reaction mixture was then transferred to a 96 well filter plate (Millipore; 0.45 µM pore size) and filtered into a receiving 96-well plate to remove the dowex suspension. 30µL of the filtered solution was then transferred to the wells of an Opti-plate (Perkin Elmer) 96 well assay plate and 120µl of Microscint 40 scintillation fluid was added. The plate was then placed on an orbital shaker for 10 min at high speed (900RPM) to mix the sample with scintillation fluid prior to quantitation using a plate based scintillation counter (Top-Count).

35 The % increase in counts in the presence of test compound at a particular concentration indicates the % increase in enzyme activity at that concentration.

Data are shown in Tables 2 to 4.

Experiment 2: Reduction of intracellular cAMP levels in MDCK cells by PDE4 long form activators

5 MDCK cells were seeded at 100,000 cells per well, and left to adhere overnight. The cells were then treated with the test compound (10  $\mu$ M) for 10 minutes, prior to stimulation with forskolin (10  $\mu$ M, Sigma) for 2 minutes. Media was aspirated, and hydrochloric acid (0.1M) was added to lyse the cells. The cAMP assay (Enzo Life Sciences) was performed according to the manufacturer's instructions.

10

Compounds of the present invention reduced intracellular cAMP levels in forskolin stimulated MDCK cells. Data for Example 1 are shown in Figure 2.

Experiment 3: Inhibition of *in vitro* cyst formation in MDCK cells treated with PDE4 long form activators

15 In this study, the well-established three-dimensional (3D) MDCK cell model is used to investigate the effects of PDE4 long form activators on the formation of kidney cysts and evaluate their potential in the treatment of polycystic kidney diseases. 3D cysts are generated based on the method of Mao *et al.* (Mao, Z., Streets, A. J., Ong, A. C. M. *Am. J. Physiol. Renal Physiol.* 300(6): F1375-F1384, 2011), with some modifications.

20

*Protocol C: Using Forskolin and vasopressin to stimulate cyst formation*

MDCK cells (50,000 cells/well) are seeded into collagen (Life Technologies; final concentration 1 mg/mL), containing 17 mM NaOH in DMEM, supplemented with 2% (v/v) 25 FBS, 2 mM L-glutamine and 2 mM L-glutamine, 1,000 U penicillin and 1,000  $\mu$ g streptomycin (DMEM-2%FBS), on ice. Upon gelling at 37°C, 1 mL of DMEM-2%FBS is added along with the test compound indicated in the presence of 10  $\mu$ M forskolin (Sigma) and 1  $\mu$ g/mL [Arg<sup>8</sup>]-vasopressin acetate salt (Sigma). Media is replenished every 2 days for 20 days; at every feed, test compound, forskolin and vasopressin are added.

30

Phase-contrast images are obtained on the Motic microscope (x200 magnification) every 2 days for 20 days. Per condition, 10 images are taken (in duplicate) and the average cyst radius measured.

35 PDE4 long form activators inhibit *in vitro* cyst formation in MDCK cells.

*Protocol D: Using Prostaglandin E2 (PGE2) to stimulate cyst formation*

Type 1 collagen (Invitrogen) is first prepared on ice by neutralising an acidic stock solution (3mg/ml) with 17mM NaOH and diluting it to 1mg/ml with DMEM, supplemented with 2% (v/v) FBS, 2 mM L-glutamine, 1,000 U penicillin and 1,000 µg streptomycin (DMEM-2%FBS). A primary Collagen layer is first added to each well and allowed to solidify at 37°C prior to

5 seeding MDCK cells (50,000 cells/well) in a secondary collagen layer and allowed to solidify at 37°C. DMEM-2% (v/v) FBS is added along with the test compound indicated in the presence of 300 nM prostaglandin E2 (Sigma Aldrich) in duplicate wells per condition. Media is replenished every 3 days for 10 days at which time the test compound and prostaglandin E2 are added.

10 Phase-contrast images are obtained on the Motic microscope (x4 magnification). 8 images are taken per condition and the cyst diameter measured (up to 150 cyst measurements per well). Cyst spheroid volume is calculated using the formula  $4/3\pi r^3$  where r is the radius of the spheroid. A mean cyst volume is then calculated per well. The mean cyst volume and standard deviation between the duplicate wells is then calculated and expressed as a %

15 Cyst Volume compared to the vehicle only (DMSO + 300nM PGE2) control wells.

PDE4 long form activators inhibit *in vitro* cyst formation in MDCK cells. Data for Example 28 are shown in Figure 3.

Experiment 4: Reversal of *in vitro* cyst formation in MDCK cells treated with PDE4 long form activators

In this study, the potential of PDE4 long form activators to reverse the formation of pre-formed cysts is evaluated. The experiment is carried out according to the method of Experiment 3. For the first 10 days, forskolin and vasopressin are added at every feed (every 2 days) but no test compound is added. For the next 10 days, the test compound, forskolin and vasopressin are added at every feed (every 2 days).

Phase-contrast images are obtained on the Motic microscope (x200 magnification) every 2 days for 20 days. Per condition, 10 images are taken (in duplicate) and the average cyst radius measured.

30 PDE4 long form activators reverse *in vitro* cyst formation in MDCK cells.

Experiment 5: Inhibition of proliferation of LNCaP human prostate cancer cells

In this study, the potential utility of PDE4 long form activators in the treatment of prostate cancer is studied using the LNCaP human prostate cancer cell line. The experiments are carried out according to the method described by Henderson *et al.* (Henderson, D. J. P., Byrne, A., Dulla, K., Jenster, G., Hoffmann, R., Baillie, G. S., Houslay, M. D. *Br. J. Cancer* 110: 1278-1287, 2014).

*LNCaP cell culture*

Androgen-sensitive (AS) LNCaP cells are maintained in RPMI1640 supplemented with 10%

FBS (Seralabs), 2mM L-glutamine and 1,000U penicillin-streptomycin. LNCaP androgen-

5 insensitive (AI) cells are generated by culturing the LNCaP-AS cells in RPMI1640 supplemented with 10% charcoal stripped FBS, 2mM L-glutamine and 1,000U penicillin-streptomycin for a minimum of four weeks. All tissue culture reagents are from Life Technologies.

10 *Xcelligence (Roche) proliferation assay*

Cell proliferation is measured as a function of changing electrical impedance. Values are represented by cell index number, a dimensionless unit of measurement representing the

cell status, which increases as cells adhere to 96-well electrode plates and divide.

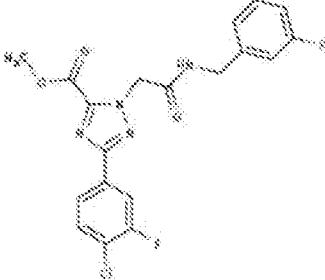
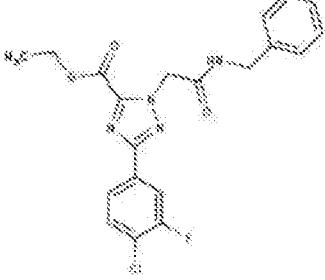
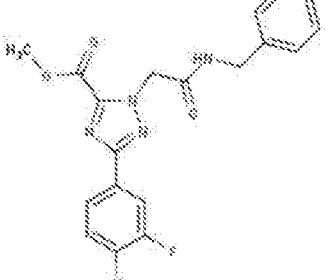
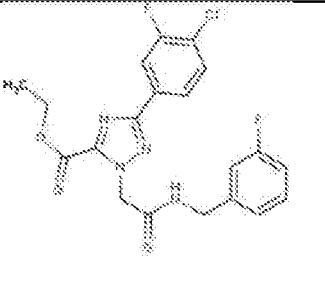
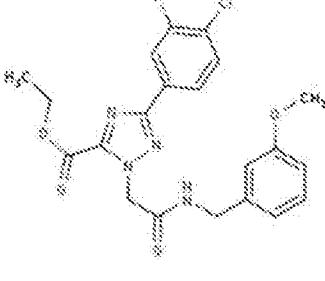
15 LNCaP AI/AS cells are plated at a density of 25,000 cells per well in a 96-well electrode plate (in triplicate), in the presence/absence of various concentrations of test compound.

Cell indices are measured every 10 minutes for up to 100 hours, analysed using RTCA software and normalised to the cell index of vehicle-treated cells (n=3).

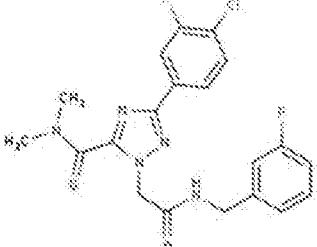
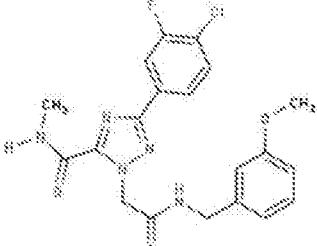
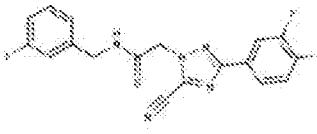
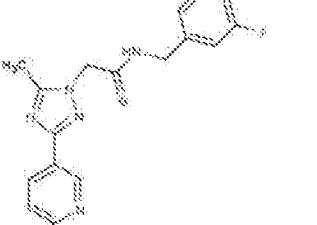
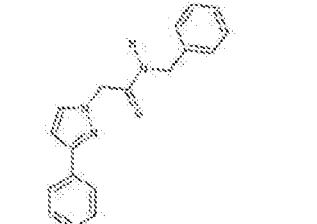
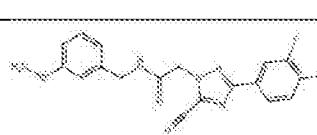
20

PDE4 long form activators inhibit the proliferation of AS and AI LNCaP human prostate cancer cells.

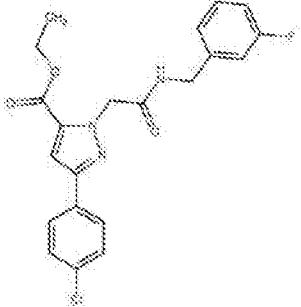
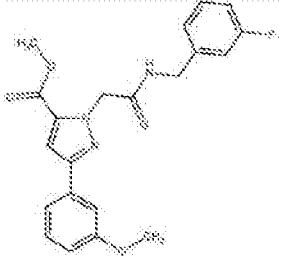
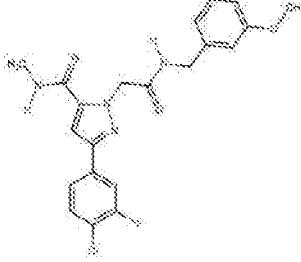
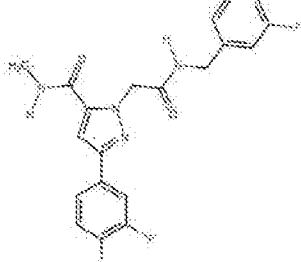
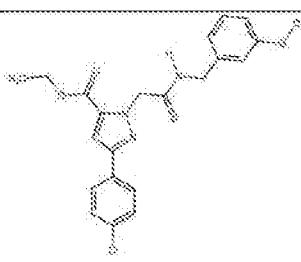
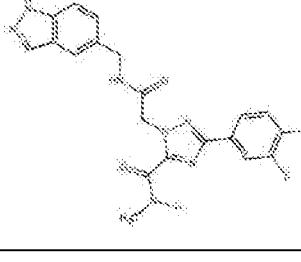
Table 1: Small molecule PDE4 long form activators (Examples 1 to 32), according to the present invention

Compound	Chemical name	Molecular weight (Daltons)	Chemical Structure
Example 1	Methyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1 <i>H</i> -1,2,4-triazole-5-carboxylate	420.8	
Example 2	Ethyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1 <i>H</i> -1,2,4-triazole-5-carboxylate	416.8	
Example 3	Methyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1 <i>H</i> -1,2,4-triazole-5-carboxylate	402.8	
Example 4	Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl-1 <i>H</i> -1,2,4-triazole-5-carboxylate	434.8	
Example 5	Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-1 <i>H</i> -1,2,4-triazole-5-carboxylate	446.9	

Compound	Chemical name	Molecular weight (Daltons)	Chemical Structure
Example 6	3-(4-chloro-3-fluorophenyl)-1- {[(3- fluorobenzyl)carbamoyl]methyl }-1 <i>H</i> -1,2,4-triazole-5- carboxylic acid	406.8	
Example 7	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl]met hyl}-1 <i>H</i> -1,2,4-triazole-5- carboxylic acid	418.8	
Example 8	3-(4-chloro-3-fluorophenyl)-1- {[(3- fluorobenzyl)carbamoyl]methyl }-1 <i>H</i> -1,2,4-triazole-5- carboxamide	405.8	
Example 9	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl]met hyl}-1 <i>H</i> -1,2,4-triazole-5- carboxamide	417.8	
Example 10	3-(4-chloro-3-fluorophenyl)-1- {[(3- fluorobenzyl)carbamoyl]methyl }- <i>N</i> -methyl-1 <i>H</i> -1,2,4-triazole- 5-carboxamide	419.8	

Compound	Chemical name	Molecular weight (Daltons)	Chemical Structure
Example 11	3-(4-chloro-3-fluorophenyl)-1- {[(3- fluorobenzyl)carbamoyl]methyl }-N,N-dimethyl-1 <i>H</i> -1,2,4- triazole-5-carboxamide	433.8	
Example 12	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl]met hyl}-N-methyl-1 <i>H</i> -1,2,4- triazole-5-carboxamide	431.8	
Example 13	2-[3-(4-chloro-3-fluorophenyl)- 5-cyano-1 <i>H</i> -1,2,4-triazol-1-yl]- N-(3-fluorobenzyl)acetamide	387.8	
Example 14	N-(3-fluorobenzyl)-2-[5- methyl-3-(pyridin-3-yl)-1 <i>H</i> - 1,2,4-triazol-1-yl]acetamide	325.3	
Example 15	N-benzyl-2-[3-(4- chlorophenyl)-1 <i>H</i> -pyrazol-1- yl]acetamide	325.8	
Example 16	2-[3-(4-chloro-3- fluorophenyl)-5-cyano-1 <i>H</i> - 1,2,4-triazol-1-yl]-N-(3- methoxybenzyl)acetamide	399.8	

Compound	Chemical name	Molecular weight (Daltons)	Chemical Structure
Example 17	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl] methyl}-N-isopropyl-1 <i>H</i> - 1,2,4-triazole-5-carboxamide	459.9	
Example 18	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl] methyl}-N,N-dimethyl-1 <i>H</i> - 1,2,4-triazole-5-carboxamide	445.9	
Example 19	3-(4-chloro-3-fluorophenyl)-1- {[(3-fluorobenzyl)carbamoyl] methyl}-N-ethyl-1 <i>H</i> -1,2,4- triazole-5-carboxamide	433.8	
Example 20	3-(4-chloro-3-fluorophenyl)-1- {[(3-fluorobenzyl)carbamoyl] methyl}-N-(2-methoxyethyl)- 1 <i>H</i> -1,2,4-triazole-5- carboxamide	463.9	
Example 21	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl] methyl}-N-(2-methoxyethyl)- 1 <i>H</i> -1,2,4-triazole-5- carboxamide	475.9	
Example 22	3-(4-chloro-3-fluorophenyl)-1- {[(3-fluorobenzyl)carbamoyl] methyl}-N-cyclohexyl-1 <i>H</i> - 1,2,4-triazole-5-carboxamide	487.9	

Compound	Chemical name	Molecular weight (Daltons)	Chemical Structure
Example 23	Ethyl 3-(4-chlorophenyl)-1- {[(3- fluorobenzyl)carbamoyl]meth- yl}-1 <i>H</i> -pyrazole-5- carboxylate	415.9	
Example 24	Methyl 1-[(3-fluorobenzyl) carbamoyl]methyl-3-(3- methoxyphenyl)-1 <i>H</i> - pyrazole-5-carboxylate	397.4	
Example 25	3-(4-chloro-3-fluorophenyl)-1- {[(3- methoxybenzyl)carbamoyl] methyl}-N-methyl-1 <i>H</i> - pyrazole-5-carboxamide	430.9	
Example 26	3-(4-chloro-3-fluorophenyl)-1- {[(3-fluorobenzyl)carbamoyl] methyl}-N-methyl-1 <i>H</i> - pyrazole-5-carboxamide	418.8	
Example 27	Ethyl 3-(4-chlorophenyl)-1- {[(3- methoxybenzyl)carbamoyl] methyl}-1 <i>H</i> -pyrazole-5- carboxylate	427.9	
Example 28	3-(4-chloro-3-fluorophenyl)-1- ({[(1 <i>H</i> -indazol-5- yl)methyl]carbamoyl}methyl)- N-methyl-1 <i>H</i> -1,2,4-triazole-5- carboxamide	441.9	

Compound	Chemical name	Molecular weight (Daltons)	Chemical Structure
Example 29	<i>N</i> -[(1 <i>H</i> -imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1 <i>H</i> -1,2,4-triazol-1-yl]acetamide	362.8	
Example 30	2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1 <i>H</i> -imidazol-1-yl]- <i>N</i> -(3,5-dichlorobenzyl)acetamide	440.7	
Example 31	Methyl 3-(4-cyanophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl-1 <i>H</i> -1,2,4-triazole-5-carboxylate	405.4	
Example 32	3-(4-cyanophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl- <i>N</i> -methyl-1 <i>H</i> -1,2,4-triazole-5-carboxamide	404.4	

Table 2: Enzyme assay data for PDE4D5, a long form of PDE4

Using the method described in Experiment 1, the following PDE4D5 activation data were obtained for compounds of the present invention.

5

Compound	Protocol A or B	% increase in PDE4D5 activity at 30 $\mu$ M*
Example 1	A	105
Example 2	A	92.9
Example 3	A	62.6
Example 17	B	81.1
Example 18	B	83.9
Example 19	B	84.1
Example 20	B	63.3
Example 21	B	105

Compound	Protocol A or B	% increase in PDE4D5 activity at 30 µM*
Example 22	B	53.1
Example 23	B	93.7
Example 24	B	87.4
Example 25	B	39.5
Example 26	B	38.2
Example 27	B	75.1
Example 28	B	101
Example 29	B	31.9
Example 30	B	87.6

\*Measured as mean % increase in counts over basal activity

Table 3: Enzyme assay data for PDE4B1, another long form of PDE4

Using the method described in Experiment 1, the following PDE4B1 activation data were  
5 obtained for compounds of the present invention.

Compound	Protocol A or B	% increase in PDE4B1 activity at 30 µM*
Example 4	B	80.5
Example 5	B	44.0
Example 8	A	50.9
Example 9	A	58.5
Example 10	B	85.1
Example 11	A	84.1
Example 12	B	89.2
Example 16	B	52.2

\*Measured as mean % increase in counts over basal activity

In addition, Examples 14 and 15 each showed a greater than 30% increase in PDE4B1  
10 activity at 10 µM.

Table 4: Enzyme assay data for PDE4B2, a short form of PDE4

Using the method described in Experiment 1, the following PDE4B2 data were obtained for  
compounds of the present invention.

15

Compound	Protocol A or B	% increase in PDE4B2 activity at 30 µM*
Example 1	A	19.5
Example 2	A	-2.5
Example 3	A	-0.9

Compound	Protocol A or B	% increase in PDE4B2 activity at 30 $\mu$ M*
Example 10	B	23.3
Example 20	B	-22.4
Example 25	B	21.0
Example 26	B	17.1
Example 27	B	7.6
Example 28	B	-7.9

\*Measured as mean % increase in counts over basal activity

All publications cited herein are incorporated herein by reference. Citation of publications is not intended as an admission that any is pertinent prior art, nor does it constitute any

5 admission as to the contents or date of the same.

Those of skill in the art will recognize that the invention can be practiced in a variety of

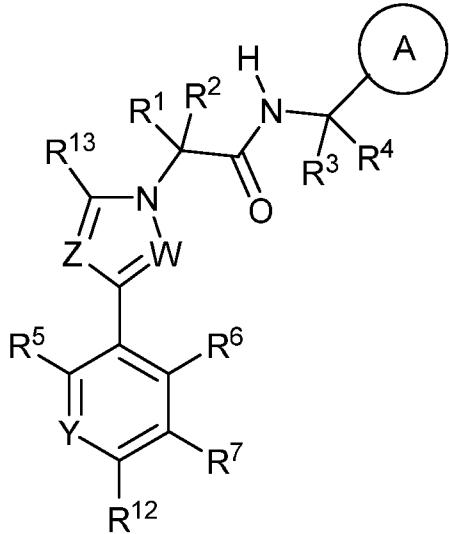
embodiments and that the foregoing description and examples are for purposes of

illustration and not limitation of the claims that follow. The invention may be embodied in

10 other specific forms without departing from the spirit or scope thereof. Changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

1. A compound for use in therapy, wherein the compound is a compound of Formula I:



5 Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-

10 NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy;

15 Y is selected from N and CR<sup>11</sup>;

R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

20 W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl; A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, a 5-membered heteroaromatic ring that contains 1 to 3 heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, and a fused 9-membered 25 bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N;

wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

5 R<sup>13</sup> is selected from -C(O)X, -CN, H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

10 X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;  
each R<sup>8a</sup>, R<sup>9a</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy; and  
each R<sup>16</sup> and R<sup>17</sup>, when present, is independently selected from H and (C1-4)alkyl;

15 provided that:  
when (i) Z is N, W is N, Y is CR<sup>11</sup> and A is an optionally substituted 6-membered aromatic ring; or (ii) A is an optionally substituted fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, or an optionally substituted fused 9-membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3  
20 heteroatoms selected from O, S and N; R<sup>13</sup> is -C(O)X or -CN.

2. A compound or pharmaceutically acceptable salt for use of claim 1, wherein:  
(i) W and Z are both N or W is N and Z is CR<sup>19</sup>; or  
(ii) Z is N and W is CR<sup>19</sup>.

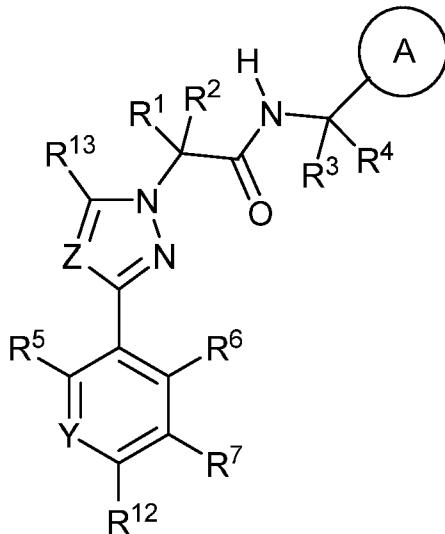
25 3. A compound or pharmaceutically acceptable salt for use of claim 1 or 2, wherein:  
R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;  
30 each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-4)alkyl;  
R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;  
R<sup>13</sup> is selected from -C(O)X, -CN, H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN  
35

and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the

5 (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

4. A compound or pharmaceutically acceptable salt for use of claim 1, wherein the compound or pharmaceutically acceptable salt is a compound of Formula Ia:



10

Formula Ia

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

15 R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

Y is selected from N and CR<sup>11</sup>;

R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy,

20 (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, and a 5-membered heteroaromatic ring that contains 1 to 3 heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five

25 substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-

NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

R<sup>13</sup> is selected from -C(O)X, -CN, H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from

5 OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-

10 4)alkyl;

each R<sup>16</sup> and R<sup>17</sup>, when present, is independently selected from H and (C1-4)alkyl;

provided that when Z is N, Y is CR<sup>11</sup> and A is an optionally substituted 6-membered aromatic ring, R<sup>13</sup> is -C(O)X or -CN.

15 5. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein R<sup>5</sup> and R<sup>6</sup> are H and/or wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H.

6. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

7. A compound or pharmaceutically acceptable salt for use of any of any of the preceding claims, wherein Y is CR<sup>11</sup> and R<sup>11</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

8. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein R<sup>19</sup>, when present, is H.

30 9. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein Z is N or CH.

10. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein R<sup>12</sup> is selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

11. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

12. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, A is a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one or two N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

13. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein R<sup>13</sup> is selected from -C(O)X, -CN, H, methyl, ethyl and methoxymethyl.

14. A compound or pharmaceutically acceptable salt for use of any of the preceding claims, wherein:

- (i) R<sup>13</sup> is not H; or
- 20 (ii) R<sup>13</sup> is selected from -C(O)X and -CN.

15. A compound or pharmaceutically acceptable salt for use of claim 1, selected from:

Methyl 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1H-1,2,4-triazole-5-carboxylate;

25 Ethyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate;

Methyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate;

30 Ethyl 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1H-1,2,4-triazole-5-carboxylate;

Ethyl 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1H-1,2,4-triazole-5-carboxylate;

35 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1H-1,2,4-triazole-5-carboxylic acid;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1H-1,2,4-triazole-5-carboxylic acid;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxamide;

5 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

10 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-fluorobenzyl)acetamide;

*N*-(3-fluorobenzyl)-2-[5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl]acetamide;

15 *N*-benzyl-2-[3-(4-chlorophenyl)-1*H*-pyrazol-1-yl]acetamide;

2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-methoxybenzyl)acetamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-isopropyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

20 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N*-ethyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N*-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

25 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N*-cyclohexyl-1*H*-1,2,4-triazole-5-carboxamide;

30 Ethyl 3-(4-chlorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylate;

Methyl 1-{[(3-fluorobenzyl) carbamoyl]methyl}-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide;

35 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide;

Ethyl 3-(4-chlorophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-{[(1*H*-indazol-5-yl)methyl]carbamoyl}methyl)-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

5 *N*-[(1*H*-imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetamide;

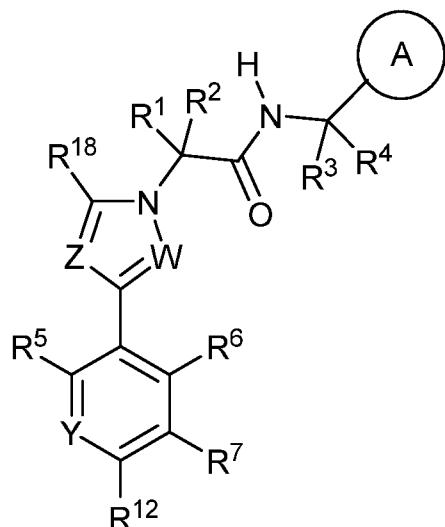
2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl)acetamide;

Methyl 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate;

10 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

and pharmaceutically acceptable salts thereof.

16. A compound of Formula II:



15 Formula II

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

20 R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy;

25 Y is selected from N and CR<sup>11</sup>;

$R^{11}$ , when present, and  $R^{12}$  are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

5 W and Z are each, independently, selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl; A is selected from a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one to three N atoms, a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, and a fused 9-membered 10 bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N;

15 wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros;

20 R<sup>18</sup> is selected from -C(O)X and -CN;  
X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;  
each R<sup>8a</sup>, R<sup>9a</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy;

25 wherein when Y is N, and A is a 6-membered aromatic ring, or a 5-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted as defined above, R<sup>18</sup> may additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with one or more substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with one or more fluoros; and each R<sup>16</sup> and R<sup>17</sup>, when present, is independently selected from H and (C1-4)alkyl.

30

17. A compound or pharmaceutically acceptable salt of claim 16, wherein:

(i) W and Z are both N or W is N and Z is CR<sup>19</sup>; or

(ii) Z is N and W is CR<sup>19</sup>.

35 18. A compound or pharmaceutically acceptable salt of claim 16 or 17, wherein:

$R^7$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; each R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup>, when present, is independently selected from H and (C1-4)alkyl;

5 R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen,

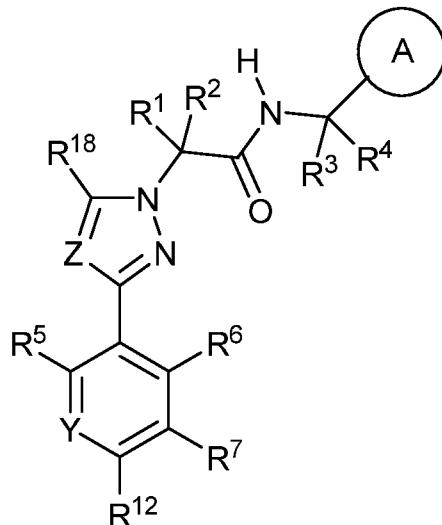
10 the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and

wherein when Y is N, and A is a 6-membered aromatic ring, or a 5-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is

15 optionally substituted as defined above, R<sup>18</sup> may additionally be selected from H, (C1-6)alkyl and (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

20

19. A compound or pharmaceutically acceptable salt of claim 16, wherein the compound or pharmaceutically acceptable salt is a compound of Formula IIa:



Formula IIa

25 or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

$R^7$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

Y is selected from N and CR<sup>11</sup>;

5  $R^{11}$ , when present, and  $R^{12}$  are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one 10 to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

15  $R^{18}$  is selected from -C(O)X and -CN;

X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

each  $R^8$ ,  $R^{8a}$ ,  $R^9$ ,  $R^{9a}$ ,  $R^{10}$  and  $R^{10a}$ , when present, is independently selected from H and (C1-4)alkyl; and

wherein when Y is N,  $R^{18}$  may additionally be selected from H, (C1-6)alkyl and (C3-20 7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-NR<sup>16</sup>R<sup>17</sup>, C(O)-OR<sup>16</sup>, S(O)<sub>2</sub>-NR<sup>16</sup>R<sup>17</sup>, CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and

each  $R^{16}$  and  $R^{17}$ , when present, is independently selected from H and (C1-4)alkyl.

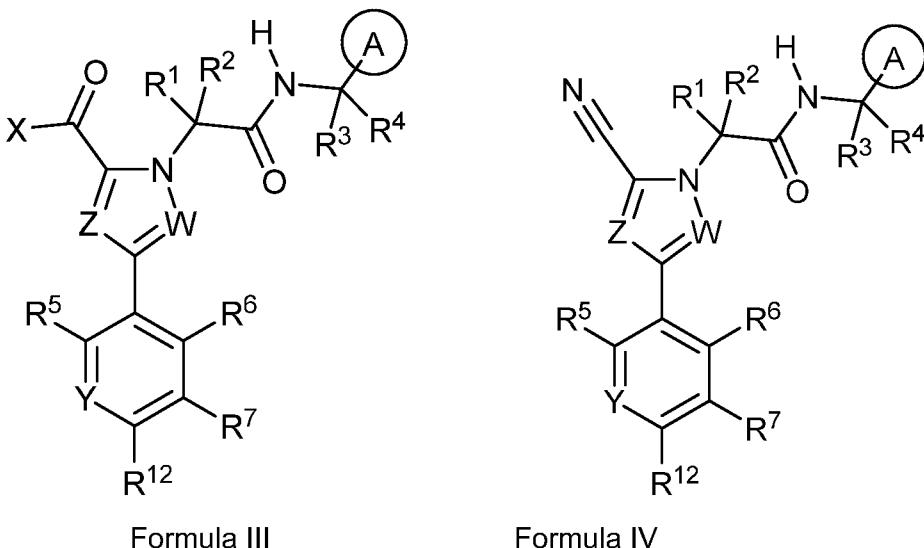
25

20. A compound or pharmaceutically acceptable salt of any of claims 16 to 19, wherein:

(i)  $R^{18}$  is not H; or

(ii)  $R^{18}$  is -C(O)X or -CN.

30 21. A compound or pharmaceutically acceptable salt of any of claims 16 to 18, wherein the compound or pharmaceutically acceptable salt is a compound of Formula III or Formula IV:



or a pharmaceutically acceptable salt thereof, wherein

$R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are independently selected from H and (C1-4)alkyl;

5  $R^5$  and  $R^6$  are independently selected from H and F;

$R^7$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

$X$  is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

10  $Y$  is selected from N and CR<sup>11</sup>;

$R^{11}$ , when present, and  $R^{12}$  are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

$W$  and  $Z$  are each, independently, selected from N and CR<sup>19</sup>, wherein  $R^{19}$  is H or (C1-4)alkyl;

15 and

$A$  is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, or wherein  $A$  is a fused 10-membered bicyclic aromatic ring system or heteroaromatic ring system that contains one to three N atoms, and a fused 9-

20 membered bicyclic aromatic heteroaromatic ring system that contains 1 to 3 heteroatoms selected from O, S and N;

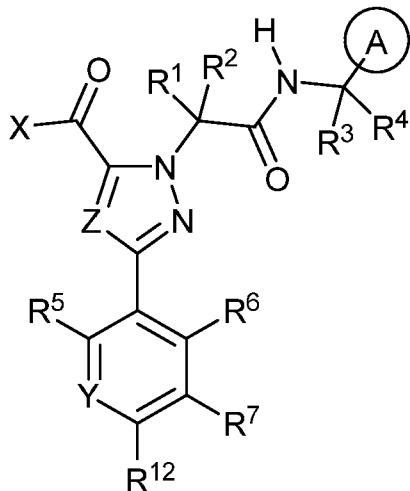
wherein  $A$  is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted

25 with 1 to 3 fluoros;

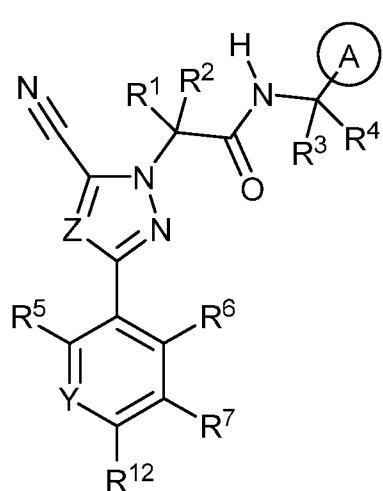
each  $R^8$ ,  $R^9$  and  $R^{10}$ , when present, is independently selected from H and (C1-4)alkyl; and

each R<sup>8a</sup>, R<sup>9a</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-6)alkyl, the (C1-6)alkyl being optionally substituted with one or more groups independently selected from fluoro, OH and (C1-4)alkyloxy.

5 22. A compound or pharmaceutically acceptable salt of any of claims 16 to 21, wherein the compound or pharmaceutically acceptable salt is a compound of Formula IIIa or Formula IVa:



Formula IIIa



Formula IVa

10 or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

15 X is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup>;

Y is selected from N and CR<sup>11</sup>;

R<sup>11</sup>, when present, and R<sup>12</sup> are independently selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

20 Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

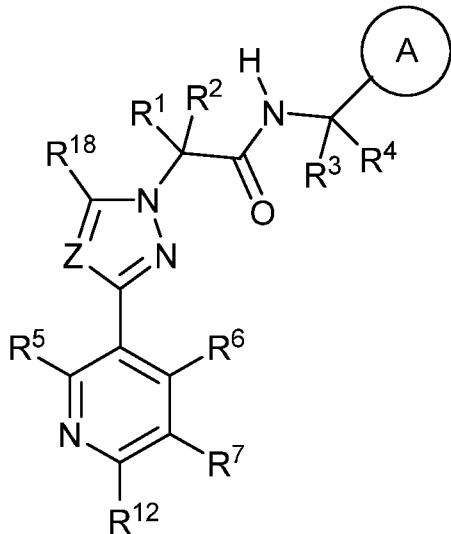
A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents

25 selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros; and

each R<sup>8</sup>, R<sup>8a</sup>, R<sup>9</sup>, R<sup>9a</sup>, R<sup>10</sup> and R<sup>10a</sup>, when present, is independently selected from H and (C1-4)alkyl.

23. A compound or pharmaceutically acceptable salt of any of claims 16 to 22, wherein Y  
5 is N.

24. A compound or pharmaceutically acceptable salt of any of claims 16 to 23, wherein  
the compound or pharmaceutically acceptable salt is a compound of Formula V:



10 Formula V

or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from H and (C1-4)alkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from H and F;

R<sup>7</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-

15 NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

R<sup>12</sup> is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-

NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

20 Z is selected from N and CR<sup>19</sup>, wherein R<sup>19</sup> is H or (C1-4)alkyl;

A is a 6-membered aromatic ring, or a 6-membered heteroaromatic ring that contains one to three N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to five substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros;

25

$R^{18}$  is  $-C(O)X$ , CN, H, (C1-6)alkyl or (C3-7)cycloalkyl, the (C1-6)alkyl and (C3-7)cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from OH, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-NR^{16}R^{17}$ ,  $C(O)-OR^{16}$ ,  $S(O)_2-NR^{16}R^{17}$ , CN and halogen, the (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3

5 fluoros;

X is selected from  $OR^{8a}$  and  $NR^{9a}R^{10a}$ ;

each  $R^8$ ,  $R^{8a}$ ,  $R^9$ ,  $R^{9a}$ ,  $R^{10}$  and  $R^{10a}$ , when present, is independently selected from H and (C1-4)alkyl; and

each  $R^{16}$  and  $R^{17}$ , when present, is independently selected from H and (C1-4)alkyl.

10 25. A compound or pharmaceutically acceptable salt of any of claims 16 to 24, wherein  $R^5$  and  $R^6$  are H and/or wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are H.

15 26. A compound or pharmaceutically acceptable salt of any of claims 16 to 25 wherein  $R^7$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

27. A compound or pharmaceutically acceptable salt of any of claims 16 to 26, wherein  $R^{19}$ , when present, is H.

20 28. A compound or pharmaceutically acceptable salt of any of claims 16 to 27, wherein Z is N or CH.

25 29. A compound or pharmaceutically acceptable salt of any of claims 16 to 23 and 25 to 28, wherein Y is  $CR^{11}$  and  $R^{11}$  is selected from H, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3

fluoros.

30. 30. A compound or pharmaceutically acceptable salt of claim 29, wherein  $R^{11}$  is H or halogen.

30

31. 31. A compound or pharmaceutically acceptable salt of any of claims 16 to 30, wherein  $R^{12}$  is selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

35 32. 32. A compound or pharmaceutically acceptable salt of any of claims 16 to 31, wherein A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl,  $C(O)-OR^8$ ,  $C(O)-NR^9R^{10}$ ,  $S(O)_2-NR^9R^{10}$ , CN and halogen, the

(C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

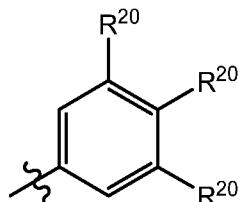
33. A compound or pharmaceutically acceptable salt of any of claims 16 to 32, wherein A is a 6-membered aromatic ring, a 6-membered heteroaromatic ring that contains one or two N atoms, or a 5-membered heteroaromatic ring that contains one to three heteroatoms selected from O, S and N, wherein A is optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

10

34. A compound or pharmaceutically acceptable salt of any of claims 16 to 33, wherein A is a phenyl ring, optionally substituted with one to three substituents selected from (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

15

35. A compound or pharmaceutically acceptable salt of any of claims 16 to 31, wherein A is:



20

wherein each R<sup>20</sup> is independently selected from hydrogen, (C1-4)alkyl, (C1-4)alkyloxy, (C1-4)alkylsulfonyl, C(O)-OR<sup>8</sup>, C(O)-NR<sup>9</sup>R<sup>10</sup>, S(O)<sub>2</sub>-NR<sup>9</sup>R<sup>10</sup>, CN and halogen, the (C1-4)alkyl, (C1-4)alkyloxy and (C1-4)alkylsulfonyl groups being optionally substituted with 1 to 3 fluoros.

25

36. A compound or pharmaceutically acceptable salt of claim 35, wherein each R<sup>20</sup> is independently selected from hydrogen, (C1-4)alkyl, (C1-4)alkyloxy, CN and halogen, the (C1-4)alkyl and (C1-4)alkyloxy groups being optionally substituted with 1 to 3 fluoros.

30

37. A compound or pharmaceutically acceptable salt of claim 35 or 36, wherein one or two instances of R<sup>20</sup> are not hydrogen.

38. A compound or pharmaceutically acceptable salt of any of claims 16 to 20 and 23 to 37, wherein: (a) Y, when present, is N and R<sup>18</sup> is selected from -C(O)X, -CN, H, methyl, ethyl and methoxymethyl; or (b) R<sup>18</sup> is -C(O)X and X is NR<sup>9a</sup>R<sup>10a</sup>.

5 39. A compound or pharmaceutically acceptable salt of any of claims 16 to 18, 21 and 25 to 37 wherein X, when present, is selected from NH<sub>2</sub>, NH(C1-6alkyl), NH(C1-2alkyloxyC1-2alkyl), N(C1-2alkyl)<sub>2</sub> or O(C1-2alkyl).

10 40. A compound or pharmaceutically acceptable salt of any of claims 16 to 38, wherein X, when present, is selected from OR<sup>8a</sup> and NR<sup>9a</sup>R<sup>10a</sup> and each R<sup>8a</sup>, R<sup>9a</sup> and R<sup>10a</sup>, when present within X, is independently selected from H and (C1-2)alkyl.

41. A compound or pharmaceutically acceptable salt of claim 16, selected from:

Methyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxylate;

Ethyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate;

Methyl 1-[(benzylcarbamoyl)methyl]-3-(4-chloro-3-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate;

20 Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxylate;

Ethyl 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxylic acid;

3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxylic acid;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxamide;

30 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-1H-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-N-methyl-1H-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-[(3-fluorobenzyl)carbamoyl]methyl]-N,N-dimethyl-1H-1,2,4-triazole-5-carboxamide;

35 3-(4-chloro-3-fluorophenyl)-1-[(3-methoxybenzyl)carbamoyl]methyl]-N-methyl-1H-1,2,4-triazole-5-carboxamide;

2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-fluorobenzyl)acetamide;

5 *N*-(3-fluorobenzyl)-2-[5-methyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl]acetamide;

2-[3-(4-chloro-3-fluorophenyl)-5-cyano-1*H*-1,2,4-triazol-1-yl]-*N*-(3-methoxybenzyl)acetamide;

10 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl] methyl}-*N*-isopropyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl] methyl}-*N,N*-dimethyl-1*H*-1,2,4-triazole-5-carboxamide;

15 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl] methyl}-*N*-ethyl-1*H*-1,2,4-triazole-5-carboxamide;

3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl] methyl}-*N*-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

15 3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl] methyl}-*N*-(2-methoxyethyl)-1*H*-1,2,4-triazole-5-carboxamide;

Ethyl 3-(4-chlorophenyl)-1-{[(3-fluorobenzyl)carbamoyl]methyl}-1*H*-pyrazole-5-carboxylate;

20 Methyl 1-{[(3-fluorobenzyl) carbamoyl]methyl}-3-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate;

3-(4-chloro-3-fluorophenyl)-1-{[(3-methoxybenzyl)carbamoyl] methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide;

25 3-(4-chloro-3-fluorophenyl)-1-{[(3-fluorobenzyl)carbamoyl] methyl}-*N*-methyl-1*H*-pyrazole-5-carboxamide;

Ethyl 3-(4-chlorophenyl)-1-{[(3-methoxybenzyl)carbamoyl] methyl}-1*H*-pyrazole-5-carboxylate;

30 3-(4-chloro-3-fluorophenyl)-1-{[(1*H*-indazol-5-yl)methyl]carbamoyl}methyl)-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

*N*-[(1*H*-imidazol-5-yl)methyl]-2-[3-(4-chloro-3-fluorophenyl)-5-ethyl-1*H*-1,2,4-triazol-1-yl]acetamide;

2-[4-(4-chloro-3-fluorophenyl)-2-ethyl-1*H*-imidazol-1-yl]-*N*-(3,5-dichlorobenzyl)acetamide;

Methyl 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-1*H*-1,2,4-triazole-5-carboxylate;

35 3-(4-cyanophenyl)-1-{[(3-methoxybenzyl)carbamoyl]methyl}-*N*-methyl-1*H*-1,2,4-triazole-5-carboxamide;

and pharmaceutically acceptable salts thereof.

42 A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt as defined in any of claims 1 to 41, and a pharmaceutically acceptable excipient.

5

43. A compound or pharmaceutically acceptable salt for use of claim 1, wherein the compound or pharmaceutically acceptable salt is as defined in any of claims 16 to 41.

44. A compound or pharmaceutically acceptable salt for use of any of claims 1 to 15 or 10 43, for use in the treatment or prevention of a disease or disorder mediated by excessive intracellular cyclic AMP signalling.

45. A method of treating or preventing a disease or disorder mediated by excessive 15 intracellular cyclic AMP signalling, comprising administering to a patient in need thereof an effective amount of a compound or a pharmaceutically acceptable salt as defined in any of claims 1 to 41.

46. Use of a compound or a pharmaceutically acceptable salt as defined in any of claims 20 1 to 41, in the manufacture of a medicament for treatment or prevention of a disease or disorder mediated by excessive intracellular cyclic AMP signalling.

47. The compound for use, use or method of any of claims 44-46 wherein the excessive intracellular cyclic AMP signalling is caused by:

- 25 a. excessive hormone levels produced by an adenoma.
- b. a gain-of-function gene mutation in a G-protein coupled receptor (GPCR);
- c. an activating mutation in the GNAS1 gene, which encodes the  $\alpha$ -subunit of the G-protein  $G_s$ ; or
- d. a bacterial toxin.

30 48. The compound for use, use or method of any of claims 44 to 47, wherein the disease is cancer.

49. The compound for use, use or method of claim 48, wherein the cancer is prostate cancer.

35

50. The compound for use, use or method of any of claims 44 to 47, wherein the disease is:

- e. pituitary adenoma, Cushing's disease, polycystic kidney disease or polycystic liver disease;
- f. hyperthyroidism, Jansens's metaphyseal chondrodysplasia, hyperparathyroidism, or familial male-limited precocious puberty;
- 5 g. McCune-Albright syndrome;
- h. cholera, whooping cough, anthrax, or tuberculosis;
- i. HIV, AIDS, or Common Variable Immunodeficiency (CVID);
- j. melanoma, pancreatic cancer, leukaemia, prostate cancer, adrenocortical tumours, testicular cancer, primary pigmented nodular adrenocortical diseases
- 10 (PPNAD), or Carney Complex;
- k. autosomal dominant polycystic kidney disease (ADPKD) or autosomal recessive polycystic kidney disease (ARPKD); or
- l. maturity onset diabetes of young type 5 (MODY5); or
- m. cardiac hypertrophy.

15

- 51. The compound for use, use or method of claim 50, wherein the disease is:
  - n. autosomal dominant polycystic kidney disease (ADPKD); or
  - o. autosomal recessive polycystic kidney disease (ARPKD).

FIGURE 1

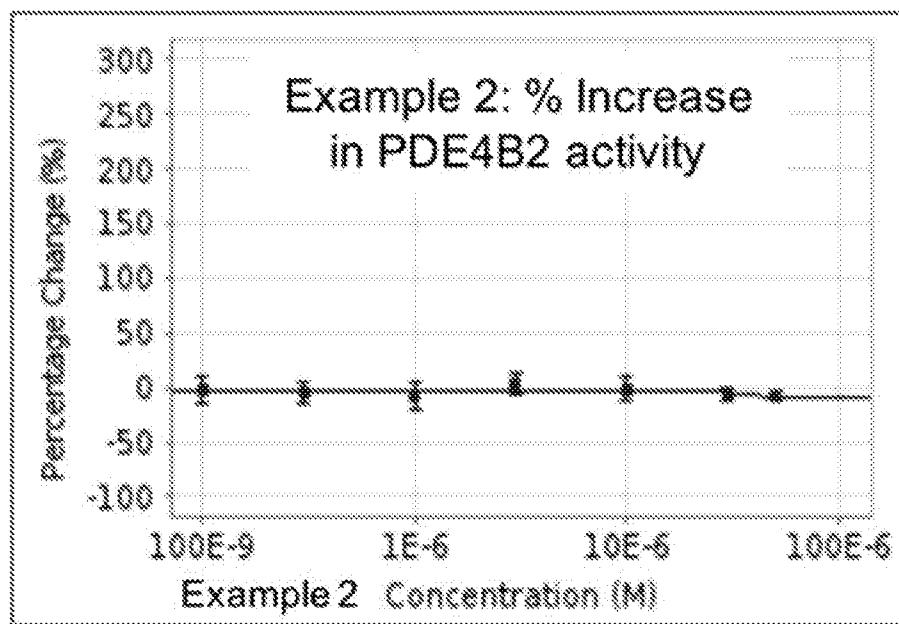
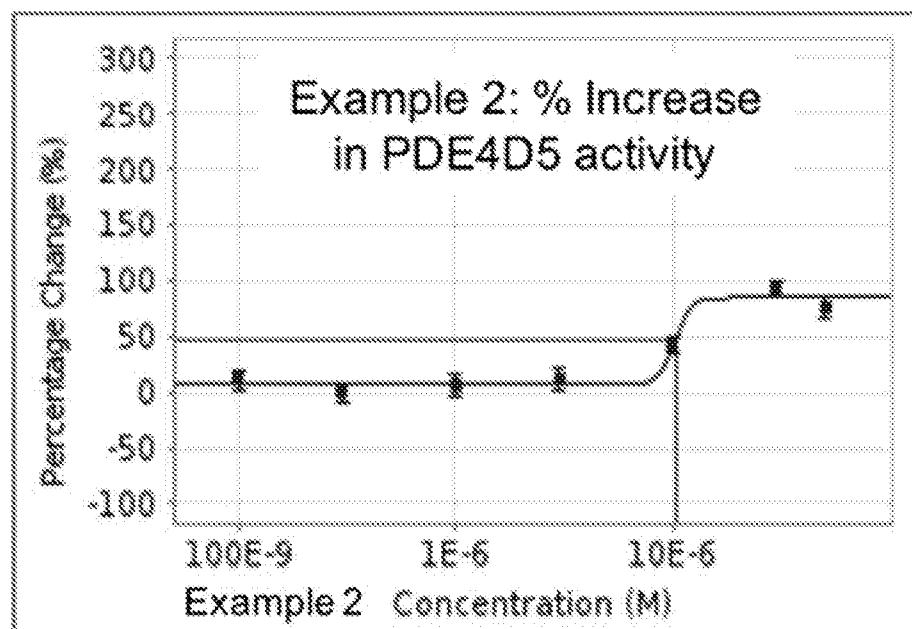


FIGURE 2

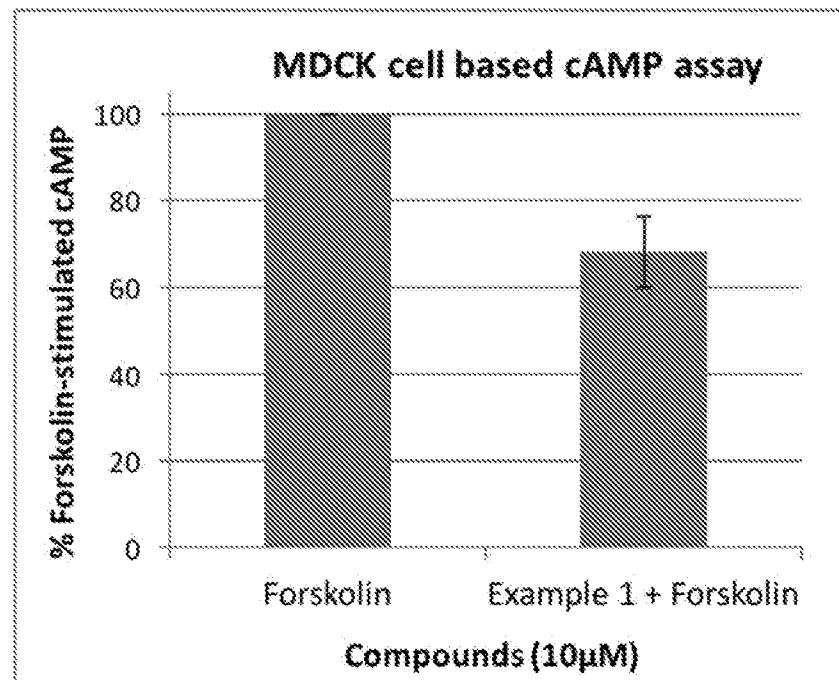
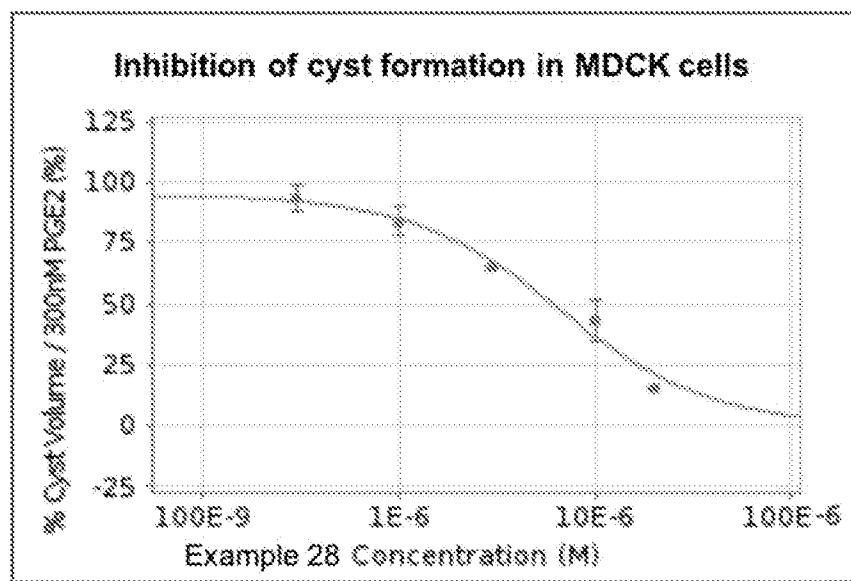


FIGURE 3



# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2017/052898

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>				
INV.	C07D403/12	A61K31/4196	C07D249/08	A61P35/00
	A61P13/00	A61P5/00	A61P11/00	A61P9/00

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

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

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

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/186900 A1 (VICKER NIGEL [GB] ET AL) 23 July 2009 (2009-07-23) abstract; claims 1,24; examples 51,52 -----	1-51
X	WO 2004/071447 A2 (TRANSTECH PHARMA INC [US]; MJALLI ADNAN M M [US]; ANDREWS ROBERT C [US] 26 August 2004 (2004-08-26) abstract; claims 1,24,; examples 64,65,71,80,82-87,91-93,102,178,271 -----	1-51
X	US 2005/137168 A1 (GOBBI L; GOBBI L C; GROEBKE Z K; GROEBKE ZBINDEN K; MOHR P; OBST U; ZB) 23 June 2005 (2005-06-23) abstract RN 854761-26-5 as well as 854761-25-4, registered as intermediates are both excluded by the present specific substituents' definitions ----- -/-	1-51

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2017	05/12/2017

Name and mailing address of the ISA/  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Goss, Ilaria

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2017/052898

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 2016/151300 A1 (MIRONID LTD [GB]) 29 September 2016 (2016-09-29) the whole document -----	1-51
A	US 2012/053218 A1 (BRUEGGEMEIER ULF [DE] ET AL) 1 March 2012 (2012-03-01) the whole document -----	1-51

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2017/052898

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US 2009186900	A1	23-07-2009	CA 2643670 A1 EP 2013176 A2 US 2009186900 A1 WO 2007096647 A2		30-08-2007 14-01-2009 23-07-2009 30-08-2007
WO 2004071447	A2	26-08-2004	AU 2004210711 A1 CA 2514363 A1 CN 1747936 A EP 1594847 A2 JP 2006518738 A US 2004192743 A1 US 2011077399 A1 WO 2004071447 A2		26-08-2004 26-08-2004 15-03-2006 16-11-2005 17-08-2006 30-09-2004 31-03-2011 26-08-2004
US 2005137168	A1	23-06-2005	AU 2004299243 A1 BR PI0417274 A CA 2549825 A1 CN 1894235 A EP 1706396 A1 JP 2007514676 A KR 20060101538 A US 2005137168 A1 WO 2005058868 A1		30-06-2005 27-03-2007 30-06-2005 10-01-2007 04-10-2006 07-06-2007 25-09-2006 23-06-2005 30-06-2005
WO 2016151300	A1	29-09-2016	NONE		
US 2012053218	A1	01-03-2012	AU 2010225241 A1 BR PI1009240 A2 CA 2755590 A1 CN 102369190 A DE 102009013642 A1 EP 2408754 A1 ES 2436630 T3 JP 2012520834 A KR 20110134914 A RU 2011141876 A US 2012053218 A1 WO 2010105750 A1 ZA 201106688 B		29-09-2011 15-03-2016 23-09-2010 07-03-2012 23-09-2010 25-01-2012 03-01-2014 10-09-2012 15-12-2011 27-04-2013 01-03-2012 23-09-2010 26-03-2014