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(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: This invention relates to compounds that inhibit or modulate the activity of Chk-1 kinase. Also provided are pharmaceutical compositions containing the compounds and the therapeutic uses of the compounds.

## PHARMACEUTICAL COMPOUNDS

This invention relates to compounds that inhibit or modulate the activity of Chk-1 kinase. Also provided are pharmaceutical compositions containing the compounds and the therapeutic uses of the compounds.

### 5 Background of the Invention

Chk-1 is a serine/threonine kinase involved in the induction of cell cycle checkpoints in response to DNA damage and replicative stress [*Clin. Can. Res.* 2007;13(7)]. Cell cycle checkpoints are regulatory pathways that control the order and timing of cell cycle transitions. Most cancer cells have impaired G1 checkpoint activation due to a defective  
10 p53 tumor suppressor protein. Hahn *et al.*, "Rules for making human tumor cells" *N. Engl. J. Med.* 2002; **347**: 1593–603 and Hollstein *et al.*, "p53 mutations in human cancers" *Science* 1991; **253**: 49–53) have reported that tumours are associated with mutations in the p53 gene, a tumour suppressor gene found in about 50% of all human cancers.

Chk-1 inhibition abrogates the intra S and G2/M checkpoints and has been shown to  
15 selectively sensitise tumour cells to well known DNA damaging agents. Examples of DNA damaging agents where this sensitising effect has been demonstrated include Gemcitabine, Pemetrexed, Cytarabine, Irinotecan, Camptothecin, Cisplatin, Carboplatin [*Clin. Cancer Res.* 2010, 16, 376], Temozolomide [*Journal of Neurosurgery* 2004, 100, 1060], Doxorubicin [*Bioorg. Med. Chem. Lett.* 2006;16:421- 6], Paclitaxel  
20 [WO2010149394], Hydroxy urea [*Nat. Cell. Biol.* 2005 Feb;7(2):195-20], the nitroimidazole hypoxia-targetted drug TH-302 (Meng *et al.*, AACR, 2013 Abstract No. 2389) and ionising radiation [*Clin. Cancer Res.* 2010, 16, 2076]. See also the review article by McNeely, S., et al., "CHEK again: Revisiting the development of CHK1 inhibitors for cancer therapy, *Pharmacology & Therapeutics* (2014), [http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/j.pharmthera.2013.10.005)  
25 [j.pharmthera.2013.10.005](http://dx.doi.org/10.1016/j.pharmthera.2013.10.005).

Recently published data have also shown that Chk-1 inhibitors may act synergistically with PARP inhibitors [*Cancer Res.*; 66: (16)], Mek inhibitors [*Blood.* 2008 September 15; 112(6): 2439–2449], Farnesyltransferase inhibitors [*Blood.* 2005 Feb 15;105(4):1706-16], Rapamycin [*Mol. Cancer Ther.* 2005 Mar;4(3):457-70], Src inhibitors [*Blood.* 2011 Feb  
30 10;117(6):1947-57] and WEE1 inhibitors (Chaudhuri *et al.*, *Haematologica*, 2013.093187).

Resistance to chemotherapy and radiotherapy, a clinical problem for conventional therapy, has been associated with activation of the DNA damage response in which Chk-1 has been implicated (Chk-1 activation is associated with radioresistance in

glioblastoma [*Nature*; 2006; 444(7):756-760] and the inhibition of Chk-1 sensitises lung cancer brain metastases to radiotherapy [*Biochem. Biophys. Res. Commun.* 2011 March 4;406(1):53-8]).

It is also envisaged that Chk-1 inhibitors, either as single agents or in combination, may  
5 be useful in treating tumour cells in which constitutive activation of DNA damage and  
checkpoint pathways drive genomic instability. This phenotype is associated with  
complex karyotypes in samples from patients with acute myeloid leukemia (AML) [*Cancer  
Research* 2009, **89**, 8652]. *In vitro* antagonisation of the Chk-1 kinase with a small  
molecule inhibitor or by RNA interference strongly reduces the clonogenic properties of  
10 high-DNA damage level AML samples. In contrast Chk-1 inhibition has no effect on  
normal hematopoietic progenitors. Furthermore, recent studies have shown that the  
tumour microenvironment drives genetic instability [*Nature*; 2008;(8):180-192] and loss of  
Chk-1 sensitises cells to hypoxia/reoxygenation [*Cell Cycle*; 2010; 9(13):2502]. In  
neuroblastoma, a kinome RNA interference screen demonstrated that loss of Chk-1  
15 inhibited the growth of eight neuroblastoma cell lines. Tumour cells deficient in Fanconi  
anemia DNA repair have shown sensitivity to Chk-1 inhibition [*Molecular Cancer* 2009,  
**8**:24]. It has been shown that the Chk-1 specific inhibitor PF-00477736 inhibits the  
growth of thirty ovarian cancer cell lines [Bukczynska et al, 23<sup>rd</sup> Lorne Cancer  
Conference] and triple negative negative breast cancer cells [*Cancer Science* 2011, **102**,  
20 882]. Also, PF-00477736 has displayed selective single agent activity in a MYC  
oncogene driven murine spontaneous cancer model [Ferrao *et al*, *Oncogene* (15 August  
2011)]. Chk-1 inhibition, by either RNA interference or selective small molecule inhibitors,  
results in apoptosis of MYC-overexpressing cells both *in vitro* and in an *in vivo* mouse  
model of B-cell lymphoma [Höglund *et al.*, *Clinical Cancer Research*, Online First  
25 September 20, 2011]. The latter data suggest that Chk-1 inhibitors would have utility for  
the treatment of MYC-driven malignancies such as B-cell lymphoma/leukemia,  
neuroblastoma and some breast and lung cancers. Ewing sarcoma cell lines have also  
been reported to be sensitive to Chk kinase inhibitors (McCalla *et al.*, Kinase Targets in  
Ewing's Sarcoma Cell Lines using RNAi-based & Investigational Agents Screening  
30 Approaches, Molecular Targets 2013, Boston, USA).

It has also been reported that mutations that reduce the activity of DNA repair pathways  
can result in synthetically lethal interactions with Chk1 inhibition. For example, mutations  
that disrupt the RAD50 complex and ATM signaling increase responsiveness to Chk1  
inhibition [Al-Ahmadie *et al.*, Synthetic lethality in ATM-deficient RAD50-mutant tumors  
35 underlie outlier response to cancer therapy]. Likewise, deficiencies in the Fanconi  
anemia homologous DNA repair pathway lead to sensitivity to Chk1 inhibition [Chen *et*

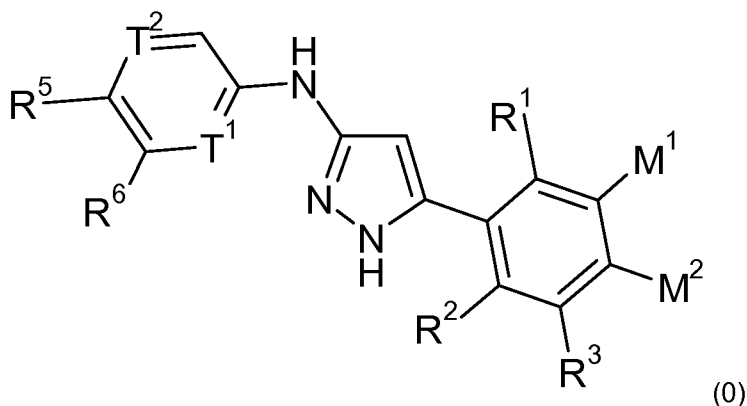
al., Chk1 inhibition as a strategy for targeting fanconi anemia (FA) DNA repair pathway deficient tumors. Mol. Cancer 2009 8:24, Duan et al., Fanconi anemia repair pathway dysfunction, a potential therapeutic target in lung cancer. Frontiers in Oncology 2014 4:1]. Also, human cells that have loss of function in the Rad17 gene product are sensitive to Chk1 suppression [Shen et al., Synthetic lethal interaction between tumor suppressor RAD17 and Chk1 kinase in human cancer cells. 2014 SACNAS National Conference Abstract].

Various attempts have been made to develop inhibitors of Chk-1 kinase. For example, WO 03/10444 and WO 2005/072733 (both in the name of Millennium) disclose aryl/heteroaryl urea compounds as Chk-1 kinase inhibitors. US2005/215556 (Abbott) discloses macrocyclic ureas as kinase inhibitors. WO 02/070494, WO2006014359 and WO2006021002 (all in the name of Icos) disclose aryl and heteroaryl ureas as Chk-1 inhibitors. Our earlier applications WO/2011/141716 and WO/2013/072502 both disclose substituted pyrazinyl-phenyl ureas as Chk-1 kinase inhibitors. WO2005/009435 (Pfizer) and WO2010/077758 (Eli Lilly) disclose aminopyrazoles as Chk-1 kinase inhibitors.

### The Invention

The present invention provides compounds having activity as Chk-1 kinase inhibitors.

Accordingly, in a first embodiment (Embodiment 1.0), the invention provides a compound of the formula (0):



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or a salt, N-oxide or tautomer thereof, wherein:

T<sup>1</sup> is selected from N and CH;

T<sup>2</sup> is selected from N, CH and CF;

R<sup>1</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy;

25 R<sup>2</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy;

R<sup>3</sup> is selected from hydrogen, methyl, fluorine, chlorine and bromine;

one of  $M^1$  and  $M^2$  is a group  $R^4$  selected from hydrogen, methyl, fluorine, chlorine and bromine; and the other of  $M^1$  and  $M^2$  is a moiety  $-A-R^7$ ;

$R^5$  is selected from hydrogen, cyano,  $C_{1-3}$  alkyl, cyclopropyl, chlorine, carboxy, and  $C_{1-3}$ -alkoxy-carbonyl;

- 5  $R^6$  is selected from hydrogen, fluorine,  $C_{1-4}$  alkyl; and  $C_{1-4}$  alkoxy optionally substituted with  $NR^dR^e$  where  $R^d$  and  $R^e$  are the same or different and each is selected from hydrogen and  $C_{1-4}$  alkyl, or  $NR^dR^e$  forms a 4 to 7 membered saturated heterocyclic ring optionally containing a second heteroatom ring member selected from N, O and S and oxidized forms of S, the saturated heterocyclic ring being optionally substituted with one  
10 or more substituents selected from oxo, methyl, hydroxy and fluorine;

A is selected from:

- (i) a bond;
- (ii)  $(CR^pR^q)_x$  where  $R^p$  and  $R^q$  are each independently hydrogen or methyl and  
15 x is 1 to 4;
- (iii) an oxygen atom;
- (iv) a group  $NR^r$  wherein  $R^r$  is hydrogen or methyl; and
- (v) a saturated chain of 2 to 10 chain members in length containing at least  
20 one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O,  $C_{1-4}$  hydrocarbyl, fluoro- $C_{1-4}$  hydrocarbyl, hydroxy- $C_{1-4}$  hydrocarbyl,  $C_{1-2}$ -alkoxy- $C_{1-4}$  hydrocarbyl, and fluorine  
25 wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;

- $R^7$  is selected from hydrogen;  $R^{11}SO_2^-$ ; amino;  $NH-Hyd^1$ ;  $N(Hyd^1)_2$ ; and a group  $Cyc^1$  wherein  $Cyc^1$  is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 10 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally  
30 substituted with one or more substituents  $R^8$ ; provided that when A is a bond,  $(CR^pR^q)_x$ , an oxygen atom or  $NR^r$ , then  $R^7$  is other than hydrogen; and provided also that when  $R^7$  is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members;

$R^8$  is selected from:

- 35
- halogen;
  - oxo;
  - cyano;

- nitro;
- a carbocyclic or heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and

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- a group R<sup>a</sup>-R<sup>b</sup>;

R<sup>a</sup> is a bond, O, CO, X<sup>1</sup>C(X<sup>2</sup>), C(X<sup>2</sup>)X<sup>1</sup>, X<sup>1</sup>C(X<sup>2</sup>)X<sup>1</sup>, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, SO<sub>2</sub>NR<sup>c</sup> or NR<sup>c</sup>SO<sub>2</sub>;  
R<sup>b</sup> is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- an acyclic C<sub>1-12</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C<sub>1-8</sub> non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; wherein one or more but not all of the carbon atoms of the acyclic C<sub>1-12</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, X<sup>1</sup>C(X<sup>2</sup>), C(X<sup>2</sup>)X<sup>1</sup> or X<sup>1</sup>C(X<sup>2</sup>)X<sup>1</sup>;

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R<sup>c</sup> is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- an acyclic C<sub>1-12</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C<sub>1-8</sub> non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; wherein one or more but not all of the carbon atoms of the acyclic C<sub>1-12</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH, N-C<sub>1-4</sub>

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alkyl, C(O)O, OC(O), NH(CO), C(O)NH, NH(CO)NH, N(C<sub>1-4</sub> alkyl)C(O), C(O)N(C<sub>1-4</sub> alkyl)

X<sup>1</sup> is O, S or NR<sup>c</sup>; and

X<sup>2</sup> is =O, =S or =NR<sup>c</sup>;

- 5 wherein R<sup>9</sup> is selected from R<sup>8</sup> provided that when the substituents R<sup>9</sup> contain a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group is unsubstituted or substituted with one or more substituents R<sup>10</sup>;
- R<sup>10</sup> is selected from halogen, oxo, cyano, and an acyclic C<sub>1-6</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano;
- 10 carboxy; amino; mono- or di-C<sub>1-2</sub> alkylamino; wherein one but not all of the carbon atoms of the acyclic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH or NMe;
- R<sup>11</sup> is selected from amino, Hyd<sup>1</sup>, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and Cyc<sup>1</sup>;
- Hyd<sup>1</sup> is a non-aromatic C<sub>1-6</sub> hydrocarbyl group optionally substituted by one or more
- 15 substituents selected from halogen, cyano, hydroxy, amino and Cyc<sup>1</sup>, wherein one or two of the carbon atoms of the non-aromatic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, NH, N-Hyd<sup>2</sup>, C(=O), S, SO or SO<sub>2</sub>, provided that at least one carbon atom of the hydrocarbyl group remains;
- Hyd<sup>2</sup> is a C<sub>1-4</sub> hydrocarbyl group;
- 20 and wherein in any group consisting of or containing a hydrocarbyl moiety, the hydrocarbyl moiety is a hydrocarbon group optionally containing one or more single, double or triple carbon-carbon bonds or combinations thereof.

Particular embodiments of the invention are as set out below in Embodiments 1.01 to 1.107.

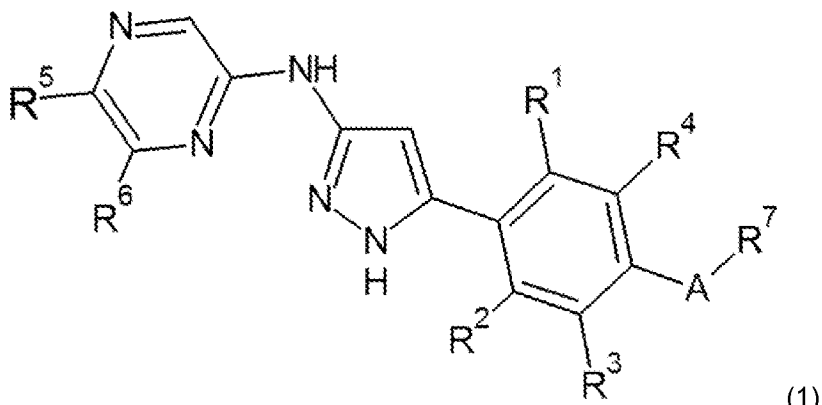
- 25 1.01 A compound according to Embodiment 1.0 wherein T<sup>2</sup> is N.
- 1.02 A compound according to Embodiment 1.01 wherein both T<sup>1</sup> and T<sup>2</sup> are N.
- 1.03 A compound according to any one of Embodiments 1.0 to 1.02 wherein M<sup>2</sup> is a moiety -A-R<sup>7</sup>.
- 1.04 A compound according to any one of Embodiments 1.0 to 1.03 wherein R<sup>5</sup> is
- 30 selected from hydrogen, cyano, C<sub>1-3</sub> alkyl, cyclopropyl and chlorine.
- 1.05 A compound according to Embodiment 1.04 wherein R<sup>5</sup> is selected from hydrogen, cyano, C<sub>1-3</sub> alkyl and cyclopropyl.

- 1.06 A compound according to Embodiment 1.05 wherein R<sup>5</sup> is selected from hydrogen, cyano and methyl.
- 1.07 A compound according to any one of Embodiments 1.0 to 1.06 wherein R<sup>6</sup> is selected from hydrogen, C<sub>1-4</sub> alkyl; and C<sub>1-4</sub> alkoxy optionally substituted with NR<sup>d</sup>R<sup>e</sup> where R<sup>d</sup> and R<sup>e</sup> are the same or different and each is selected from hydrogen and C<sub>1-4</sub> alkyl, or NR<sup>d</sup>R<sup>e</sup> forms a 4 to 7 membered saturated heterocyclic ring optionally containing a second heteroatom ring member selected from N, O and S and oxidized forms of S, the saturated heterocyclic ring being optionally substituted with one or more substituents selected from oxo, methyl, hydroxy and fluorine.
- 1.08 A compound according to any one of Embodiments 1.0 to 1.07 wherein A is selected from:
- (i) a bond;
  - (ii) (CR<sup>p</sup>R<sup>q</sup>)<sub>x</sub> where R<sup>p</sup> and R<sup>q</sup> are each independently hydrogen or methyl and x is 1 to 4;
  - (iii) an oxygen atom;
  - (iv) a group NR<sup>f</sup> wherein R<sup>f</sup> is hydrogen or methyl; and
  - (v) a saturated chain of 2 to 10 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbonyl and fluorine wherein two hydrocarbonyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members.
- 1.09 A compound according to any one of Embodiments 1.0 to 1.08 wherein A is selected from:
- (i) a bond;
  - (ii) CH<sub>2</sub>;
  - (iii) an oxygen atom; and
  - (iv) a saturated chain of 2 to 10 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents



selected from =O, C<sub>1-4</sub> hydrocarbonyl and fluorine wherein two hydrocarbonyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members.

1.1 A compound according to Embodiment 1.0 wherein the compound is of the formula (1):



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or a salt, N-oxide or tautomer thereof, wherein:

A is selected from:

- (i) a bond; and
- (ii) a saturated chain of 2 to 10 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbonyl and fluorine wherein two hydrocarbonyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;

- R<sup>1</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbonyl and C<sub>1-4</sub> hydrocarbonyloxy;
- R<sup>2</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbonyl and C<sub>1-4</sub> hydrocarbonyloxy;
- R<sup>3</sup> is selected from hydrogen, methyl, chlorine and bromine;
- R<sup>4</sup> is selected from hydrogen, methyl, chlorine and bromine;
- R<sup>5</sup> is selected from hydrogen, cyano and methyl;
- R<sup>6</sup> is selected from hydrogen, C<sub>1-4</sub> alkyl; and C<sub>1-4</sub> alkoxy optionally substituted with NR<sup>d</sup>R<sup>e</sup> where R<sup>d</sup> and R<sup>e</sup> are the same or different and each is selected from hydrogen and C<sub>1-4</sub> alkyl, or NR<sup>d</sup>R<sup>e</sup> forms a 4 to 7 membered saturated heterocyclic ring optionally containing a second heteroatom ring member selected from N, O and S and oxidized forms of S, the saturated heterocyclic ring being optionally substituted with one or more substituents selected from oxo, methyl, hydroxy and fluorine;

R<sup>7</sup> is selected from hydrogen; R<sup>11</sup>SO<sub>2</sub>-; amino, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 10 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>; provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members;

R<sup>8</sup> is selected from:

- halogen;
- oxo;
- cyano;
- nitro;
- a carbocyclic or heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
- a group R<sup>a</sup>-R<sup>b</sup>;

R<sup>a</sup> is a bond, O, CO, X<sup>1</sup>C(X<sup>2</sup>), C(X<sup>2</sup>)X<sup>1</sup>, X<sup>1</sup>C(X<sup>2</sup>)X<sup>1</sup>, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, SO<sub>2</sub>NR<sup>c</sup> or NR<sup>c</sup>SO<sub>2</sub>;

R<sup>b</sup> is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- an acyclic C<sub>1-12</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C<sub>1-8</sub> non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; wherein one or more but not all of the carbon atoms of the acyclic C<sub>1-12</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, X<sup>1</sup>C(X<sup>2</sup>), C(X<sup>2</sup>)X<sup>1</sup> or X<sup>1</sup>C(X<sup>2</sup>)X<sup>1</sup>;

R<sup>c</sup> is:

- hydrogen;

- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- 5 • an acyclic C<sub>1-12</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C<sub>1-8</sub> non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the
- 10 carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; wherein one or more but not all of the carbon atoms of the acyclic C<sub>1-12</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH, N-C<sub>1-4</sub> alkyl, C(O)O, OC(O), NH(CO), C(O)NH, NH(CO)NH, N(C<sub>1-4</sub> alkyl)C(O), C(O)N(C<sub>1-4</sub> alkyl)
- 15 X<sup>1</sup> is O, S or NR<sup>c</sup>; and  
X<sup>2</sup> is =O, =S or =NR<sup>c</sup>;  
wherein R<sup>9</sup> is selected from R<sup>8</sup> provided that when the substituents R<sup>9</sup> contain a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group is unsubstituted or substituted with one or more substituents R<sup>10</sup>;
- 20 R<sup>10</sup> is selected from halogen, oxo, cyano, and an acyclic C<sub>1-6</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di-C<sub>1-2</sub> alkylamino; wherein one but not all of the carbon atoms of the acyclic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH or NMe;
- 25 R<sup>11</sup> is selected from amino, Hyd<sup>1</sup>, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and Cyc<sup>1</sup>;  
Hyd<sup>1</sup> is a non-aromatic C<sub>1-6</sub> hydrocarbyl group optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, amino and Cyc<sup>1</sup>, wherein one or two of the carbon atoms of the non-aromatic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, NH, N-Hyd<sup>2</sup>, C(=O), S, SO or SO<sub>2</sub>, provided that at least one carbon atom
- 30 of the hydrocarbyl group remains;  
Hyd<sup>2</sup> is a C<sub>1-4</sub> hydrocarbyl group;  
and wherein in any group consisting of or containing a hydrocarbyl moiety, the hydrocarbyl moiety is a hydrocarbon group optionally containing one or more single, double or triple carbon-carbon bonds or combinations thereof.
- 35 1.2 A compound according to any one of Embodiments 1.0 to 1.1 wherein R<sup>1</sup> is selected from hydrogen, fluorine, C<sub>1-3</sub> hydrocarbyl and C<sub>1-3</sub> hydrocarbyloxy.

- 1.3 A compound according to Embodiment 1.2 wherein  $R^1$  is selected from hydrogen, fluorine,  $C_{1-2}$  hydrocarbyl and  $C_{1-2}$  hydrocarbyloxy.
- 1.4 A compound according to Embodiment 1.3 wherein  $R^1$  is selected from hydrogen, fluorine, methyl and methoxy.
- 5 1.5 A compound according to Embodiment 1.1 wherein  $R^1$  is selected from hydrogen and  $C_{1-4}$  hydrocarbyloxy.
- 1.6 A compound according to Embodiment 1.5 wherein  $R^1$  is selected from hydrogen and methoxy.
- 1.7 A compound according to Embodiment 1.6 wherein  $R^1$  is hydrogen.
- 10 1.8 A compound according to Embodiment 1.6 wherein  $R^1$  is methoxy.
- 1.9 A compound according to any one of Embodiments 1.0 to 1.8 wherein  $R^2$  is selected from hydrogen, fluorine,  $C_{1-3}$  hydrocarbyl and  $C_{1-3}$  hydrocarbyloxy.
- 1.9A A compound according to Embodiment 1.9 wherein  $R^2$  is selected from hydrogen, fluorine and  $C_{1-3}$  hydrocarbyloxy.
- 15 1.10 A compound according to Embodiment 1.9 wherein  $R^2$  is selected from hydrogen, fluorine,  $C_{1-2}$  hydrocarbyl and  $C_{1-2}$  hydrocarbyloxy.
- 1.11 A compound according to Embodiment 1.10 wherein  $R^2$  is selected from hydrogen, fluorine, methyl and methoxy.
- 1.12 A compound according to any one of Embodiments 1.0 to 1.8 wherein  $R^2$  is selected from hydrogen and  $C_{1-4}$  hydrocarbyloxy.
- 20 1.13 A compound according to Embodiment 1.12 wherein  $R^2$  is selected from hydrogen and methoxy.
- 1.14 A compound according to Embodiment 1.13 wherein  $R^2$  is hydrogen.
- 1.15 A compound according to Embodiment 1.13 wherein  $R^2$  is methoxy.
- 25 1.16 A compound according to any one of Embodiments 1.0 to 1.1 wherein one of  $R^1$  and  $R^2$  is hydrogen and the other is methoxy.

- 1.17 A compound according to Embodiment 1.1 wherein both of R<sup>1</sup> and R<sup>2</sup> are methoxy.
- 1.18 A compound according to any one of Embodiments 1.0 to 1.1 wherein both of R<sup>1</sup> and R<sup>2</sup> are hydrogen.
- 5 1.19 A compound according to any one of Embodiments 1.0 to 1.18 wherein R<sup>3</sup> is selected from hydrogen and chlorine.
- 1.20 A compound according to any one of Embodiments 1.0 to 1.19 wherein R<sup>4</sup> is selected from hydrogen, methyl and chlorine.
- 1.21 A compound according to Embodiment 1.19 or Embodiment 1.20 wherein one of  
10 R<sup>3</sup> and R<sup>4</sup> is hydrogen and the other is chlorine.
- 1.22 A compound according to Embodiment 1.19 or Embodiment 1.20 wherein both of R<sup>3</sup> and R<sup>4</sup> are hydrogen.
- 1.23 A compound according to any one of Embodiments 1.0 to 1.1 wherein R<sup>1</sup> is methoxy and R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are all hydrogen.
- 15 1.24 A compound according to any one of Embodiments 1.0 to 1.1 wherein R<sup>1</sup> and R<sup>2</sup> are both methoxy and R<sup>3</sup> and R<sup>4</sup> are both hydrogen.
- 1.25 A compound according to any one of Embodiments 1.0 to 1.1 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are all hydrogen.
- 1.26 A compound according to any one of Embodiments 1.0 to 1.1 wherein R<sup>1</sup> is  
20 methoxy, R<sup>2</sup> is hydrogen, R<sup>3</sup> is chlorine and R<sup>4</sup> is hydrogen.
- 1.27 A compound according to any one of Embodiments 1.0 to 1.26 wherein R<sup>5</sup> is selected from hydrogen and cyano.
- 1.28 A compound according to Embodiment 1.27 wherein R<sup>5</sup> is cyano.
- 1.29 A compound according to Embodiment 1.27 wherein R<sup>5</sup> is hydrogen.
- 25 1.30 A compound according to any one of Embodiments 1.0 to 1.29 wherein R<sup>6</sup> is selected from hydrogen, methyl and methoxy.
- 1.30A A compound according to Embodiment 1.30 wherein R<sup>6</sup> is hydrogen.

1.30B A compound according to any one of Embodiments 1.1 to 1.30A wherein A is selected from:

- 5
- (i) a bond;
  - (ii)  $(CR^pR^q)_x$  where  $R^p$  and  $R^q$  are each independently hydrogen or methyl and x is 1 to 3;
  - (iii) an oxygen atom;
  - (iv) a group  $NR^r$  wherein  $R^r$  is hydrogen or methyl; and
  - (v) a saturated chain of 2 to 8 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O,  $C_{1-4}$  hydrocarbyl, hydroxy- $C_{1-4}$  hydrocarbyl,  $C_{1-2}$ -alkoxy- $C_{1-4}$  hydrocarbyl, and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to
- 10
- 15
- 20
- provided that when A is a bond,  $CR^pR^q$  or an oxygen atom, then  $R^7$  is other than hydrogen; and provided also that when  $R^7$  is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

1.30C A compound according to Embodiment 1.30B wherein A is selected from:

- 25
- (i) a bond;
  - (ii)  $(CR^pR^q)_x$  where  $R^p$  and  $R^q$  are each independently hydrogen or methyl and x is 1 to 3;
  - (iii) an oxygen atom;
  - (iv) a group  $NR^r$  wherein  $R^r$  is hydrogen or methyl; and
  - (v) a saturated chain of 2 to 6 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O,  $C_{1-4}$  hydrocarbyl, hydroxy- $C_{1-4}$  hydrocarbyl,  $C_{1-2}$ -alkoxy- $C_{1-4}$  hydrocarbyl, and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to
- 30
- 35
- five ring members;

provided that when A is a bond, CR<sup>p</sup>R<sup>q</sup> or an oxygen atom, then R<sup>7</sup> is other than hydrogen; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

- 5 1.30D A compound according to Embodiment 1.30C wherein A is selected from:
- (i) a bond;
  - (ii) (CR<sup>p</sup>R<sup>q</sup>)<sub>x</sub> where R<sup>p</sup> and R<sup>q</sup> are each independently hydrogen or methyl and x is 1;
  - (iii) an oxygen atom;
  - 10 (iv) a group NR<sup>r</sup> wherein R<sup>r</sup> is hydrogen or methyl; and
  - (v) a saturated chain of 2 to 6 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen,
  - 15 sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl, and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;
  - 20 provided that when A is a bond, CR<sup>p</sup>R<sup>q</sup> or an oxygen atom, then R<sup>7</sup> is other than hydrogen; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members

- 1.30E A compound according to Embodiment 1.30D wherein A is selected from:
- (i) a bond;
  - 25 (ii) CR<sup>p</sup>R<sup>q</sup> where R<sup>p</sup> and R<sup>q</sup> are each independently hydrogen or methyl;
  - (iii) an oxygen atom; and
  - (v) a saturated chain of 2 to 6 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen,
  - 30 sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;

provided that when A is a bond, CR<sup>p</sup>R<sup>q</sup> or an oxygen atom, then R<sup>7</sup> is other than hydrogen; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

1.30F A compound according to Embodiment 1.30E wherein A is selected from:

- 5 (i) a bond;
- (ii) CR<sup>p</sup>R<sup>q</sup> where R<sup>p</sup> and R<sup>q</sup> are each independently hydrogen or methyl;
- (iii) an oxygen atom; and
- (v) a saturated chain of 2 to 5 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from
- 10 nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally
- 15 link to form a ring of three to five ring members;
- provided that when A is a bond, CR<sup>p</sup>R<sup>q</sup> or an oxygen atom, then R<sup>7</sup> is other than hydrogen; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

20 1.30G A compound according to Embodiment 1.30F wherein A is selected from:

- (i) a bond;
- (ii) CH<sub>2</sub>;
- (iii) an oxygen atom; and
- (v) a saturated chain of 2 to 5 chain members in length containing a single
- 25 heteroatom chain member which is nitrogen or oxygen; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl and fluorine;
- provided that when A is a bond, CH<sub>2</sub> or an oxygen atom, then R<sup>7</sup> is other than hydrogen; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length
- 30 of at least four chain members and contains at least two heteroatom chain members.

1.30H A compound according to Embodiment 1.30G wherein A is selected from:

- (i) a bond;
- (ii) CH<sub>2</sub>;
- 35 (iii) an oxygen atom; and



(v) a saturated chain of 2 to 5 chain members in length having the formula  $-(\text{CR}^{\text{v}}\text{R}^{\text{w}})_m\text{-J-(CR}^{\text{x}}\text{R}^{\text{y}})_n\text{-}$ ; wherein J is  $\text{NR}^z$ , O or  $\text{NHC(=O)}$ ;  $\text{R}^{\text{v}}$ ,  $\text{R}^{\text{w}}$ ,  $\text{R}^{\text{x}}$ ,  $\text{R}^{\text{y}}$  and  $\text{R}^z$  are each hydrogen or methyl; m is 0, 1, 2 or 3 and n is 0, 1, 2 or 3 wherein the sum of m and n is no greater than 4 or, when J is  $\text{NH(=O)}$ , the sum of m and n is no greater than 3;  
 5 provided that  $\text{R}^7$  is other than hydrogen.

1.30J A compound according to Embodiment 1.30H wherein A is selected from:  
 (i) a bond;  
 (ii)  $\text{CH}_2$ ;  
 10 (iii) an oxygen atom; and  
 (v) a saturated chain of 2 to 4 chain members in length having the formula  $-(\text{CR}^{\text{v}}\text{R}^{\text{w}})_m\text{-J-(CR}^{\text{x}}\text{R}^{\text{y}})_n\text{-}$ ; wherein J is  $\text{NR}^z$ , O or  $\text{NHC(=O)}$ ;  $\text{R}^{\text{v}}$ ,  $\text{R}^{\text{w}}$ ,  $\text{R}^{\text{x}}$ ,  $\text{R}^{\text{y}}$  and  $\text{R}^z$  are each hydrogen or methyl; m is 0, 1 or 2 and n is 0, 1 or 2 wherein the sum of m and n is no greater than 3 or, when J is  $\text{NH(=O)}$ , the sum of m and n is no greater than 2;  
 15 provided that  $\text{R}^7$  is other than hydrogen.

1.30K A compound according to any one of Embodiments 1.0 to 1.30C wherein, when A is  $(\text{CR}^{\text{p}}\text{R}^{\text{q}})_x$ , then x is 1, 2 or 3.

1.30L A compound according to any one of Embodiments 1.0 to 1.30C wherein, when A is  $(\text{CR}^{\text{p}}\text{R}^{\text{q}})_x$ , then x is 1 or 2.  
 20

1.30M A compound according to any one of Embodiments 1.0 to 1.30C wherein, when A is  $(\text{CR}^{\text{p}}\text{R}^{\text{q}})_x$ , then x is 1.

1.31 A compound according to Embodiment 1.30B wherein A is selected from:  
 (i) a bond; and  
 25 (ii) a saturated chain of 2 to 8 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from  $=\text{O}$ ,  $\text{C}_{1-4}$  hydrocarbyl and fluorine  
 30 wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;

provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

- 1.32 A compound according to Embodiment 1.31 wherein A is selected from:
- 5 (i) a bond; and  
(ii) a saturated chain of 2 to 6 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen,  
10 sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;  
provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that when R<sup>7</sup> is  
15 hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

- 1.33 A compound according to Embodiment 1.32 wherein A is selected from:
- (i) a bond; and  
(ii) a saturated chain of 2 to 5 chain members in length containing at least one  
20 carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphinyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl and fluorine  
25 wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;  
provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members.

- 30 1.34 A compound according to Embodiment 1.33 wherein A is selected from:  
(i) a bond; and  
(ii) a saturated chain of 2 to 5 chain members in length containing a single heteroatom chain member which is nitrogen or oxygen; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub>

hydrocarbonyl and fluorine; provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that R<sup>7</sup> is other than hydrogen.

- 1.35 A compound according to Embodiment 1.34 wherein A is selected from:
- (i) a bond; and
  - (ii) a saturated chain of 2 to 5 chain members in length containing a single heteroatom chain member which is nitrogen; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbonyl and fluorine; provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that R<sup>7</sup> is other than hydrogen.
- 1.36 A compound according to Embodiment 1.35 wherein A is selected from:
- (i) a bond; and
  - (ii) a saturated chain of 2 to 5 chain members in length containing a single heteroatom chain member which is nitrogen; the saturated chain being optionally substituted with one or more substituents selected from methyl and fluorine;
- provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that R<sup>7</sup> is other than hydrogen.
- 1.37 A compound according to Embodiment 1.36 wherein A is selected from:
- (i) a bond; and
  - (ii) a saturated chain of 2 to 5 chain members in length containing a single heteroatom chain member which is nitrogen; the saturated chain being optionally substituted with one or more methyl groups; provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that R<sup>7</sup> is other than hydrogen.
- 1.38 A compound according to Embodiment 1.37 wherein A is selected from:
- (i) a bond; and
  - (ii) a saturated chain of 2 to 5 chain members in length having the formula  $-(CR^vR^w)_m-NH-(CR^xR^y)_n-$ ; wherein R<sup>v</sup>, R<sup>w</sup>, R<sup>x</sup> and R<sup>y</sup> are each hydrogen or methyl; m is 0, 1, 2 or 3 and n is 0, 1, 2 or 3 wherein the sum of m and n is no greater than 4; provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that R<sup>7</sup> is other than hydrogen.
- 1.39 A compound according to Embodiment 1.38 wherein A is selected from:
- (i) a bond; and
  - (ii) a saturated chain of 2 to 4 chain members in length having the formula  $-(CR^vR^w)_m-NH-(CR^xR^y)_n-$ ; wherein R<sup>v</sup>, R<sup>w</sup>, R<sup>x</sup> and R<sup>y</sup> are each hydrogen or

methyl; m is 0, 1 or 2 and n is 0, 1 or 2 wherein the sum of m and n is no greater than 3; provided that when A is a bond, then R<sup>7</sup> is Cyc<sup>1</sup>; and provided also that R<sup>7</sup> is other than hydrogen.

- 1.40 A compound according to any one of Embodiments 1.30H, 1.30J, 1.38 and 1.39  
5 wherein no more than two R<sup>v</sup>, R<sup>w</sup>, R<sup>x</sup> or R<sup>y</sup> groups are methyl.
- 1.41 A compound according to any one of Embodiments 1.30B, 1.30C, 1.30K, 1.30L,  
1.38 and 1.39 wherein all of R<sup>v</sup>, R<sup>w</sup>, R<sup>x</sup> and R<sup>y</sup> are hydrogen.
- 1.42 A compound according to Embodiment 1.41 wherein one R<sup>v</sup>, R<sup>w</sup>, R<sup>x</sup> or R<sup>y</sup> group is  
methyl and the others are all hydrogen.
- 10 1.43 A compound according to any one of Embodiments 1.0 to 1.42 wherein A is a  
saturated chain.
- 1.43A A compound according to any one of Embodiments 1.0 to 1.30A wherein A is  
selected from a bond; -CH<sub>2</sub>-NH-C(=O)-, -NH-CH<sub>2</sub>-  
; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-N(Me)-(CH<sub>2</sub>)-(CH<sub>2</sub>)-  
15 ; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CHMe)-; -(CH<sub>2</sub>)-NH-(CHMe  
e)-(CH<sub>2</sub>)-; -NH-CH<sub>2</sub>-CH<sub>2</sub>-; -(CH<sub>2</sub>)-NH-(CMe<sub>2</sub>)-(CH<sub>2</sub>)-; -O-; -O-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-  
; -(CH<sub>2</sub>)-NMe-; and -CH<sub>2</sub>-.
- 1.44 A compound according to any one of Embodiments 1.0 to 1.30A wherein A is  
selected from a bond; -NH-CH<sub>2</sub>-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-N(Me)-(CH<sub>2</sub>)-  
20 ; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; and -(CH<sub>2</sub>)-NH-(CHMe)-.
- 1.45 A compound according to Embodiment 1.44 wherein A is a bond.
- 1.46 A compound according to Embodiment 1.44 wherein A is selected from -NH-CH<sub>2</sub>-  
; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-;  
and -(CH<sub>2</sub>)-NH-(CHMe)-.
- 25 1.47 A compound according to Embodiment 1.46 wherein A is selected  
from -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-;  
and -(CH<sub>2</sub>)-NH-(CHMe)-.
- 1.48 A compound according to Embodiment 1.47 wherein A is -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-.
- 1.49 A compound according to Embodiment 1.47 wherein A is -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-.

- 1.50 A compound according to Embodiment 1.47 wherein A is  $-(\text{CH}_2)-(\text{CH}_2)-\text{NH}-(\text{CH}_2)-$ .
- 1.51 A compound according to Embodiment 1.47 wherein A is  $-(\text{CH}_2)-\text{NH}-(\text{CHMe})-$ .
- 1.51A A compound according to Embodiment 1.43A wherein A is  $-\text{CH}_2-\text{NH}-\text{C}(=\text{O})-$ .
- 1.51B A compound according to Embodiment 1.43A wherein A is  $-\text{NH}-\text{CH}_2-$ .
- 5 1.51C A compound according to Embodiment 1.43A wherein A is  $-(\text{CH}_2)-\text{N}(\text{Me})-(\text{CH}_2)-(\text{CH}_2)-$ .
- 1.51D A compound according to Embodiment 1.43A wherein A is  $-(\text{CH}_2)-\text{NH}-(\text{CHMe})-(\text{CH}_2)-$ .
- 1.51E A compound according to Embodiment 1.43A wherein A is  $-\text{NH}-\text{CH}_2-\text{CH}_2-$ .
- 10 1.51F A compound according to Embodiment 1.43A wherein A is  $-(\text{CH}_2)-\text{NH}-(\text{CMe}_2)-(\text{CH}_2)-$ .
- 1.51G A compound according to Embodiment 1.43A wherein A is  $-\text{O}-$ .
- 1.51H A compound according to Embodiment 1.43A wherein A is  $-\text{O}-(\text{CH}_2)-$ .
- 1.51J A compound according to Embodiment 1.43A wherein A is  $-(\text{CH}_2)-\text{NH}-$ .
- 15 1.51K A compound according to Embodiment 1.43A wherein A is  $-(\text{CH}_2)-\text{NMe}-$ .
- 1.51L A compound according to Embodiment 1.43A wherein A is  $-\text{CH}_2-$ .
- 1.51M A compound according to to any one of Embodiments 1.0 to 1.30A wherein A is a group  $\text{NR}^f$  wherein  $\text{R}^f$  is hydrogen or methyl.
- 1.51N A compound according to Embodiment 1.51M wherein  $\text{R}^f$  is hydrogen.
- 20 151P A compound according to any one of Embodiments 1.0 to 1.51N wherein  $\text{R}^7$  is selected from hydrogen;  $\text{R}^{11}\text{SO}_2-$ ; amino;  $\text{NH}-\text{Hyd}^1$ ;  $\text{N}(\text{Hyd}^1)_2$ ; and a group  $\text{Cyc}^1$  wherein  $\text{Cyc}^1$  is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 9 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted
- 25 with one or more substituents  $\text{R}^8$ ; provided that when A is a bond,  $(\text{CR}^p\text{R}^q)_x$ , an oxygen atom or  $\text{NR}^f$ , then  $\text{R}^7$  is other than hydrogen; and provided also that when  $\text{R}^7$  is hydrogen,

then A has a chain length of at least four chain members and contains at least two heteroatom chain members;

1.52 A compound according to Embodiment 1.51P wherein  $R^7$  is selected from hydrogen;  $R^{11}SO_2$ ; amino, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> which is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 9 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents  $R^8$ .

1.53 A compound according to Embodiment 1.52 wherein  $R^7$  is selected from hydrogen;  $R^{11}SO_2$ ; amino, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> which is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 8 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents  $R^8$ .

1.54 A compound according to Embodiment 1.53 wherein  $R^7$  is selected from hydrogen;  $R^{11}SO_2$ ; amino, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> which is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 7 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents  $R^8$ .

1.55 A compound according to Embodiment 1.54 wherein  $R^7$  is selected from hydrogen;  $R^{11}SO_2$ ; amino, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> which is a carbocyclic or heterocyclic aromatic or non-aromatic group of 5 or 6 ring members of which 0 to 2 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents  $R^8$ .

1.56 A compound according to Embodiment 1.54 wherein  $R^7$  is selected from  $R^{11}SO_2$ ; amino, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> which is a carbocyclic or heterocyclic aromatic or non-aromatic group of 5, 6 or 7 ring members of which 0 to 2 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents  $R^8$ .

1.57 A compound according to any one of Embodiments 1.0 to 1.56 wherein  $R^7$  is a group Cyc<sup>1</sup>.

- 1.57A A compound according to Embodiment 1.57 wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 9 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 5
- 1.57B A compound according to Embodiment 1.57A wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 8 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 10
- 1.57C A compound according to Embodiment 1.57B wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 7 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 15
- 1.57D A compound according to Embodiment 1.57C wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 7 ring members of which 0 to 2 are selected from O and N, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 20
- 1.57E A compound according to Embodiment 1.57D wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group selected from cyclopropane, phenyl, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, piperazine, morpholine and 1,4-diazepane, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 25
- 1.58 A compound according to Embodiment 1.56 wherein R<sup>7</sup> is selected from R<sup>11</sup>SO<sub>2</sub><sup>-</sup>; amino, NH-Hyd<sup>1</sup> and N(Hyd<sup>1</sup>)<sub>2</sub>.
- 1.59 A compound according to Embodiment 1.56 wherein R<sup>7</sup> is R<sup>11</sup>SO<sub>2</sub><sup>-</sup>.
- 1.60 A compound according to Embodiment 1.56 wherein R<sup>7</sup> is selected from amino, NH-Hyd<sup>1</sup> and N(Hyd<sup>1</sup>)<sub>2</sub>.
- 30
- 1.61 A compound according to any one of Embodiments 1.0 to 1.57 wherein the moiety A-R<sup>7</sup> is other than an optionally substituted biphenyl group.

- 1.61A A compound according to any one of Embodiments 1.0 to 1.57 wherein, when A is a bond and R<sup>7</sup> is Cyc<sup>1</sup>, Cyc<sup>1</sup> is a non-aromatic carbocyclic or heterocyclic group.
- 1.61B A compound according to any one of Embodiments 1.0 to 1.57, 1.61 and 1.61A wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic group of 5 to 9 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.62 A compound according to any one of Embodiments 1.57, 1.61, 1.61A and 1.61B wherein Cyc<sup>1</sup> is a benzene ring which is optionally substituted with one or more substituents R<sup>8</sup>.
- 1.63 A compound according to any one of Embodiments 1.57, 1.61, 1.61A and 1.61B wherein Cyc<sup>1</sup> is a heterocyclic aromatic group of 5 to 9 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the heterocyclic aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.64 A compound according to any one of Embodiments 1.57, 1.61, 1.61A and 1.61B wherein Cyc<sup>1</sup> is a heterocyclic non-aromatic group of 4 to 7 ring members of which 1 or 2 are selected from O, N and S and oxidised forms thereof, the heterocyclic non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.65 A compound according to Embodiment 1.64 wherein Cyc<sup>1</sup> is a heterocyclic non-aromatic group of 5, 6 or 7 ring members of which 1 or 2 are selected from O, N and S and oxidised forms thereof, the heterocyclic non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.66 A compound according to Embodiment 1.64 wherein Cyc<sup>1</sup> is a heterocyclic non-aromatic group selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine-S-S-dioxide, azepane, diazepane, tetrahydrofuran and tetrahydropyran the heterocyclic non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.67 A compound according to Embodiment 1.66 wherein Cyc<sup>1</sup> is selected from pyrrolidine, piperidine, piperazine, morpholine, azepane and diazepane, the heterocyclic non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.68 A compound according to Embodiment 1.67 wherein Cyc<sup>1</sup> is selected from pyrrolidine, piperidine, piperazine and morpholine, the heterocyclic non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.



- 1.69 A compound according to Embodiment 1.68 wherein Cyc<sup>1</sup> is selected from piperidine and morpholine, the heterocyclic non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.70 A compound according to Embodiment 1.69 wherein Cyc<sup>1</sup> is piperidine which is optionally substituted with one or more substituents R<sup>8</sup>.
- 1.71 A compound according to Embodiment 1.69 wherein Cyc<sup>1</sup> is morpholine which is optionally substituted with one or more substituents R<sup>8</sup>.
- 1.71A A compound according to Embodiment 1.68 wherein Cyc<sup>1</sup> is piperazine optionally substituted with one or more substituents R<sup>8</sup>.
- 1.72 A compound according to to any one of Embodiments 1.57, 1.61, 1.61A and 1.61B wherein Cyc<sup>1</sup> is selected from a benzene ring, piperidine and morpholine, each being optionally substituted with one or more substituents R<sup>8</sup>.
- 1.73 A compound according to any one of Embodiments 1.1 to 1.57 and 1.61 to 1.72 wherein R<sup>8</sup> is selected from:
- fluorine;
  - chlorine;
  - bromine;
  - oxo;
  - cyano;
  - a carbocyclic or heterocyclic group having from 3 to 7 ring members, of which 0, 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
  - a group R<sup>a</sup>-R<sup>b</sup>.
- 1.74 A compound according to Embodiment 1.73 wherein R<sup>8</sup> is selected from:
- fluorine;
  - chlorine;
  - bromine;
  - oxo;
  - cyano;
  - a carbocyclic group having from 3 to 6 ring members, the carbocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;

- a heterocyclic group having from 4 to 7 ring members, of which 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
- 5      • a group R<sup>a</sup>-R<sup>b</sup>.

1.75 A compound according to any one of Embodiments 1.1 to 1.57 and 1.61 to 1.74 wherein R<sup>8</sup> is selected from:

- fluorine;
- chlorine;
- 10      • bromine;
- oxo;
- cyano;
- a carbocyclic or heterocyclic group having from 3 to 7 ring members, of which 0, 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
- 15      • a group R<sup>a</sup>-R<sup>b</sup>;

R<sup>a</sup> is a bond, O, CO, X<sup>1</sup>C(X<sup>2</sup>), C(X<sup>2</sup>)X<sup>1</sup>, X<sup>1</sup>C(X<sup>2</sup>)X<sup>1</sup>, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, SO<sub>2</sub>NR<sup>c</sup> or NR<sup>c</sup>SO<sub>2</sub>;

R<sup>b</sup> is:

- 20      • hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 7 ring members, of which 0, 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- 25      • an acyclic C<sub>1-6</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; fluorine; cyano; carboxy; amino; mono- or di-C<sub>1-2</sub> hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 7 ring members, of which 0, 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; wherein one or two but not all of the carbon atoms of the acyclic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH, NMe, CO<sub>2</sub>, OC(=O), CONH, NHCO; CON(Me) and N(Me)CO;
- 30

R<sup>c</sup> is hydrogen or C<sub>1-4</sub> hydrocarbyl;

35      X<sup>1</sup> is O, S or NR<sup>c</sup>; and

X<sup>2</sup> is =O, =S or =NR<sup>c</sup>;

wherein R<sup>9</sup> is selected from R<sup>8</sup> provided that the substituents R<sup>9</sup> do not contain a carbocyclic or heterocyclic group.

- 1.76 A compound according to Embodiment 1.75 wherein R<sup>8</sup> is selected from:
- fluorine;
  - 5 • chlorine;
  - bromine;
  - oxo;
  - cyano;
  - 10 • a carbocyclic group having 3 to 6 ring members, the carbocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
  - a heterocyclic group having from 4 to 7 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
  - 15 • a group R<sup>a</sup>-R<sup>b</sup>;
- R<sup>a</sup> is a bond, O, CO, OC(O), C(O)O, NR<sup>c</sup>C(O), C(O)NR<sup>c</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, SO<sub>2</sub>NR<sup>c</sup> or NR<sup>c</sup>SO<sub>2</sub>;
- R<sup>b</sup> is:
- hydrogen;
  - 20 • a carbocyclic group having 3 to 6 ring members, the carbocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
  - a heterocyclic group having from 4 to 7 ring members, of which 0, 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more
  - 25 substituents R<sup>9</sup>;
  - an acyclic C<sub>1-4</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; fluorine; cyano; carboxy; amino; mono- or di-C<sub>1-2</sub> hydrocarbylamino; and carbocyclic groups having from 3 to 6 ring members and heterocyclic groups having from 4 to 7 ring members, of which 1 or
  - 30 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic groups being optionally substituted with one or more substituents R<sup>9</sup>; wherein one but not all of the carbon atoms of the acyclic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH, NMe, CO<sub>2</sub>, OC(=O), CONH, NHCO; CON(Me) and N(Me)CO;
- 35 R<sup>c</sup> is hydrogen or C<sub>1-4</sub> alkyl;  
X<sup>1</sup> is O, S or NR<sup>c</sup>; and

$X^2$  is =O, =S or =NR<sup>c</sup>;

wherein R<sup>9</sup> is selected from fluorine, chlorine, bromine, oxo, cyano, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> cycloalkyl, cyclopropylmethyl, C<sub>1-4</sub> alkoxy, hydroxy, amino, mon- or di-C<sub>1-4</sub> alkylamino, carbamoyl, mono- or diC<sub>1-4</sub>alkylcarbamoyl, aminosulphonyl, mono-or di-

5 C<sub>1-4</sub>alkylaminosulphonyl, C<sub>1-4</sub>alkylsulphonamido, and when R<sup>9</sup> consists of or contains a C<sub>1-4</sub> alkyl group, the C<sub>1-4</sub> alkyl group is optionally substituted with one or more fluorine atoms or by C<sub>1-2</sub> alkoxy.

1.77 A compound according to Embodiment 1.76 wherein R<sup>8</sup> is selected from:

- fluorine;
- 10 • chlorine;
- bromine;
- oxo;
- cyano;
- a carbocyclic group having 3 to 6 ring members, the carbocyclic group being
- 15 optionally substituted with one or more substituents R<sup>9</sup>;
- a heterocyclic group having from 4 to 7 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
- 20 • a group R<sup>a</sup>-R<sup>b</sup>;

R<sup>a</sup> is a bond, O, CO, OC(O), C(O)O, NR<sup>c</sup>C(O), C(O)NR<sup>c</sup>, NR<sup>c</sup>C(O)NR<sup>c</sup>, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, SO<sub>2</sub>NR<sup>c</sup> or NR<sup>c</sup>SO<sub>2</sub>;

R<sup>b</sup> is:

- hydrogen;
- 25 • a carbocyclic group having 3 to 6 ring members, the carbocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- a heterocyclic group having from 4 to 7 ring members, of which 0, 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more
- 30 substituents R<sup>9</sup>;
- an acyclic C<sub>1-4</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; fluorine; cyano; carboxy; amino; mono- or di-C<sub>1-2</sub> hydrocarbylamino; and carbocyclic groups having from 3 to 6 ring members and heterocyclic groups having from 4 to 7 ring members, of which 1 or
- 35 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic groups being optionally substituted with

one or more substituents  $R^9$ ; wherein one but not all of the carbon atoms of the acyclic  $C_{1-6}$  hydrocarbonyl group may optionally be replaced by O, S, SO,  $SO_2$ , NH, NMe,  $CO_2$ ,  $OC(=O)$ , CONH, NHCO;  $CON(Me)$  and  $N(Me)CO$ ;

$R^c$  is hydrogen or  $C_{1-4}$  alkyl;

5  $X^1$  is O, S or  $NR^c$ ; and

$X^2$  is  $=O$ ,  $=S$  or  $=NR^c$ ;

wherein  $R^9$  is selected from fluorine, chlorine, bromine, oxo, cyano,  $C_{1-4}$  alkyl,  $C_{3-4}$  cycloalkyl, cyclopropylmethyl,  $C_{1-4}$  alkoxy, hydroxy, amino, mono- or di- $C_{1-4}$  alkylamino, carbamoyl, mono- or di- $C_{1-4}$ alkylcarbamoyl, aminosulphonyl, mono- or di-

10  $C_{1-4}$ alkylaminosulphonyl,  $C_{1-4}$ alkylsulphonamido, and when  $R^9$  consists of or contains a  $C_{1-4}$  alkyl group, the  $C_{1-4}$  alkyl group is optionally substituted with one or more fluorine atoms or by  $C_{1-2}$  alkoxy.

1.78 A compound according to Embodiment 1.77 wherein  $R^8$  is selected from:

- fluorine;
- 15 • chlorine;
- bromine;
- oxo;
- cyano;
- a carbocyclic group having 3 to 5 ring members;
- 20 • a heterocyclic group having from 5 to 6 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ; and
- a group  $R^a-R^b$ ;
- 25  $R^a$  is a bond, O, CO,  $OC(O)$ ,  $C(O)O$ ,  $NR^cC(O)$ ,  $C(O)NR^c$ ,  $NR^cC(O)NR^c$ , S, SO,  $SO_2$ ,  $NR^c$ ,  $SO_2NR^c$  or  $NR^cSO_2$ ;

$R^b$  is:

- hydrogen;
- a carbocyclic group having 3 to 5 ring members;
- 30 • a heterocyclic group having from 5 to 6 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ;
- a  $C_{1-4}$  alkyl group optionally substituted with one or more substituents selected
- 35 from hydroxy; oxo; fluorine; cyano; amino; mono- or di-methylamino; carbocyclic groups having from 3 to 5 ring members and heterocyclic groups having from 5 to

6 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic groups being optionally substituted with one or more substituents R<sup>9</sup>;

R<sup>c</sup> is hydrogen or methyl;

- 5 wherein, (i) when the carbocyclic or heterocyclic groups are non-aromatic, R<sup>9</sup> is selected from fluorine, oxo, cyano, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> cycloalkyl, cyclopropylmethyl, C<sub>1-4</sub> alkoxy, hydroxy, amino, mon- or di-C<sub>1-4</sub> alkylamino, carbamoyl, mono- or di-C<sub>1-4</sub> alkylcarbamoyl, aminosulphonyl, mono- or di-C<sub>1-4</sub> alkylaminosulphonyl, C<sub>1-4</sub> alkylsulphonamido, and when R<sup>9</sup> consists of or contains a C<sub>1-4</sub> alkyl group, the C<sub>1-4</sub> alkyl group is optionally substituted
- 10 with C<sub>1-2</sub> alkoxy; and (ii) when the carbocyclic or heterocyclic groups are aromatic, R<sup>9</sup> is selected from fluorine, chlorine, bromine, cyano, C<sub>1-4</sub> alkyl, C<sub>3-4</sub> cycloalkyl, cyclopropylmethyl, C<sub>1-4</sub> alkoxy, hydroxy, amino, mon- or di-C<sub>1-4</sub> alkylamino, carbamoyl, mono- or di-C<sub>1-4</sub> alkylcarbamoyl, aminosulphonyl, mono- or di-C<sub>1-4</sub> alkylaminosulphonyl, C<sub>1-4</sub> alkylsulphonamido, and when R<sup>9</sup> consists of or contains a C<sub>1-4</sub> alkyl group, the C<sub>1-4</sub>
- 15 alkyl group is optionally substituted with one or more fluorine atoms or by C<sub>1-2</sub> alkoxy.

1.79 A compound according to Embodiment 1.78 wherein R<sup>8</sup> is selected from:

- fluorine;
- chlorine;
- bromine;

20

- oxo;
- cyano;
- a heterocyclic group having from 5 to 6 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;

25

- and
- a group R<sup>a</sup>-R<sup>b</sup>;

R<sup>a</sup> is a bond, O, CO or SO<sub>2</sub>;

R<sup>b</sup> is:

- cyclopropyl;

30

- a heterocyclic group having from 5 to 6 ring members, of which 1 or 2 are heteroatom ring members selected from O, N and S, the carbocyclic or heterocyclic group being optionally substituted with one or more methyl substituents R<sup>9</sup>;
- a C<sub>1-4</sub> alkyl group optionally substituted with one or more substituents selected

35

- from oxo; fluorine; cyano; amino; mono- or di-methylamino; cyclopropyl; heterocyclic groups having from 5 to 6 ring members, of which 1 or 2 are

heteroatom ring members selected from O, N and S, the carbocyclic or heterocyclic groups being optionally substituted with one or more methyl substituents R<sup>9</sup>;

- 1.79A A compound according to Embodiment 1.76 wherein R<sup>8</sup> is selected from:
- 5
- fluorine;
  - chlorine;
  - oxo;
  - cyano;
  - a group R<sup>a</sup>-R<sup>b</sup>;
- 10 R<sup>a</sup> is a bond, O, CO or SO<sub>2</sub>;  
R<sup>b</sup> is selected from:
- cyclopropyl; and
  - a C<sub>1-4</sub> alkyl group optionally substituted with one or more substituents selected from hydroxy; methoxy; oxo; fluorine; cyano; amino; mono- or di-methylamino;
- 15 cyclopropyl.
- 1.79B A compound according to Embodiment 1.79 wherein R<sup>8</sup> is selected from fluorine, C<sub>1-3</sub> alkyl, cyclopropylcarbonyl, dimethylaminoacetyl, aminocarbonylmethyl and hydroxyethyl.
- 1.79C A compound according to Embodiment 1.79 wherein R<sup>8</sup> is selected from C<sub>1-4</sub> alkyl.
- 20 1.79D A compound according to Embodiment 1.79C wherein R<sup>8</sup> is selected from C<sub>1-3</sub> alkyl.
- 1.79E A compound according to Embodiment 1.79D wherein R<sup>8</sup> is selected from methyl, ethyl and isopropyl.
- 1.79F A compound according to Embodiment 1.79E wherein R<sup>8</sup> is methyl.
- 25 1.79G A compound according to Embodiment 1.79E wherein R<sup>8</sup> is ethyl.
- 1.79H A compound according to Embodiment 1.79E wherein R<sup>8</sup> is isopropyl.
- 1.80 A compound according to Embodiment 1.77 wherein:
- (i) Cyc<sup>1</sup> is a non-aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> hydrocarbyl, C<sub>1-4</sub>hydrocarbylsulfonyl, oxo, di-C<sub>1-4</sub>hydrocarbylamino-C<sub>1-4</sub>alkanoyl; and C<sub>1-4</sub>
- 30 hydrocarbylcarbonyl; or

- (ii) Cyc<sup>1</sup> is an aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> hydrocarbyl; halogen; C<sub>1-4</sub> hydrocarbyloxy; cyano; methylenedioxy; carbamoyl; mono- or di-C<sub>1-4</sub> alkylcarbamoyl; a 5- or 6-membered saturated heterocyclic ring containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic ring being optionally substituted with one or more C<sub>1-4</sub> alkyl group substituents; wherein the hydrocarbyl moieties in each of the C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy groups are optionally substituted with one or more substituents selected from fluorine, hydroxy, amino, mono- or di-C<sub>1-4</sub> alkylamino, oxo and C<sub>1-2</sub> alkyl.
- 5
- 1.81 A compound according to Embodiment 1.80 wherein:
- 10 (i) Cyc<sup>1</sup> is a non-aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> hydrocarbyl, C<sub>1-4</sub>hydrocarbylsulfonyl, oxo, di-C<sub>1-4</sub>hydrocarbylaminoacetyl and C<sub>1-4</sub> hydrocarbylcarbonyl; or
- (ii) Cyc<sup>1</sup> is an aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> hydrocarbyl, halogen, C<sub>1-4</sub> hydrocarbyloxy, cyano, morpholinyl, piperazinyl, N-methylpiperazinyl and methylenedioxy, wherein the hydrocarbyl moieties in each of the C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy groups are optionally substituted with one or more substituents selected from fluorine, hydroxy, amino, mono- or di-C<sub>1-4</sub> alkylamino, oxo and C<sub>1-2</sub> alkyl.
- 15
- 1.82 A compound according to Embodiment 1.81 wherein:
- (i) Cyc<sup>1</sup> is a non-aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> alkyl, C<sub>1-4</sub>alkylsulfonyl, oxo, di-C<sub>1-4</sub>alkylaminoacetyl and cyclopropylcarbonyl; or
- 20
- (ii) Cyc<sup>1</sup> is an aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> alkyl, halogen, C<sub>1-4</sub> alkoxy, trifluoromethyl, trifluoromethoxy, morpholinyl, piperazinyl, N-methylpiperazinyl and methylenedioxy.
- 1.83 A compound according to Embodiment 1.82 wherein:
- 25 (i) Cyc<sup>1</sup> is a non-aromatic group and R<sup>8</sup> is absent or is selected from methyl, methylsulfonyl, oxo, N,N-dimethylaminoacetyl and cyclopropylcarbonyl; or
- (ii) Cyc<sup>1</sup> is an aromatic group and R<sup>8</sup> is absent or is selected from fluorine, chlorine, methoxy, trifluoromethyl, trifluoromethoxy, morpholinyl, piperazinyl, N-methylpiperazinyl and methylenedioxy.
- 30 1.84 A compound according to Embodiment 1.83 wherein:



(i) Cyc<sup>1</sup> is a non-aromatic heterocyclic group and R<sup>8</sup> is absent or is selected from methyl and cyclopropylcarbonyl; or

(ii) Cyc<sup>1</sup> is a benzene ring and R<sup>8</sup> is absent or is selected from fluorine.

1.85 A compound according to any one of Embodiments 1.0 to 1.57E and 1.61 to 1.84  
5 wherein 0, 1, 2, 3 or 4 substituents R<sup>8</sup> are present in R<sup>7</sup>.

1.86 A compound according to Embodiment 1.85 wherein 0, 1, 2 or 3 substituents R<sup>8</sup>  
are present in R<sup>7</sup>.

1.87 A compound according to Embodiment 1.86 wherein 0, 1 or 2 substituents R<sup>8</sup> are  
present in R<sup>7</sup>.

10 1.88 A compound according to Embodiment 1.87 wherein 0 substituents R<sup>8</sup> are present  
in R<sup>7</sup>.

1.89 A compound according to Embodiment 1.87 wherein 1 substituent R<sup>8</sup> is present in  
R<sup>7</sup>.

1.90 A compound according to Embodiment 1.87 wherein 2 substituents R<sup>8</sup> are present  
15 in R<sup>7</sup>.

1.91 A compound according to Embodiment 1.86 wherein 3 substituents R<sup>8</sup> are present  
in R<sup>7</sup>.

1.92 A compound according to any one of Embodiments 1.0 to 1.57 wherein R<sup>7</sup> is  
selected from:

20 (i) phenyl optionally substituted with one or more substituents selected from  
methyl, fluorine, chlorine, methoxy, cyano, trifluoromethyl, trifluoromethoxy,  
difluoromethyl, difluoromethoxy, methylenedioxy, morpholinyl, piperazinyl, N-  
methylpiperazinyl, acetyl, carbamoyl, methylcarbamoyl and dimethylcarbamoyl;

(ii) cyclohexyl, morpholin-4-yl, morpholin-2-yl, 4-  
25 cyclopropylcarbonylmorpholin-2-yl, N-methylpiperazinyl, N-ethylpiperazinyl, N-  
isopropylpiperazinyl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, 1-methylsulfonyl-  
piperidin-4-yl, 1-cyclopropylcarbonylpiperidin-1-yl, 1,4-diazepanyl, 4-methyl-diazepan-1-  
yl, , 4,4-difluoropiperidinyl, pyrrolidinyl, 3,3-difluoropyrrolidinyl, pyrrolidon-1-yl and  
tetrahydropyran-4-yl.

1.92A A compound according to any one of Embodiments 1.0 to 1.57 wherein R<sup>7</sup> is selected from:

(phenyl optionally substituted with one or more substituents selected from methyl, fluorine, chlorine, methoxy, cyano, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, methylenedioxy, morpholinyl, piperazinyl, N-methylpiperazinyl, acetyl, carbamoyl, methylcarbamoyl and dimethylcarbamoyl;

(ii) cyclopropyl, cyclohexyl, pyridyl, methylazetidiny, fluoro-methyl-azetidiny, morpholinyl, cyclopropylcarbonylmorpholinyl, piperazinyl, methylpiperazinyl, dimethylpiperazinyl, ethyl-methyl-piperazinyl, ethylpiperazinyl, isopropylpiperazinyl, piperidinyl, methylpiperidinyl, fluoropiperidinyl, difluoropiperidinyl, fluoro-ethyl-piperidin, fluoro-methyl-piperidinyl, difluoro-methyl-piperidinyl, difluoro-ethyl-piperidinyl, fluoro-isopropyl-piperidinyl, dimethyl-piperidinyl, ethyl-piperidinyl, methoxyethyl-piperidinyl, hydroxyethyl-piperidinyl, isopropyl-piperidinyl, aminocarbonylmethyl-piperidinyl, methylsulfonyl-piperidinyl, cyclopropylcarbonylpiperidinyl, diazepanyl, methyl-diazepanyl, ethyl-diazepanyl, isopropyl-diazepanyl, pyrrolidinyl, methyl-pyrrolidinyl, isopropyl-pyrrolidinyl, difluoropyrrolidinyl, pyrrolidonyl, tetrahydrofuranyl, tetrahydropyranyl, ethylamino, N-isopropyl-N-methylamino

1.92B A compound according to Embodiment 1.92A wherein R<sup>7</sup> is selected from phenyl; cyclopropyl, 2-pyridyl, 1-methyl-azetid-3-yl, 3-fluoro-1-methyl-azetid-3-yl, morpholin-4-yl, morpholin-2-yl, 4-cyclopropylcarbonylmorpholin-2-yl, piperazinyl, 2-methyl-piperazin-4-yl, 1,2-dimethyl-piperazin-4-yl, 1-ethyl-2-methyl-piperazin-4-yl, N-methylpiperazinyl, N-ethylpiperazinyl, N-isopropylpiperazinyl, piperidin-1-yl, piperidin-1-yl, piperidin-2-yl, 1-methyl-piperidin-2-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 4-fluoro-piperidin-4-yl, 1-methyl-piperidin-4-yl, 4-fluoro-1-ethyl-piperidin-4-yl, 3-fluoro-1-ethyl-piperidin-4-yl, 3-fluoro-1-methyl-piperidin-4-yl, 3,3-difluoro-1-methyl-piperidin-4-yl, 3,3-difluoro-1-ethyl-piperidin-4-yl, 4-fluoro-1-isopropyl-piperidin-4-yl, 3-fluoro-1-isopropyl-piperidin-4-yl, 2,6-dimethyl-piperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(2-methoxyethyl)-piperidin-4-yl, 1-(2-hydroxyethyl)-piperidin-4-yl, 1-isopropyl-piperidin-4-yl, 1-aminocarbonylmethyl-piperidin-4-yl, 1-methylsulfonyl-piperidin-4-yl, 1-cyclopropylcarbonylpiperidin-1-yl, 1,4-diazepanyl, 4-methyl-diazepan-1-yl, 4-ethyl-diazepan-1-yl, 4-isopropyl-diazepan-1-yl, 4,4-difluoropiperidinyl, pyrrolidinyl, 1-methyl-pyrrolidin-3-yl, 1-isopropyl-pyrrolidin-3-yl, 3,3-difluoropyrrolidinyl, pyrrolidon-1-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-y, ethylamino and N-isopropyl-N-methylamino.

1.93 A compound according to Embodiment 1.92 wherein R<sup>7</sup> is selected from phenyl, fluorophenyl, 4-morpholinyl, 1-methyl-4-piperidinyl and 1-cyclopropylcarbonyl-piperidin-4-yl.

1.94 A compound according to Embodiment 1.1 wherein:

- 5 R<sup>1</sup> is hydrogen or methoxy;  
R<sup>2</sup> is hydrogen or methoxy;  
R<sup>3</sup> is hydrogen;  
R<sup>4</sup> is hydrogen;  
R<sup>5</sup> is hydrogen or cyano;
- 10 R<sup>6</sup> is hydrogen;  
A is selected from a bond, -NH-CH<sub>2</sub>-  
; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-;  
and -(CH<sub>2</sub>)-NH-(CHMe)-; and  
R<sup>7</sup> is selected from phenyl, 4-fluorophenyl, 4-morpholinyl, 1-methyl-4-piperidinyl and 1-  
15 cyclopropylcarbonyl-piperidin-4-yl.

1.95 A compound according to Embodiment 1.1 wherein:

- R<sup>1</sup> is methoxy;  
R<sup>2</sup> is hydrogen or methoxy;  
R<sup>3</sup> is hydrogen;
- 20 R<sup>4</sup> is hydrogen;  
R<sup>5</sup> is cyano;  
R<sup>6</sup> is hydrogen;  
A is selected from a bond, -NH-CH<sub>2</sub>-  
; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-;  
25 and -(CH<sub>2</sub>)-NH-(CHMe)-; and  
R<sup>7</sup> is selected from phenyl, 4-fluorophenyl, 4-morpholinyl, 1-methyl-4-piperidinyl and 1-  
cyclopropylcarbonyl-piperidin-4-yl.

1.96 A compound according to Embodiment 1.95 wherein:

- R<sup>1</sup> is methoxy;
- 30 R<sup>2</sup> is hydrogen or methoxy;  
R<sup>3</sup> is hydrogen;  
R<sup>4</sup> is hydrogen;  
R<sup>5</sup> is cyano;  
R<sup>6</sup> is hydrogen;

A is selected from a  
bond,  $-(\text{CH}_2)\text{-NH}(\text{CH}_2)\text{-}$ ;  $-(\text{CH}_2)\text{-NH}(\text{CH}_2)\text{-(CH}_2)\text{-}$ ;  $-(\text{CH}_2)\text{-(CH}_2)\text{-NH}(\text{CH}_2)\text{-}$ ;  
and  $-(\text{CH}_2)\text{-NH}(\text{CHMe})\text{-}$ ; and  
 $\text{R}^7$  is selected from phenyl, 4-fluorophenyl, 4-morpholinyl, 1-methyl-4-piperidinyl and 1-  
5 cyclopropylcarbonyl-piperidin-4-yl.

1.97 A compound according to Embodiment 1.96 wherein:  
 $\text{R}^1$  is methoxy;  
 $\text{R}^2$  is hydrogen or methoxy;  
 $\text{R}^3$  is hydrogen;  
10  $\text{R}^4$  is hydrogen;  
 $\text{R}^5$  is cyano;  
 $\text{R}^6$  is hydrogen; and  
(i) when A is a bond,  $\text{R}^7$  is 1-methyl-4-piperidinyl; or  
(ii) when A is  $-(\text{CH}_2)\text{-NH}(\text{CH}_2)\text{-}$ ,  $\text{R}^7$  is selected from phenyl, 4-fluorophenyl and 1-  
15 cyclopropylcarbonyl-piperidin-4-yl; or  
(iii) when A is  $(\text{CH}_2)\text{-NH}(\text{CH}_2)\text{-(CH}_2)\text{-}$ ,  $\text{R}^7$  is 4-morpholinyl; or  
(iv) when A is  $-(\text{CH}_2)\text{-(CH}_2)\text{-NH}(\text{CH}_2)\text{-}$ ,  $\text{R}^7$  is phenyl; or  
(v) when A is  $-(\text{CH}_2)\text{-NH}(\text{CHMe})\text{-}$ ,  $\text{R}^7$  is 4-fluorophenyl.

1.97A A compound according to Embodiment 1.0 wherein:  
20  $\text{R}^1$  is methoxy;  
 $\text{R}^2$  is hydrogen;  
 $\text{R}^3$  is hydrogen;  
 $\text{R}^4$  is hydrogen;  
 $\text{R}^5$  is cyano;  
25  $\text{R}^6$  is hydrogen;  
A is a bond; and  
 $\text{R}^7$  is piperazinyl optionally substituted with one or two  $\text{C}_{1-4}$  alkyl substituents.

1.97B A compound according to Embodiment 1.97A wherein  $\text{R}^7$  is piperazinyl optionally  
substituted with one or two  $\text{C}_{1-4}$  alkyl substituents provided that the aggregate number of  
30 carbon atoms present in the substituents does not exceed four.

1.97C A compound according to Embodiment 1.97A or 1.97B wherein  $\text{R}^7$  is piperazinyl  
which is (i) unsubstituted; or (ii) monosubstituted with a substituent selected from methyl,  
ethyl and isopropyl; or (iii) is disubstituted with two methyl substituents.

- 1.97D A compound according to Embodiment 1.97A or 1.97B wherein R<sup>7</sup> is piperazinyl which is (ii) monosubstituted with a substituent selected from methyl, ethyl and isopropyl; or (iii) is disubstituted with two methyl substituents.
- 1.97E A compound according to Embodiment 1.97D wherein R<sup>7</sup> is piperazinyl which is monosubstituted on a nitrogen atom thereof with a substituent selected from methyl, ethyl and isopropyl.
- 1.97F A compound according to Embodiment 1.97D wherein R<sup>7</sup> is piperazinyl which is monosubstituted on a carbon atom thereof with a substituent selected from methyl, ethyl and isopropyl.
- 10 1.97G A compound according to Embodiment 1.97C which is disubstituted on a single carbon atom thereof with two methyl substituents.
- 1.98 A compound according to Embodiment 1.0 or Embodiment 1.1 which is selected from:
- 15 5-[5-(4-benzylamino-2,6-dimethoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile;
- 5-[5-(4-benzylamino-2-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile;
- 5-[5-[4-(benzylamino-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 5-[5-[4-(2-benzylamino-ethyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 20 5-[5-[4-(benzylamino-methyl)-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 5-[5-(4-[(S)-1-(4-fluoro-phenyl)-ethylamino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 25 5-[5-(4-[(R)-1-(4-fluoro-phenyl)-ethylamino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 5-(5-[4-[(4-fluoro-benzylamino)-methyl]-2-methoxy-phenyl]-1H-pyrazol-3-ylamino)-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 5-(5-[2-methoxy-4-[(2-morpholin-4-yl-ethylamino)-methyl]-phenyl]-1H-pyrazol-3-ylamino)-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 30

- (5-{2-methoxy-4-[(2-morpholin-4-yl-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-pyrazin-2-yl-amine (e.g. the hydrochloride salt);
- 5-{5-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- 5 5-[5-(4-[(1-cyclopropane-carbonyl-piperidin-4-ylmethyl)-amino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);
- N-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]cyclopropanecarboxamide;
- 5-[[5-[2-methoxy-4-[(tetrahydropyran-4-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[2-methoxy-4-[[methyl(2-morpholinoethyl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(2-morpholinoethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[4-[1-[2-(dimethylamino)acetyl]-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[[(1R)-1-methyl-2-morpholino-ethyl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(1,1-dimethyl-2-morpholino-ethyl)amino]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 20 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-fluoro-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile;
- 30 6-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile;

- N-[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]-5-methyl-pyrazin-2-amine;
- 5-[[5-[4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)oxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-  
5 carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 2-fluoro-4-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]benzotrile;
- 10 5-[[5-[2-methoxy-4-[(2-pyridylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[5-fluoro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(3S)-pyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-  
15 carbonitrile;
- 5-[[5-[2-methoxy-4-(pyrrolidin-2-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methylpyrrolidin-2-yl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 20 5-[[5-[2-methoxy-4-(4-piperidylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-isopropoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-  
25 carbonitrile;
- 5-[[5-[2-methoxy-4-(3-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(1-methyl-3-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(1-methyl-2-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-  
30 carbonitrile;
- 5-[[5-[2-methoxy-4-[(3S)-1-methylpyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-chloro-N-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]pyrazin-2-amine;  
5-chloro-N-[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]pyrazin-2-amine;  
5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carboxylic acid;  
5 5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
5-[[5-[4-[(2S,6S)-2,6-dimethyl-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
5-[[5-(2-methoxy-4-tetrahydropyran-4-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
10 2-fluoro-4-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]benzotrile;  
6-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile;  
5-[[5-[2-fluoro-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile;  
5-[[5-[2-isopropoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
15 5-[[5-[4-(1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
N-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]-5-methyl-pyrazin-2-amine;  
5-[[5-[4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
5-[[5-[2-methoxy-4-(4-piperidyloxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
20 5-[[5-[5-fluoro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
5-[[5-[4-[(isopropylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
5-[[5-[4-(1-ethyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-  
25 carbonitrile;  
5-[[5-[4-(1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;  
2-[4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-1-piperidyl]acetamide;



- 5-[[5-[2-methoxy-4-[[methyl(tetrahydropyran-4-yl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-fluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5 5-[[5-[2-methoxy-4-(1-methylazetid-3-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(3-fluoro-1-methyl-azetid-3-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[5-chloro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[5-chloro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[3-chloro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[3-chloro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- methyl 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carboxylate;
- 5-[[5-[2-methoxy-4-[(tetrahydrofuran-3-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 20 5-[[5-[2-methoxy-4-[[methyl(tetrahydrofuran-3-yl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(tetrahydropyran-4-ylmethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[2-methoxy-4-(tetrahydropyran-4-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(3-fluoroazetid-3-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 30 5-[[5-[2-methoxy-4-[(3R)-1-methylpyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-(2-methoxy-4-morpholino-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-ethylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;;
- 5-[[5-[4-(4-isopropylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(3R)-3-methylpiperazin-1-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-ethyl-1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[4-(4-isopropyl-1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(1-ethyl-4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-fluoro-1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[4-(1-ethyl-3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(3-fluoro-1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 20 5-[[5-[2-methoxy-4-[1-(2-methoxyethyl)-4-piperidyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(ethylaminomethyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(cyclopropylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[4-[(3R)-3,4-dimethylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R)-4-ethyl-3-methyl-piperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 30 5-[[5-[4-[(3S)-1-isopropylpyrrolidin-3-yl]oxy-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[(3R)-1-isopropylpyrrolidin-3-yl]oxy-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R,S),4(R,S))-3-fluoro-1-methyl-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5 5-[[5-[4-(3,3-difluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(1-ethyl-3,3-difluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[1-(2-hydroxyethyl)-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[4-[[isopropyl(methyl)amino] methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[2-methoxy-4-(morpholinomethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2R)-1-methylpyrrolidin-2-yl]methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride;
- 5-[[5-[2-methoxy-4-[(2S)-1-methylpyrrolidin-2-yl]methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride;
- 20 5-[[5-[2-methoxy-4-(oxazol-4-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[1-(2-fluoroethyl)-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)methylamino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)methylamino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)methylamino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 30 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)amino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[(1-ethyl-4-piperidyl)amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)oxymethyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[4-[(1-isopropyl-4-piperidyl)oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-(2-fluoro-6-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2R)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[2-methoxy-4-[(2R)-4-ethylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2S)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2S)-4-ethylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-
- 20 carbonitrile;
- 5-[[5-(2,6-dimethoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2,6-dimethoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[4-[[3R]-3-fluoropyrrolidin-1-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[3S]-3-methoxypyrrolidin-1-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[3R]-3-methoxypyrrolidin-1-yl]methyl]phenyl]-1H-pyrazol-3-
- 30 yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[2R]-1-ethylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[[[(2R)-1-isopropylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2S)-1-ethylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5 5-[[5-[4-[[[(2S)-1-isopropylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(cyclopropylmethylamino) methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[[(3R)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[2-methoxy-4-[[[(3S)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R)-4-isopropyl-3-methyl-piperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[4-[(1-ethyl-4-piperidyl)oxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)oxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-ethylpiperazin-1-yl)-2-fluoro-6-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 20 5-[[5-[4-(4-isopropylpiperazin-1-yl)-2-fluoro-6-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3S)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[4-[[[(3S)-1-isopropylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3R)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3R)-1-isopropylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 30 5-[[5-[4-(4-isobutylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[(1-ethyl-4-piperidyl)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5 5-[[5-[4-[(1-ethyl-4-piperidyl)methyl-methyl-amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(isobutylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(2R)-4-isopropylmorpholin-2-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 10 5-[[5-[4-[(1-isopropyl-4-piperidyl)methyl-methyl-amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[2R)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 15 5-[[5-[4-[(2S)-4-isopropylmorpholin-2-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[2R)-1-isopropylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[2S)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 20 5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[2S)-1-isopropylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[3S)-1-isopropylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 25 5-[[5-[4-[[3R)-1-isopropylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[3R)-1-ethylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 30 5-[[5-[4-[[3S)-1-ethylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(3S)-3-methylpiperazin-1-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(3R)-3-ethylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5 5-[[5-[4-[(3S)-3-isopropylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(3R)-3-isopropylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

10 5-[[5-[4-(3,3-dimethylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

and salts and tautomers thereof.

1.99 A compound according to any one of Embodiments 1.1 to 1.98 having a molecular weight of up to 1000, for example less than 750.

15 1.100 A compound according to Embodiment 1.99 having a molecular weight of less than 700.

1.101 A compound according to Embodiment 1.100 having a molecular weight of less than 650.

1.102 A compound according to Embodiment 1.101 having a molecular weight of less than 600 or less than 550.

20 1.103 A compound according to Embodiment 1.102 having a molecular weight of less than 530, for example up to 525.

1.104 A compound according to Embodiment 1.1 which is the title compound of any one of Examples 1 to 12 below.

25 1.105 A compound according to any one of Embodiments 1.1 to 1.104 which is in the form of a salt.

1.106 A compound according to Embodiment 1.105 wherein the salt is an acid addition salt.

1.107 A compound according to Embodiment 1.105 or Embodiment 1.106 wherein the salt is a pharmaceutically acceptable salt.

### Definitions

In this application, the following definitions apply, unless indicated otherwise.

The term “non-aromatic carbocyclic or heterocyclic group” embraces unsaturated ring systems without aromatic character, partially saturated and fully saturated carbocyclic and heterocyclic ring systems. The terms “unsaturated” and “partially saturated” refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a C=C, C≡C or N=C bond. The term “fully saturated” refers to rings where there are no multiple bonds between ring atoms. Saturated carbocyclic groups include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cycloheptenyl and cyclooctenyl.

Examples of non-aromatic heterocyclic groups include morpholine, thiomorpholine and its S-oxide and S,S-dioxide, piperidine, N-alkyl piperidines, piperidone, pyrrolidine, pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran, imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines.

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, and cycloheptenyl.

The term “hydrocarbyl” as used herein is used in its standard IUPAC sense to refer to moieties consisting of carbon and hydrogen atoms, i.e. hydrocarbon moieties.

In addition to carbon-hydrogen bonds, the hydrocarbyl groups can contain one or more single, double or triple carbon-carbon bonds. The hydrocarbyl groups can be aromatic or non-aromatic. Examples of non-aromatic hydrocarbyl groups include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkylalkenyl and cycloalkylalkynyl groups.

The term “alkyl” covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups.



Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

- 5 Examples of aromatic hydrocarbyl groups are phenyl and naphthyl.

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred. When attached to a non-aromatic moiety, fluorine is preferred.

### Salts

- 10 The compounds of the invention may be presented in the form of salts.

The salts (as defined in Embodiments 1.105 to 1.107) are typically acid addition salts.

The salts can be synthesized from the parent compound by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8,

- 15 Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free base form of the compound with the acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

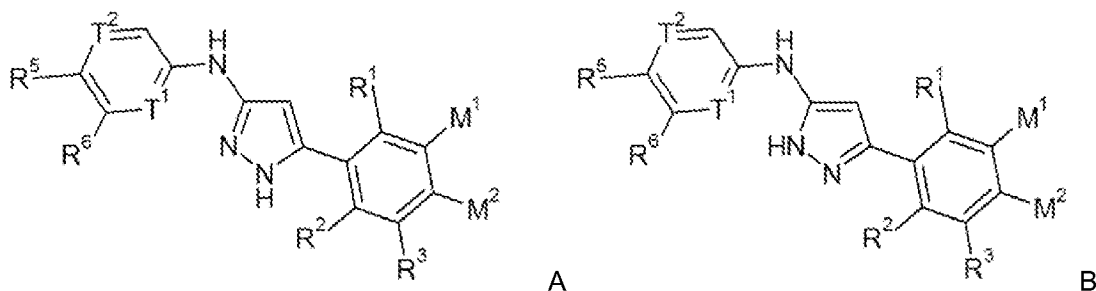
- 20 Acid addition salts (as defined in Embodiment 1.106) may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1S)-camphor-10-sulphonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulphuric, ethane-  
25 1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic),  $\alpha$ -oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, (+)-L-lactic, ( $\pm$ )-DL-lactic, lactobionic, maleic, malic, (-)-L-malic, malonic, ( $\pm$ )-DL-mandelic, methanesulphonic, naphthalene-2-sulphonic, naphthalene-1,5-disulphonic,  
30 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, *p*-toluenesulphonic, undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

#### Geometric isomers and tautomers

The compounds of the invention may exist in a number of different geometric isomeric, and tautomeric forms and references to the compounds of formula (0) or formula (1) as defined in Embodiments 1.0 to 1.107 include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (0) or formula (1) or subgroups, subsets, preferences and examples thereof.

For example, the compounds of formula (0) may exist in either or both of tautomeric forms A and B below.



Although only tautomeric form A is shown in the formula drawings in this application, it should be understood that formula (0) and the other formulae in this application are intended to cover both tautomeric forms.

#### Optical Isomers

Where compounds of the formula contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to the compounds include all optical isomeric forms thereof (e.g. enantiomers, epimers and diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) or two or more optical isomers, unless the context requires otherwise.

The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers, or *d* and *l* isomers) or they may be characterised in terms of their absolute

stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4<sup>th</sup> Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 385-415.

- 5 Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid,  
10 (-)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

Where compounds of the invention exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer,  
15 for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (0) or formula  
20 (1) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (0) or formula (1) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

#### Isotopes

- 25 The compounds of the invention as defined in any one of Embodiments 1.0 to 1.107 may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope <sup>1</sup>H, <sup>2</sup>H (D), and <sup>3</sup>H (T). Similarly, references to carbon and oxygen include within their scope respectively <sup>12</sup>C, <sup>13</sup>C and <sup>14</sup>C and <sup>16</sup>O and <sup>18</sup>O.
- 30 The isotopes may be radioactive or non-radioactive. In one embodiment of the invention, the compounds contain no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

### Solvates

Compounds of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 may form solvates.

5 Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and dimethylsulphoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating  
10 solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis (TGE), differential scanning calorimetry (DSC) and X-ray crystallography.

The solvates can be stoichiometric or non-stoichiometric solvates.

15 Particularly preferred solvates are hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates.

For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn et al., Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

### 20 Prodrugs

The compounds of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 may be presented in the form of a pro-drug.

By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (0) or formula (1), as defined in any one of  
25 Embodiments 1.0 to 1.107.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any hydroxyl groups present in the parent compound with, where  
30 appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for

example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

#### Complexes and clathrates

Also encompassed by formula (0) or formula (1) or subgroups, subsets, preferences and examples thereof are complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds.

#### Biological Activity

The compounds of the formulae (1) and sub-groups thereof are potent inhibitors of Chk-1 and consequently are expected to be beneficial alone or in combination with various chemotherapeutic agents or radiation for treating a wide spectrum of proliferative disorders.

Preferred compounds of the formula (0) or formula (1) are those compounds that have  $IC_{50}$  values of less than  $0.1 \mu M$  against Chk-1 kinase. Particularly preferred compounds are those that have  $IC_{50}$  values of less than  $0.01 \mu M$  against Chk-1 kinase. Still more preferred compounds are those that have  $IC_{50}$  values of less than  $0.001 \mu M$  against Chk-1 kinase.

Accordingly, in further embodiments (Embodiments 2.1 to 2.14), the invention provides:

- 2.1 A compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 for use in medicine or therapy.
- 2.2 A compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 for use as a Chk-1 kinase inhibitor.
- 2.3 A compound of the formula (0) or formula (1) for use as defined in Embodiment 2.2 wherein the compound has an  $IC_{50}$  values of less than  $1 \mu M$  against Chk-1 kinase (e.g. when determined according the assays described herein).
- 2.4 A compound of the formula (0) or formula (1) for use as defined in Embodiment 2.3 wherein the compound has an  $IC_{50}$  value of less than  $0.1 \mu M$  against Chk-1 kinase.
- 2.5 A compound of the formula (0) or formula (1) for use as defined in Embodiment 2.3 wherein the compound has an  $IC_{50}$  value of less than  $0.01 \mu M$  against Chk-1 kinase.
- 2.6 A compound of the formula (0) or formula (1) for use as defined in Embodiment 2.3 wherein the compound has an  $IC_{50}$  value of less than  $0.001 \mu M$  against Chk-1 kinase.
- 2.7 A compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6 for use in enhancing a therapeutic effect of

radiation therapy or chemotherapy in the treatment of a proliferative disease such as cancer.

2.8 A compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6 for use in the treatment of a proliferative disease  
5 such as cancer.

2.9 The use of a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6 for the manufacture of a medicament for enhancing a therapeutic effect of radiation therapy or chemotherapy in the treatment of a proliferative disease such as cancer.

10 2.10 The use of a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6 for the manufacture of a medicament for the treatment of a proliferative disease such as cancer.

2.11 A method for the prophylaxis or treatment of a proliferative disease such as cancer, which method comprises administering to a patient in combination with  
15 radiotherapy or chemotherapy a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6.

2.12 A method for the prophylaxis or treatment of a proliferative disease such as cancer, which method comprises administering to a patient a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6.

20 2.13 A compound for use, use or method as defined in any one of Embodiments 2.7 to 2.12 wherein the cancer is selected from carcinomas, for example carcinomas of the bladder, breast, colon, kidney, epidermis, liver, lung, oesophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, gastrointestinal system, or skin, hematopoietic tumours such as leukaemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's  
25 lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; hematopoietic tumours of myeloid lineage, for example acute and chronic myelogenous leukaemias, myelodysplastic syndrome, or promyelocytic leukaemia; thyroid follicular cancer; tumours of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; tumours of the central or peripheral nervous system, for example astrocytoma,  
30 neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratocanthoma; thyroid follicular cancer; Ewing's sarcoma or Kaposi's sarcoma.

2.14 A compound for use, use or method according to Embodiment 2.13 wherein the cancer is selected from breast cancer, colon cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, glioma, Ewing's sarcoma and leukemia.

It is also envisaged that the Chk-1 inhibitors of the invention may be useful in treating  
5 tumours in which there is a defective DNA repair mechanism or a defective cell cycle, for  
example a cancer in which mutations (e.g. in p53) have led to the G1/S DNA damage  
checkpoint being lost (see the introductory section of this application). The Chk-1  
inhibitors of the invention may also be useful in treating RAD17 mutant tumours, ATM-  
deficient RAD50-mutant tumours and fanconi anaemia. Accordingly in further  
10 embodiments (Embodiments 2.15 to 2.24), the invention provides:

2.15 A compound for use, use or method as defined in any one of Embodiments 2.7 to  
2.14 wherein the cancer is one which is characterized by a defective DNA repair  
mechanism or defective cell cycle.

2.16 A compound for use, use or method according to Embodiment 2.15 wherein the  
15 cancer is a p53 negative or mutated tumour.

2.17 A compound for use, use or method as defined in any one of Embodiments 2.7 to  
2.14 wherein the cancer is an MYC oncogene-driven cancer.

2.18 A compound for use, use or method according to Embodiment 2.16 wherein the  
MYC oncogene-driven cancer is a B-cell lymphoma, leukemia, neuroblastoma, breast  
20 cancer or lung cancer.

2.19 A compound of the formula (0) or formula (1) as defined in any one of  
Embodiments 1.0 to 1.107 for use in the treatment of a patient suffering from a p53  
negative or mutated tumour (e.g. a cancer selected from breast cancer, colon cancer,  
lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, glioma, and leukemia) in  
25 combination with radiotherapy or chemotherapy.

2.20 A compound for use according to any one of Embodiments 2.7 to 2.19 wherein, in  
addition to administration of a compound of the formula (0) or formula (1) as defined in  
any one of Embodiments 1.0 to 1.107, the treatment comprises administration to a patient  
of a chemotherapeutic agent selected from cytarabine, etoposide, gemcitabine and SN-  
30 38.

2.21 The use of a compound of the formula (0) or formula (1) as defined in any one of  
Embodiments 1.0 to 1.107 or 2.3 to 2.6 for the manufacture of a medicament for the  
treatment of a patient suffering from a cancer which is characterised by a defective DNA  
repair mechanism or defective cell cycle.

2.22 The use according to Embodiment 2.21 wherein the cancer is a p53 negative or mutated tumour.

2.23 A method for the treatment of a patient (e.g. a human patient) suffering from a cancer which is characterised by a defective DNA repair mechanism or defective cell  
5 cycle, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6.

2.24 A method according to Embodiment 2.23 wherein the cancer is a p53 negative or mutated tumour.

10 2.25 A compound for use, use or method as defined in any one of Embodiments 2.7 to 2.14 wherein the cancer is a RAD17-mutant tumour or an ATM-deficient RAD50-mutant tumour.

2.26 A compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6 for use in the treatment of Fanconi anaemia.

15 2.27 The use of a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6 for the manufacture of a medicament for the treatment of Fanconi anaemia.

2.28 A method of treating Fanconi anaemia in a subject (e.g. a human subject) in need thereof, which method comprises administering to the subject a therapeutically effective  
20 amount of a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 or 2.3 to 2.6.

The Chk-1 inhibitor compounds of the invention may be used alone or they may be used in combination with DNA-damaging anti-cancer drugs and/or radiation therapy to treat subjects with multi-drug resistant cancers. A cancer is considered to be resistant to a  
25 drug when it resumes a normal rate of tumour growth while undergoing treatment with the drug after the tumour had initially responded to the drug. A tumour is considered to "respond to a drug" when it exhibits a decrease in tumor mass or a decrease in the rate of tumour growth.

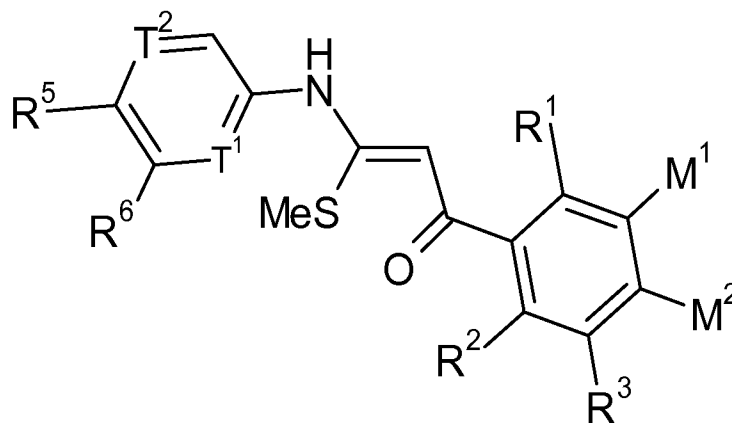
#### **Methods for the Preparation of Compounds of the Formulae (0) and (1)**

30 Compounds of the formulae (0) and (1) can be prepared in accordance with synthetic methods well known to the skilled person and as described herein.



Accordingly, in another embodiment (Embodiment 3.1), the invention provides a process for the preparation of a compound as defined in any one of Embodiments 1.0 to 1.107, which process comprises:

(A) the reaction of a compound of formula (11):

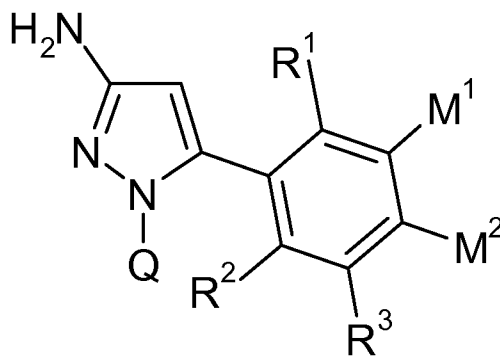


5

(11)

or a protected form thereof, wherein  $R^1$  to  $R^6$ ,  $T^1$  and  $T^2$  are as hereinbefore defined; with hydrazine, followed by removal of any protecting groups present, where required; or

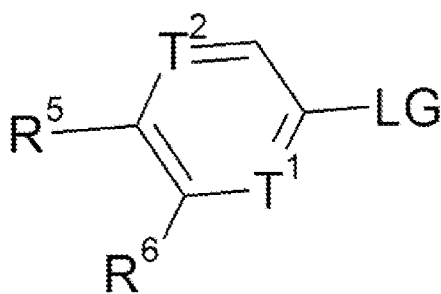
(B) the reaction of a compound of the formula (12):



10

(12)

(or its pyrazole-ring tautomer) wherein  $R^1$  to  $R^3$ ,  $M^1$  and  $M^2$  are as hereinbefore defined, and Q is hydrogen or a protecting group PG; with a compound of the formula (13):



(13)

where  $R^5$  and  $R^6$  are as hereinbefore defined and LG is a leaving group or atom such as bromine, in the presence of a base such as a metal hydride base (e.g. sodium hydride), followed by removal of any protecting group PG where necessary; and thereafter:

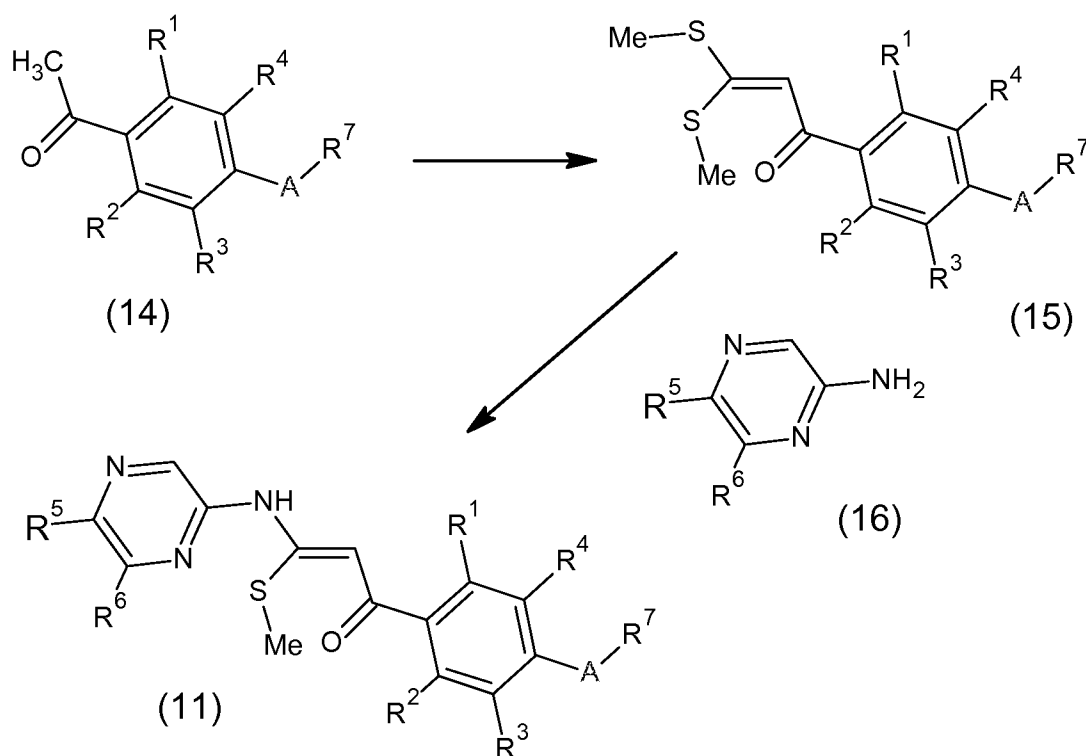
- 5 (C) optionally converting one compound of the formula (0) or (1), into another compound of the formula (0) or (1).

In formula (11), a nitrogen atom forming part of the moiety A in  $M^1$  or  $M^2$  may be protected by an amino group protecting group. The protecting group, when present, is a group capable of protecting the amino function against unwanted side reactions and  
 10 examples of such protecting groups are well known to the skilled person, see the reference book (*Protective Groups in Organic Synthesis* (Greene and Wuts) referred to below.

A particularly preferred protecting group is the *tert*-butoxycarbonyl (Boc) group. The Boc group may readily be removed when required by treatment with an acid such as  
 15 hydrochloric acid or trifluoroacetic acid.

In process variant (A), the reaction of the compound of formula (11) with hydrazine is typically carried out in a polar solvent such as ethanol or aqueous ethanol in the presence of acetic acid, with moderate heating, for example to a temperature of about 60 °C.

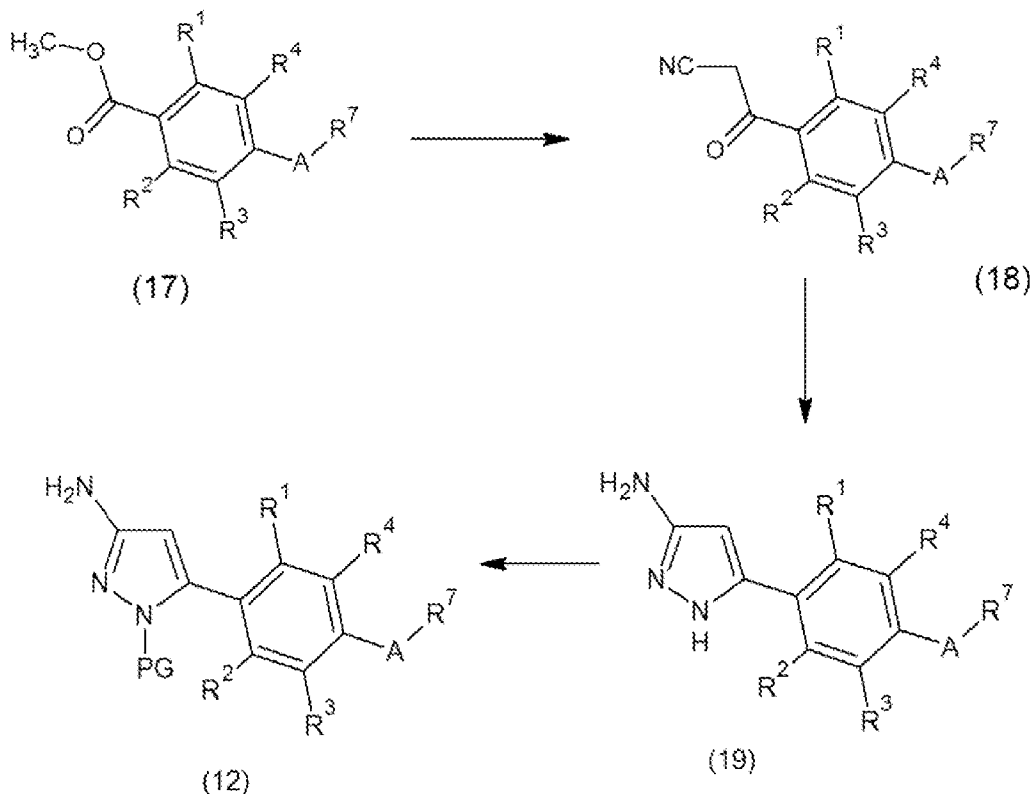
Compounds of the formula (11) wherein  $R^1$  to  $R^4$ , A and  $R^7$  are as defined in formula (1),  
 20 can be prepared by the sequence of reactions shown in Scheme 1.



Scheme 1

- Compounds of the formula (14) can be prepared by the methods described below in the Examples section below or by methods analogous thereto. The compound of formula (14) is reacted with carbon disulfide and iodomethane in the presence of a metal hydride base such as sodium hydride in a polar solvent such as dimethyl sulfoxide, THF or DMF to give the intermediate (15). The intermediate (15) is then reacted with the aminopyrazine (16) in the presence of a metal hydride base (such as sodium hydride) in a polar solvent such as THF to give the compound (11).
- 10 In process variant (B), the compound of formula ((12) is typically reacted with the pyrazine compound (13) in the presence of a metal hydride base such as sodium hydride in a non-protic polar solvent such as THF. The reaction is typically carried out at low temperature, for example around 0 °C. The leaving group LG is typically a halogen such as bromine. When a metal hydride base is used, the moiety Q is preferably a protecting group PG such as a Boc group. As an alternative to using a metal hydride base, a non-nucleophilic (or poorly nucleophilic) base such as N,N-diisopropylethylamine (DIPEA) can be used, in which case a protecting group can be omitted from the pyrazole ring (i.e. Q = hydrogen).

Compounds of the formula (12) wherein R<sup>1</sup> to R<sup>4</sup>, A and R<sup>7</sup> are as defined in formula (1) and PG is a protecting group can be prepared by the sequence of reactions shown in Scheme 2.



5

Scheme 2

Compounds of the formula (17) can be prepared by the methods described below in the Examples section or by methods analogous thereto. The compound of formula (17) is reacted with acetonitrile in the presence of an alkyl lithium base such as butyl lithium to give the cyano compound of formula (18). The reaction is typically carried out in an inert non-polar aprotic solvent such as toluene at a low temperature, for example about -78 °C.

The cyano compound of formula (18) is then reacted with hydrazine in a polar solvent such as ethanol in the presence of acetic acid to give the pyrazole (19). The nitrogen atom at the 1-position of the pyrazole ring is then protected with a *tert*-butyloxycarbonyl (Boc) protecting group by reaction with Boc-anhydride in THF in the presence of a metal hydride base such as sodium hydride to give the pyrazole intermediate (12) where PG is Boc. The reaction is typically carried out at a low temperature, for example a temperature of about 0 °C.

Once formed, one compound of the formula (0) or (1), or a protected derivative thereof, can be converted into another compound of the formula (0) or (1) by methods well known to the skilled person. Examples of synthetic procedures for converting one functional group into another functional group are set out in standard texts such as *Advanced*  
5 *Organic Chemistry* and *Organic Syntheses* (see references above) or *Fieser's Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2).

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule.  
10 Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Greene and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

Compounds made by the foregoing methods may be isolated and purified by any of a variety of methods well known to those skilled in the art and examples of such methods  
15 include recrystallisation and chromatographic techniques such as column chromatography (e.g. flash chromatography) and HPLC.

Many of the synthetic intermediates of the formulae (11) to (19) described above and in the reaction schemes and examples below are novel and, as such, represent a further aspect of the invention.

## 20 **Pharmaceutical Formulations**

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

Accordingly, in another embodiment (Embodiment 4.1) of the invention, there is provided a pharmaceutical composition comprising at least one compound of the formula (0) or  
25 formula (1) as defined in any one of Embodiments 1.0 to 1.107 together with a pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipient can be, for example, a carrier (e.g. a solid, liquid or semi-solid carrier), a diluent or bulking agent, a granulating agent, coating agent, binding agent, disintegrant, lubricating agent, preservative, antioxidant, buffering agent,  
30 suspending agent, thickening agent, flavouring agent, sweetener, taste masking agent or any other excipient conventionally used in pharmaceutical compositions. Examples of excipients for various types of pharmaceutical compositions are set out in more detail below.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct  
5 delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers,  
10 bacteriostats, co-solvents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, *inter alia*, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended  
15 recipient. Pharmaceutical formulations for parenteral administration may also take the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents (R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230).

A drug molecule that is ionizable can be solubilized to the desired concentration by pH  
20 adjustment if the drug's  $pK_a$  is sufficiently away from the formulation pH value. The acceptable range is pH 2-12 for intravenous and intramuscular administration, but subcutaneously the range is pH 2.7-9.0. The solution pH is controlled by either the salt form of the drug, strong acids/bases such as hydrochloric acid or sodium hydroxide, or by solutions of buffers which include but are not limited to buffering solutions formed from glycine, citrate, acetate, maleate,  
25 succinate, histidine, phosphate, tris(hydroxymethyl)-aminomethane (TRIS), or carbonate.

The combination of an aqueous solution and a water-soluble organic solvent/surfactant (i.e., a cosolvent) is often used in injectable formulations. The water-soluble organic solvents and surfactants used in injectable formulations include but are not limited to propylene glycol, ethanol, polyethylene glycol 300, polyethylene glycol 400, glycerin, dimethylacetamide (DMA), N-  
30 methyl-2-pyrrolidone (NMP; Pharmasolve), dimethylsulphoxide (DMSO), Solutol HS 15, Cremophor EL, Cremophor RH 60, and polysorbate 80. Such formulations can usually be, but are not always, diluted prior to injection.

Propylene glycol, PEG 300, ethanol, Cremophor EL, Cremophor RH 60, and polysorbate 80 are the entirely organic water-miscible solvents and surfactants used in commercially available

injectable formulations and can be used in combinations with each other. The resulting organic formulations are usually diluted at least 2-fold prior to IV bolus or IV infusion.

Alternatively increased water solubility can be achieved through molecular complexation with cyclodextrins.

- 5 The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

The pharmaceutical formulation can be prepared by lyophilising a compound of formula  
10 (0) or formula (1) or acid addition salt thereof. Lyophilisation refers to the procedure of freeze-drying a composition. Freeze-drying and lyophilisation are therefore used herein as synonyms. A typical process is to solubilise the compound and the resulting formulation is clarified, sterile filtered and aseptically transferred to containers appropriate for lyophilisation (e.g. vials). In the case of vials, they are partially stoppered with lyo-  
15 stoppers. The formulation can be cooled to freezing and subjected to lyophilisation under standard conditions and then hermetically capped forming a stable, dry lyophile formulation. The composition will typically have a low residual water content, e.g. less than 5% e.g. less than 1% by weight based on weight of the lyophile.

The lyophilisation formulation may contain other excipients for example, thickening  
20 agents, dispersing agents, buffers, antioxidants, preservatives, and tonicity adjusters. Typical buffers include phosphate, acetate, citrate and glycine. Examples of antioxidants include ascorbic acid, sodium bisulphite, sodium metabisulphite, monothioglycerol, thiourea, butylated hydroxytoluene, butylated hydroxyl anisole, and ethylenediaminetetraacetic acid salts. Preservatives may include benzoic acid and its  
25 salts, sorbic acid and its salts, alkyl esters of *para*-hydroxybenzoic acid, phenol, chlorobutanol, benzyl alcohol, thimerosal, benzalkonium chloride and cetylpyridinium chloride. The buffers mentioned previously, as well as dextrose and sodium chloride, can be used for tonicity adjustment if necessary.

Bulking agents are generally used in lyophilisation technology for facilitating the process  
30 and/or providing bulk and/or mechanical integrity to the lyophilized cake. Bulking agent means a freely water soluble, solid particulate diluent that when co-lyophilised with the compound or salt thereof, provides a physically stable lyophilized cake, a more optimal freeze-drying process and rapid and complete reconstitution. The bulking agent may also be utilised to make the solution isotonic.

35 The water-soluble bulking agent can be any of the pharmaceutically acceptable inert solid

materials typically used for lyophilisation. Such bulking agents include, for example, sugars such as glucose, maltose, sucrose, and lactose; polyalcohols such as sorbitol or mannitol; amino acids such as glycine; polymers such as polyvinylpyrrolidone; and polysaccharides such as dextran.

- 5 The ratio of the weight of the bulking agent to the weight of active compound is typically within the range from about 1 to about 5, for example of about 1 to about 3, e.g. in the range of about 1 to 2.

Alternatively they can be provided in a solution form which may be concentrated and sealed in a suitable vial. Sterilisation of dosage forms may be via filtration or by  
10 autoclaving of the vials and their contents at appropriate stages of the formulation process. The supplied formulation may require further dilution or preparation before delivery for example dilution into suitable sterile infusion packs.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

- 15 In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion.

In another preferred embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules,  
20 caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

- 25 Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn  
30 starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example



phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed  
5 from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal  
10 tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may  
15 be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated  
20 in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

The compound of formula (0) or formula (1), as defined in any one of Embodiments 1.0 to 1.107, or a prodrug thereof, may be formulated with a carrier and administered in the form  
25 of nanoparticles. Nanoparticles offer the possibility of direct penetration into the cell. Nanoparticle drug delivery systems are described in "Nanoparticle Technology for Drug Delivery", edited by Ram B Gupta and Uday B. Kompella, Informa Healthcare, ISBN 9781574448573, published 13<sup>th</sup> March 2006. Nanoparticles for drug delivery are also described in J. Control. Release, 2003, 91 (1-2), 167-172, and in Sinha *et al.*, Mol.  
30 Cancer Ther. August 1, (2006) 5, 1909.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient  
35 always has access to the package insert contained in the patient pack, normally missing

in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

5 Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

10 Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

15 Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administered in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

20 The compounds of the formula (0) or formula (1) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within this range, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

25 For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

### 30 **Methods of Treatment**

It is envisaged that the compounds of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 as defined herein will be useful either alone or in combination therapy with chemotherapeutic agents (particularly DNA-damaging agents)

or radiation therapy in the prophylaxis or treatment of a range of proliferative disease states or conditions. Examples of such disease states and conditions are set out above.

The compounds of formula (0) or formula (1), whether administered alone, or in combination with DNA damaging agents and other anti-cancer agents and therapies, are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

According to another embodiment of the invention, Embodiment 5.1, there is provided a combination of a compound of formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 together with another chemotherapeutic agent, for example an anticancer drug.

Examples of chemotherapeutic agents that may be co-administered with the compounds of formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 include:

- Topoisomerase I inhibitors
- Antimetabolites
- Tubulin targeting agents
- DNA binder and topoisomerase II inhibitors
- Alkylating Agents
- Monoclonal Antibodies.
- Anti-Hormones
- Signal Transduction Inhibitors
- Proteasome Inhibitors
- DNA methyl transferases
- Cytokines and retinoids
- Hypoxia triggered DNA damaging agents (e.g. Tirapazamine, TH-302)

Particular examples of chemotherapeutic agents that may be administered in combination with the compounds of formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107 include:

nitrogen mustards such as mechlorethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil;

nitrosoureas such as carmustine, lomustine and semustine;

- ethyleneimine/methylmelamine compounds such as triethylenemelamine, triethylene thiophosphoramidate and hexamethylmelamine;
- alkyl sulphonates such as busulfan;
- triazines such as dacarbazine
- 5 Antimetabolites such as folates, methotrexate, trimetrexate, 5-fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside, 5-azacytidine, 2, 2'-difluorodeoxycytidine, 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin, erythrohydroxynonyl-adenine, fludarabine phosphate and 2-chlorodeoxyadenosine;
- 10 type I topoisomerase inhibitors such as camptothecin, topotecan and irinotecan;
- type II topoisomerase inhibitors such as the epipodophylotoxins (e.g. etoposide and teniposide);
- antimitotic drugs such as paclitaxel, Taxotere, Vinca alkaloids (e.g. vinblastine, vincristine, vinorelbine) and estramustine (e.g. estramustine phosphate);
- 15 antibiotics such as actinomycin D, daunomycin (rubidomycin), doxorubicin (adriamycin), mitoxantrone, idarubicin, bleomycin, mithramycin, mitomycin C and dactinomycin
- enzymes such as L-asparaginase;
- cytokines and biological response modifiers such as interferon ( $\alpha$ ,  $\beta$ ,  $\gamma$ ), interleukin-2, GM-CSF and GM-CSF:
- 20 retinoids such as retinoic acid derivatives (e.g. bexarotene);
- radiosensitisers such as metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, nicotinamide, 5-bromodeoxyuridine, 5-iododeoxyuridine and bromodeoxycytidine;
- platinum compounds such as cisplatin, carboplatin, spiroplatin, iroplatin, onnaplatin,
- 25 tetraplatin and oxaliplatin;
- anthracenediones such as mitoxantrone;
- ureas such as hydroxyurea;
- hydrazine derivatives such as N-methylhydrazine and procarbazine;
- adrenocortical suppressants such as mitotane and aminoglutethimide;
- 30 adrenocorticosteroids and antagonists such as prednisone, dexamethasone and aminoglutethimide;

progestins such as hydroxyprogesterone (e.g. hydroxyprogesterone caproate), medroxyprogesterone (e.g. medroxyprogesterone acetate) and megestrol (e.g. megestrol acetate);

oestrogens such as diethylstilbestrol and ethynyl estradiol;

5 anti-oestrogens such as tamoxifen;

androgens such as testosterone (e.g. testosterone propionate) and fluoxymesterone;

anti-androgens such as flutamide and leuprolide;

nonsteroidal anti-androgens such as flutamide; and

10 signal transduction inhibitors such as PARP inhibitors [e.g. as disclosed in *Cancer Res.*; 66: (16)], Mek inhibitors [e.g. as disclosed in *Blood*. 2008 September 15; 112(6): 2439–2449], farnesyltransferase inhibitors [e.g. as disclosed in *Blood*. 2005 Feb 15;105(4):1706-16], wee1 inhibitors [e.g. as disclosed in *Haematologica* 2013.093187 (epub ahead of print)], rapamycin and Src inhibitors [e.g. as disclosed in *Blood*. 2011 Feb 10;117(6):1947-57].

15 Examples of the chemotherapeutic agents than may be used in combination with the Chk-1 inhibitor compounds of Embodiments 1.0 to 1.107 as defined herein include the chemotherapeutic agents described in Blasina *et al.*, *Mol. Cancer Ther.*, 2008, 7(8), 2394-2404, Ashwell *et al.*, *Clin. Cancer Res.*, 2008, 14(13), 4032-4037, Ashwell *et al.*, *Expert Opin. Investig. Drugs*, 2008, 17(9), 1331-1340, *Trends in Molecular Medicine* February 20 2011, Vol. 17, No. 2 and *Clin Cancer Res*; 16(2) January 15, 2010.

Particular examples of chemotherapeutic agents that may be used in combination with the Chk-1 inhibitor compounds of Embodiments 1.0 to 1.107 as defined herein include antimetabolites (such as capecitabine, cytarabine, fludarabine, gemcitabine and pemetrexed), Topoisomerase-I inhibitors (such as SN38, topotecan, irinotecan), platinum 25 compounds (such as carboplatin, oxaloplatin and cisplatin), Topoisomerase-II inhibitors (such as daunorubicin, doxorubicin and etoposide), thymidylate synthase inhibitors (such as 5-fluorouracil), mitotic inhibitors (such as docetaxel, paclitaxel, vincristine and vinorelbine, ) and alkylating agents (such as mitomycin C).

A further set of chemotherapeutic agents that may be used in combination with the Chk-1 30 inhibitor compounds of Embodiments 1.0 to 1.107 as defined herein includes agents that induce stalled replication forks (see Ashwell *et al.*, *Clin. Cancer Res.*, above), and examples of such compounds include gemcitabine, 5-fluorouracil and hydroxyurea.

The compounds of the invention and combinations with chemotherapeutic agents or radiation therapies as described above may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a pulsatile or continuous manner.

5 The compounds of the invention will be administered in an effective amount, i.e. an amount which is effective to bring about the desired therapeutic effect either alone (in monotherapy) or in combination with one or more chemotherapeutic agents or radiation therapy. For example, the "effective amount" can be a quantity of compound which, when administered alone or together with a DNA-damaging drug or other anti-cancer  
10 drug to a subject suffering from cancer, slows tumour growth, ameliorates the symptoms of the disease and/or increases longevity. More particularly, when used in combination with radiation therapy, with a DNA-damaging drug or other anti-cancer drug, an effective amount of the Chk-1 inhibitor of the invention is the quantity in which a greater response is achieved when the Chk-1 inhibitor is co-administered with the DNA damaging anti-  
15 cancer drug and/or radiation therapy compared with when the DNA damaging anti-cancer drug and/or radiation therapy is administered alone. When used as a combination therapy, an "effective amount" of the DNA damaging drug and/or an "effective" radiation dose are administered to the subject, which is a quantity in which anti-cancer effects are normally achieved. The Chk-1 inhibitors of the invention and the DNA damaging anti-  
20 cancer drug can be co-administered to the subject as part of the same pharmaceutical composition or, alternatively, as separate pharmaceutical compositions.

When administered as separate pharmaceutical compositions, the Chk-1 inhibitor of the invention and the DNA-damaging anti-cancer drug (and/or radiation therapy) can be administered simultaneously or at different times, provided that the enhancing effect of  
25 the Chk-1 inhibitor is retained.

In one embodiment, a compound of any one of Embodiments 1.0 to 1.107 as defined herein is administered before (e.g by up to 8 hours or up to 12 hours or up to one day before) administration of the DNA-damaging anticancer drug.

In another embodiment, a compound of any one of Embodiments 1.0 to 1.107 as defined  
30 herein is administered after (e.g by up to 8 hours or up to 12 hours or up to 24 hours or up to 30 hours or up to 48 hours after) administration of the DNA-damaging anticancer drug. In another embodiment, a first dose of a compound of any one of Embodiments 1.0 to 1.107 as defined herein is administered one day after administration of the DNA-damaging anticancer drug and a second dose of the said compound is administered two  
35 days after administration of the DNA-damaging anticancer drug.

In a further embodiment, a first dose of a compound of any one of Embodiments 1.0 to 1.107 as defined herein is administered one day after administration of the DNA-damaging anticancer drug, a second dose of the said compound is administered two days after administration of the DNA-damaging anticancer drug, and third dose of the said  
5 compound is administered three days after administration of the DNA-damaging anticancer drug.

Particular dosage regimes comprising the administration of a compound of any one of Embodiments 1.0 to 1.107 as defined herein and a DNA-damaging anticancer drug may be as set out in WO2010/118390 (Array Biopharma), the contents of which are  
10 incorporated herein by reference.

The amount of Chk-1 inhibitor compound of the invention and (in the case of combination therapy) the DNA damaging anti-cancer drug and radiation dose administered to the subject will depend on the nature and potency of the DNA damaging anti-cancer drug, the type and severity of the disease or condition and on the characteristics of the subject,  
15 such as general health, age, sex, body weight and tolerance to drugs. The skilled person will be able to determine appropriate dosages depending on these and other factors. Effective dosages for commonly used anti-cancer drugs and radiation therapy are well known to the skilled person.

A typical daily dose of the compound of formula (0) or formula (1), whether administered  
20 on its own in monotherapy or administered in combination with a DNA damaging anticancer drug, can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 5 nanograms to 25 milligrams per kilogram of bodyweight, and more usually 10 nanograms to 15 milligrams per kilogram (e.g. 10 nanograms to 10 milligrams, and more typically 1 microgram per kilogram to 20 milligrams per kilogram, for  
25 example 1 microgram to 10 milligrams per kilogram) per kilogram of bodyweight although higher or lower doses may be administered where required. The compound can be administered on a daily basis or on a repeat basis every 2, or 3, or 4, or 5, or 6, or 7, or 10 or 14, or 21, or 28 days for example.

Ultimately, however, the quantity of compound administered and the type of composition  
30 used will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

### **Methods of Diagnosis**

Prior to administration of a compound of the formula (0) or formula (1) as defined in any one of Embodiments 1.0 to 1.107, a patient may be screened to determine whether a  
35 cancer from which the patient is or may be suffering is one which would be susceptible to

treatment with either a Chk-1 kinase inhibitor compound or a combination of a chemotherapeutic agent (such as a DNA-damaging agent) and a Chk-1 kinase inhibitor compound.

5 More particularly, a patient may be screened to determine whether a cancer from which the patient is or may be suffering is one which is characterised by a defective DNA repair mechanism or a defective cell cycle, for example a defective cell cycle due to a p53 mutation or is a p53 negative cancer.

10 Cancers which are characterised by p53 mutations or the absence of p53 can be identified, for example, by the methods described in Allred *et al.*, J. Nat. Cancer Institute, Vol. 85, No. 3, 200-206 (1993) and the methods described in the articles listed in the introductory part of this application. For example, p53 protein may be detected by immuno-histochemical methods such as immuno-staining.

15 The diagnostic tests are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, or urine.

20 In addition to p53, mutations to other DNA repair factors such as RAD17, RAD50, and members of the Fanconi's anaemia complementation group may be predictive of response to Chk1 inhibitors alone, or in combination with chemotherapy. Cancers which contain mutations in these DNA repair pathways may be identified by DNA sequence analysis of tumor biopsy tissue or circulating tumor DNA (ctDNA) or, in the case of Fanconi's anaemia, by evaluating DNA foci formation in tumor biopsy specimens using an antibody to FANCD2, as described in Duan *et al.*, *Frontiers in Oncology* vol.4, 1-8 (2014).

25 Thus, the compounds of any one of Embodiments 1.0 to 1.107 may be used to treat members of a sub-population of patients who have been screened (for example by testing one or more biological samples taken from the said patients) and have been found to be suffering from a cancer characterised by p53 mutation or a p53 negative cancer, or a cancer containing a RAD17 or RAD50 mutation, or a mutation in a member of the Fanconi's anaemia complementation group.

### **EXAMPLES**

30 The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the following abbreviations are used.



	ACN	acetonitrile
	Ac <sub>2</sub> O	acetic anhydride
	AcOH	acetic acid
	AIBN	azobisisobutyronitrile
5	AlCl <sub>3</sub>	aluminium chloride
	aq	aqueous
	Boc <sub>2</sub> O	di-tert-butyl dicarbonate
	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	DAST	Diethylaminosulfur trifluoride
10	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
	DIPEA	diisopropylethylamine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
15	EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
	Et <sub>3</sub> N	triethylamine
	Et <sub>2</sub> O	diethyl ether
	EtOAc	ethyl acetate
	EtOH	ethanol
20	HCl	hydrogen chloride
	HPLC	high performance liquid chromatography
	LCMS	liquid chromatography-mass spectrometry
	LiHMDS	lithium bis(trimethylsilyl)amide
	MeCN	acetonitrile
25	MeOH	methanol
	Mesyl	methanesulfonyl
	NaBH <sub>4</sub>	sodium borohydride
	NaBH(AcO) <sub>3</sub>	sodium triacetoxymborohydride
	NaH	sodium hydride
30	NaHCO <sub>3</sub>	sodium hydrogen carbonate
	NaOH	sodium hydroxide
	Na <sub>2</sub> SO <sub>4</sub>	sodium sulfate
	NBS	N-bromosuccinimide
	NH <sub>3</sub>	ammonia
35	NH <sub>4</sub> Cl	ammonium chloride
	NMR	nuclear magnetic resonance

	PdCl <sub>2</sub> (dppf).DCM	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
	TBAF	tetrabutylammonium fluoride
	TBDMS	tert-butyldimethylsilyl
5	THF	tetrahydrofuran
	TMOA	trimethylorthoacetate
	TMS	trimethylsilyl

Proton magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on a Bruker 400 instrument  
 10 operating at 400 MHz, in DMSO-d<sub>6</sub> or MeOH-d<sub>4</sub> (as indicated) at 27°C, unless otherwise  
 stated and are reported as follows: chemical shift δ/ppm (multiplicity where s=singlet,  
 d=doublet, dd, double doublet, t=triplet, q=quartet, m=multiplet, br=broad, number of  
 protons). The residual protic solvent was used as the internal reference.

Liquid chromatography and mass spectroscopy analyses were carried out using the  
 15 system and operating conditions set out below. Where atoms with different isotopes are  
 present and a single mass quoted, the mass quoted for the compound is the  
 monoisotopic mass (i.e. <sup>35</sup>Cl; <sup>79</sup>Br etc.)

#### LCMS CONDITIONS

The LCMS data given in the following examples were obtained using Method A or Method  
 20 B as set out below.

#### LCMS Method A

Samples were analysed by reverse phase HPLC-MS using a Waters 2795 Alliance HT  
 HPLC, a Micromass ZQ mass spectrometer and a Waters 996 photodiode array UV  
 detector. The LCMS used electrospray ionisation and the chromatography system as  
 25 follows:

#### Mass Spectrometer:

	Ionization mode:	Positive	Negative
	Capillary Voltage:	3.20kV	-3.00kV
	Cone Voltage:	30V	-30V
30	Source Temperature:	110 °C	110 °C
	Desolvation Temperature:	350°C	350°C
	Cone Gas Flow:	30 L/Hr	30 L/Hr
	Desolvation Gas Flow:	400 L/Hr	400 L/Hr

Scan duration: 0.50 seconds 0.50 seconds  
 Interscan delay: 0.20 seconds 0.20 seconds  
 Mass range: 80 to 1000 AMU 80 to 1000 AMU

LCMS was carried using a BEH C18 X 2.1mm, 1.7 micron column. Column flow was 0.55 ml/min and the mobile phase used were 0.1 % formic acid in water and 5 mM ammonium acetate (A) and 0.1 % formic acid in acetonitrile (B), with an injection volume of 10 µL.

The gradient was as described below.

Time (min)	%A	%B
0.01	95	5
0.40	95	5
0.80	65	35
1.20	45	55
2.50	0	100
3.30	0	100
3.31	95	5
4.00	95	5

LCMS Method B

10 Samples were analysed by reverse phase HPLC-MS using a Waters 2795 Alliance HPLC, an Acquity QDA mass spectrometer and a Waters 996 photodiode array UV detector. The LCMS used electrospray ionisation and the chromatography system as follows:

Mass Spectrometer:

15 Ionization mode: Positive Negative  
 Capillary Voltage: 1.50kV -0.80kV  
 Cone Voltage: 10V -30V  
 Source Temperature: 120 °C 120 °C  
 Desolvation Temperature: 600°C 600°C  
 20 Scan duration: 0.50 seconds 0.50 seconds  
 Interscan delay: 0.10 seconds 0.10 seconds  
 Mass range: 100 to 700 AMU 100 to 700 AMU

LCMS was carried using a X-BRIDGE C18 100 x 4.6mm, 5 micron column. Column flow was 1.0 ml/min and the mobile phase used were 0.1 % formic acid in water (A) and methanol (B), with an injection volume of 10 µL.

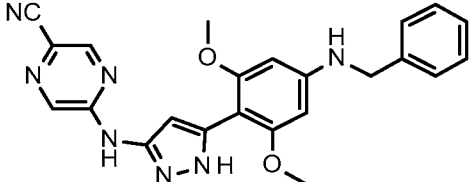
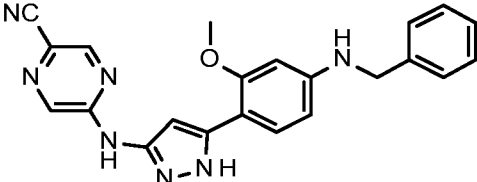
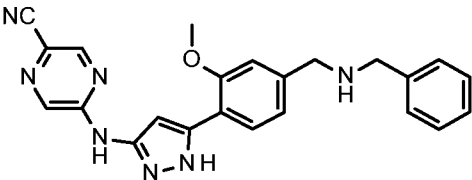
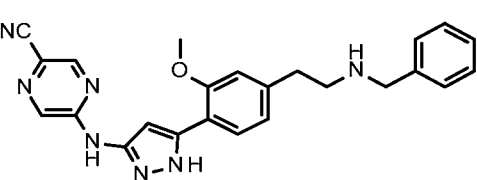
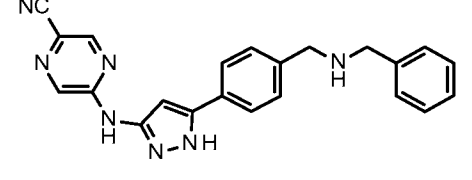
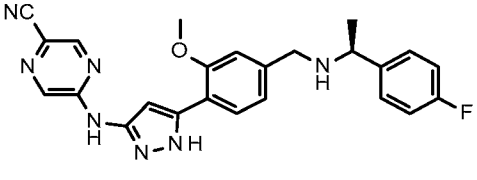
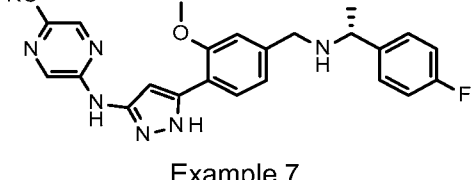
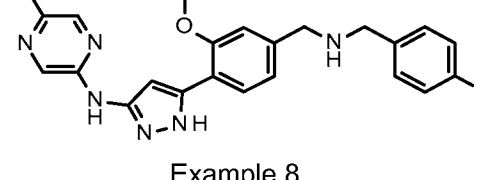
The gradient was as described below.

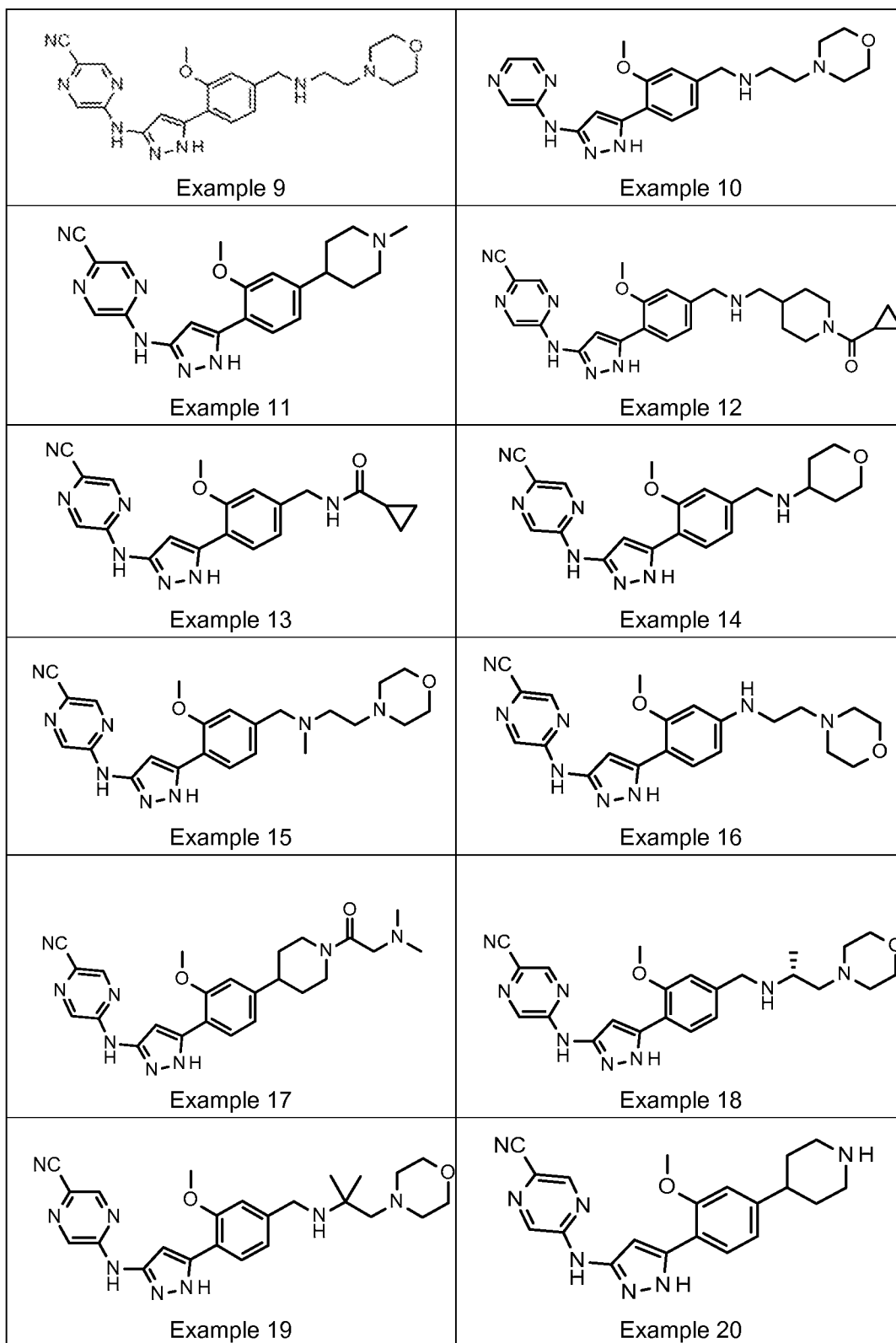
Time (min)	%A	%B
0.01	90	10
3.00	10	90
6.00	0	100
7.01	90	10
10.00	90	10

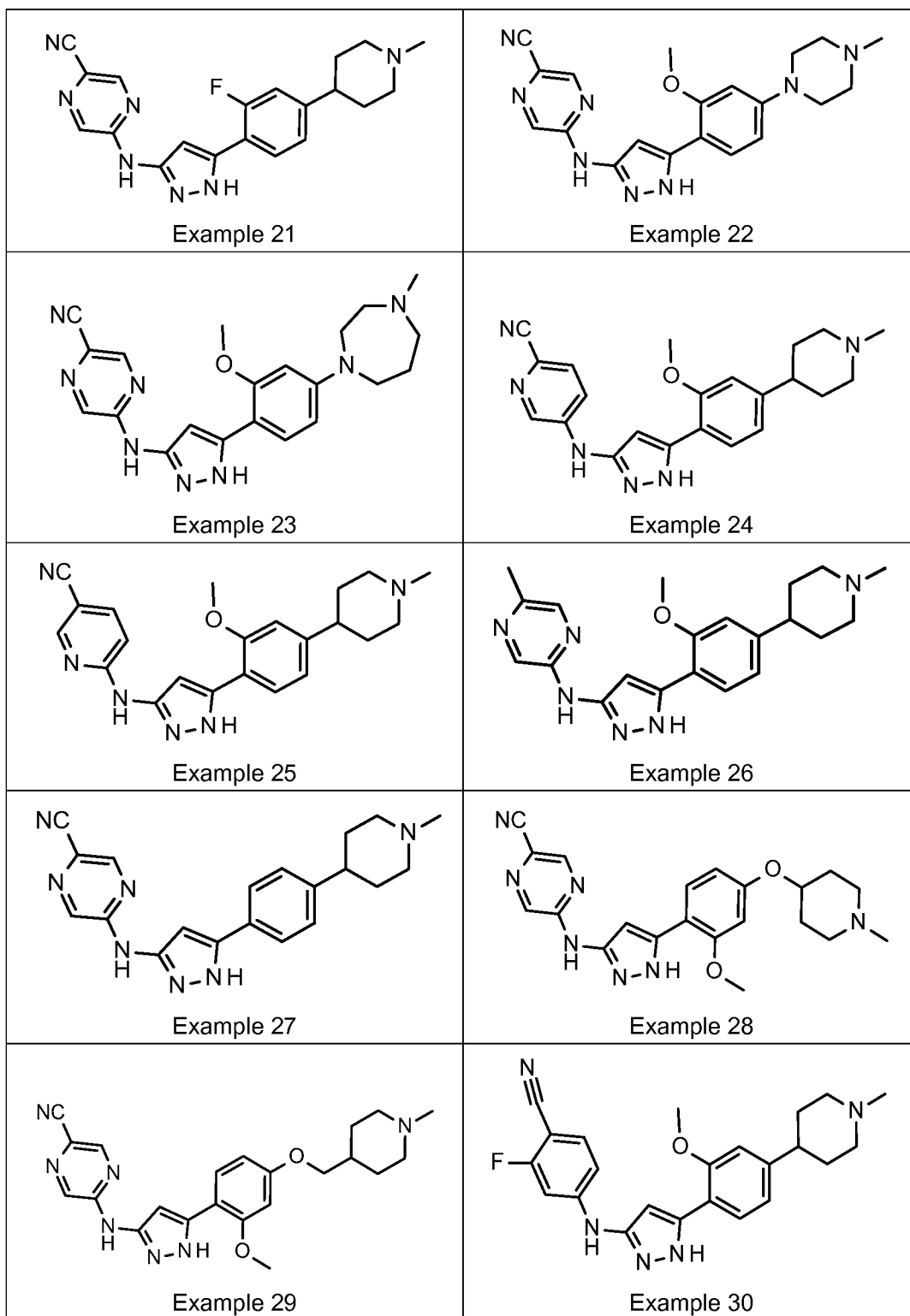
### EXAMPLES 1 TO 163

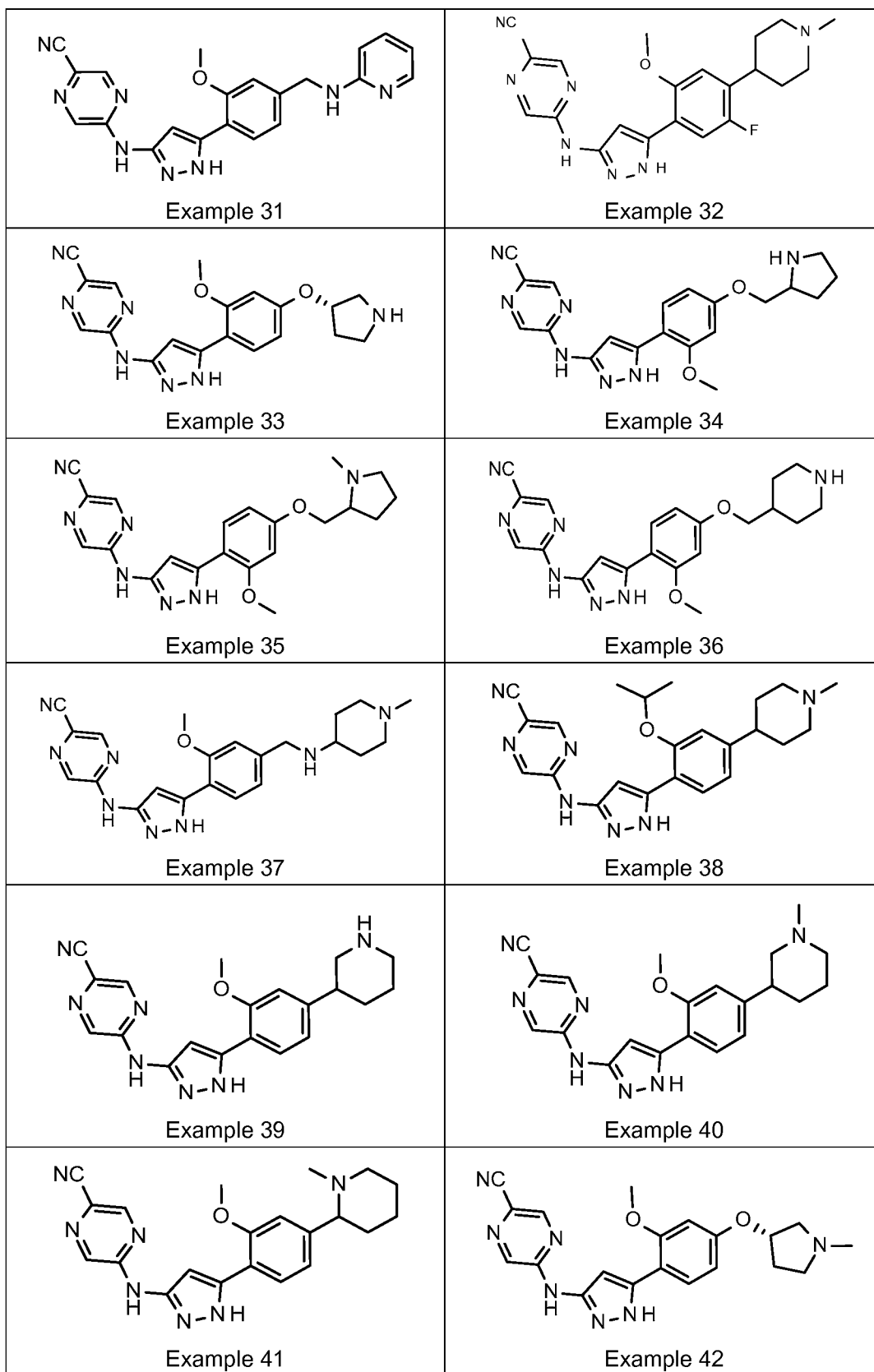
The compounds of Examples 1 to 163 shown in Table 1 below have been prepared. Their NMR and LCMS properties are set out in Table 2.

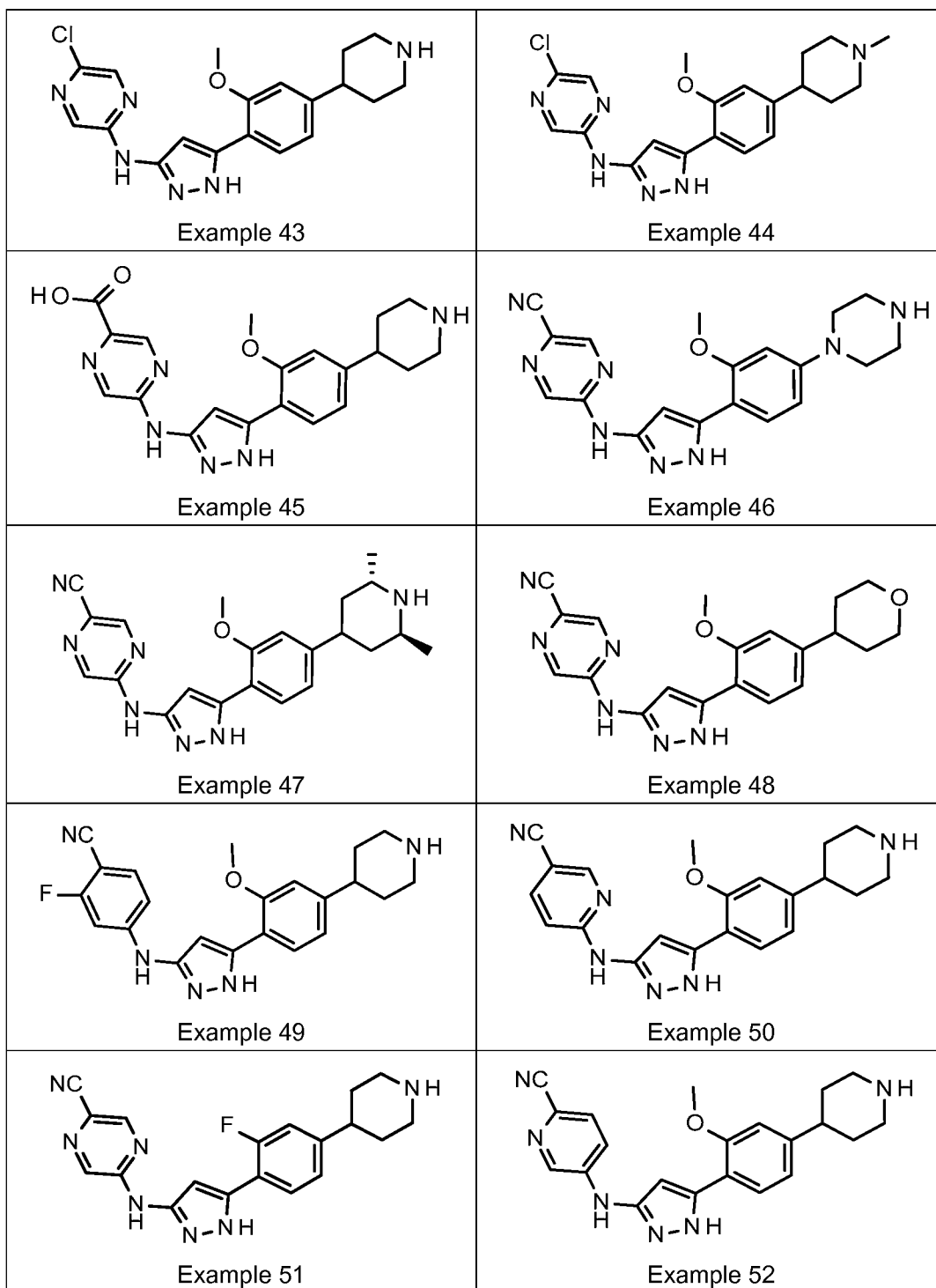
Table 1

 <p>Example 1</p>	 <p>Example 2</p>
 <p>Example 3</p>	 <p>Example 4</p>
 <p>Example 5</p>	 <p>Example 6</p>
 <p>Example 7</p>	 <p>Example 8</p>

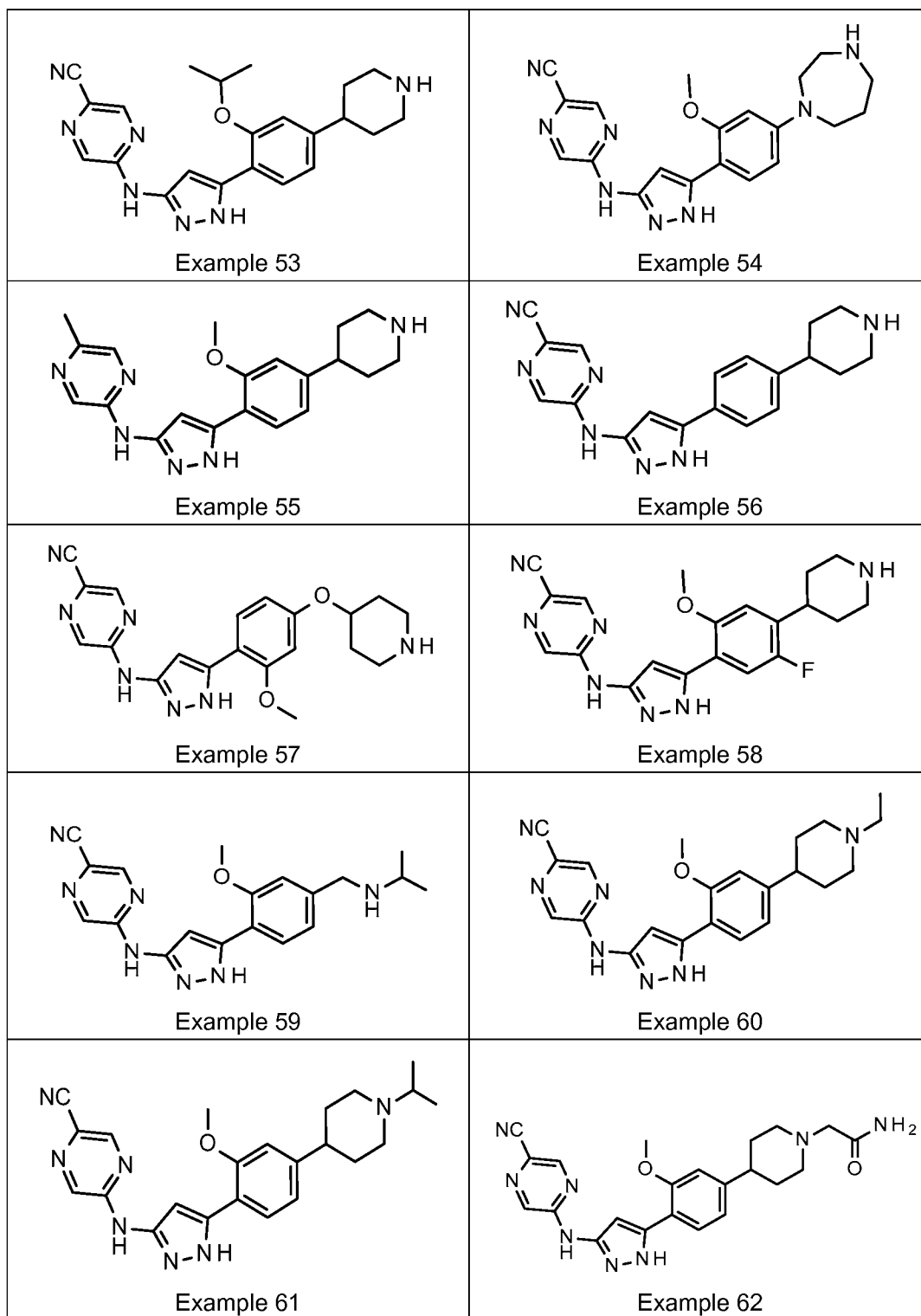


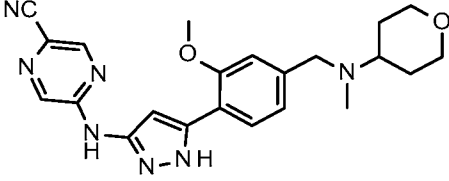
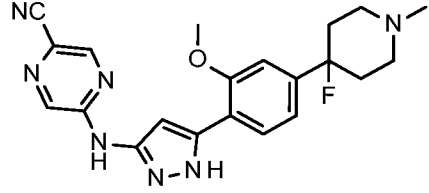
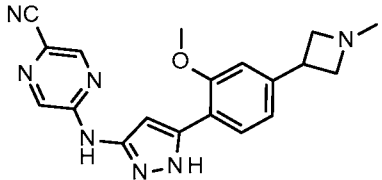
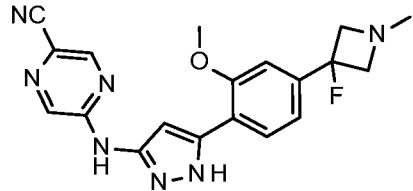
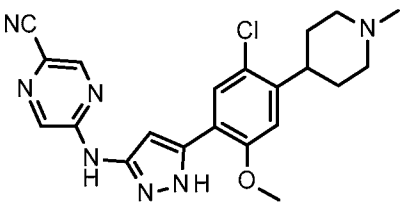
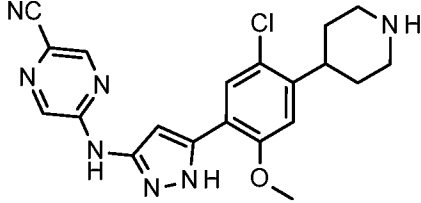
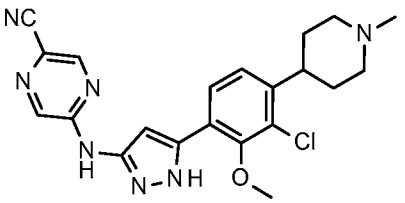
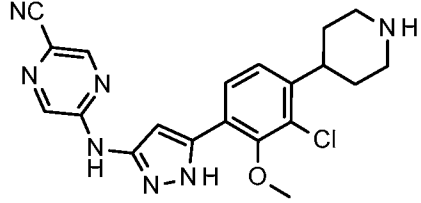
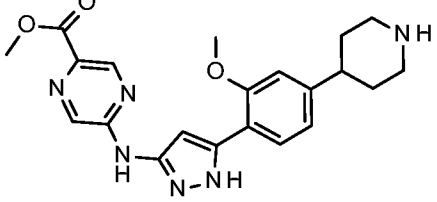
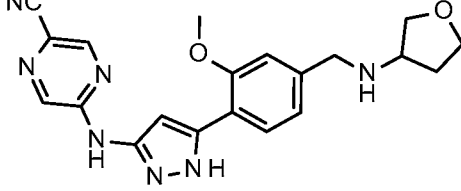
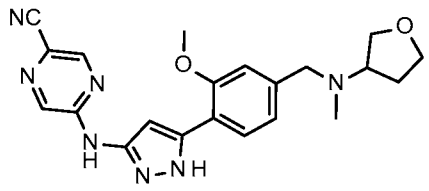
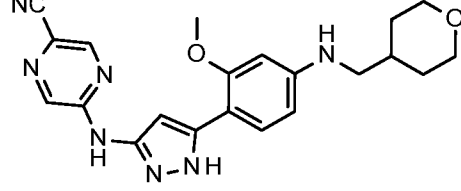


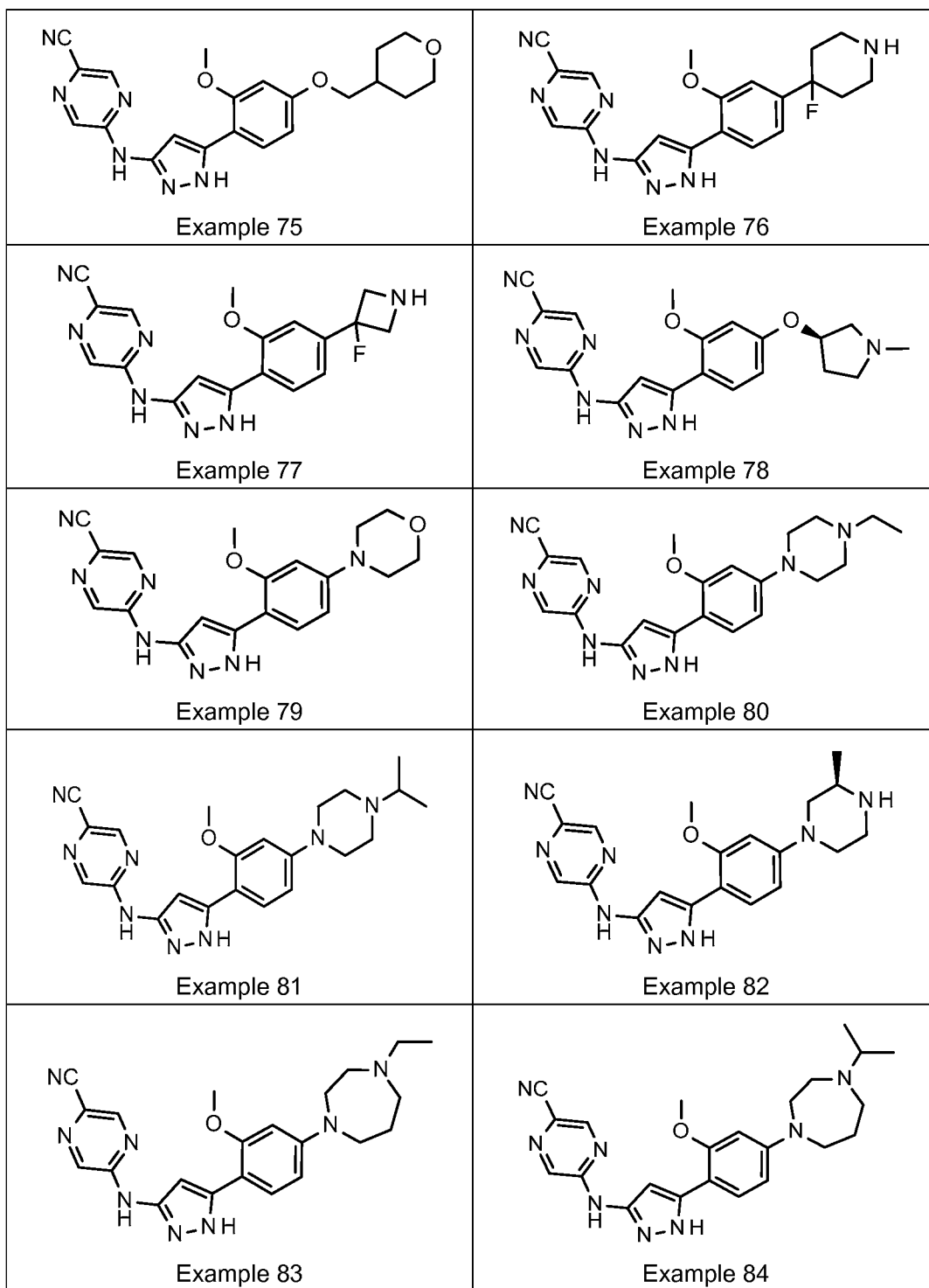


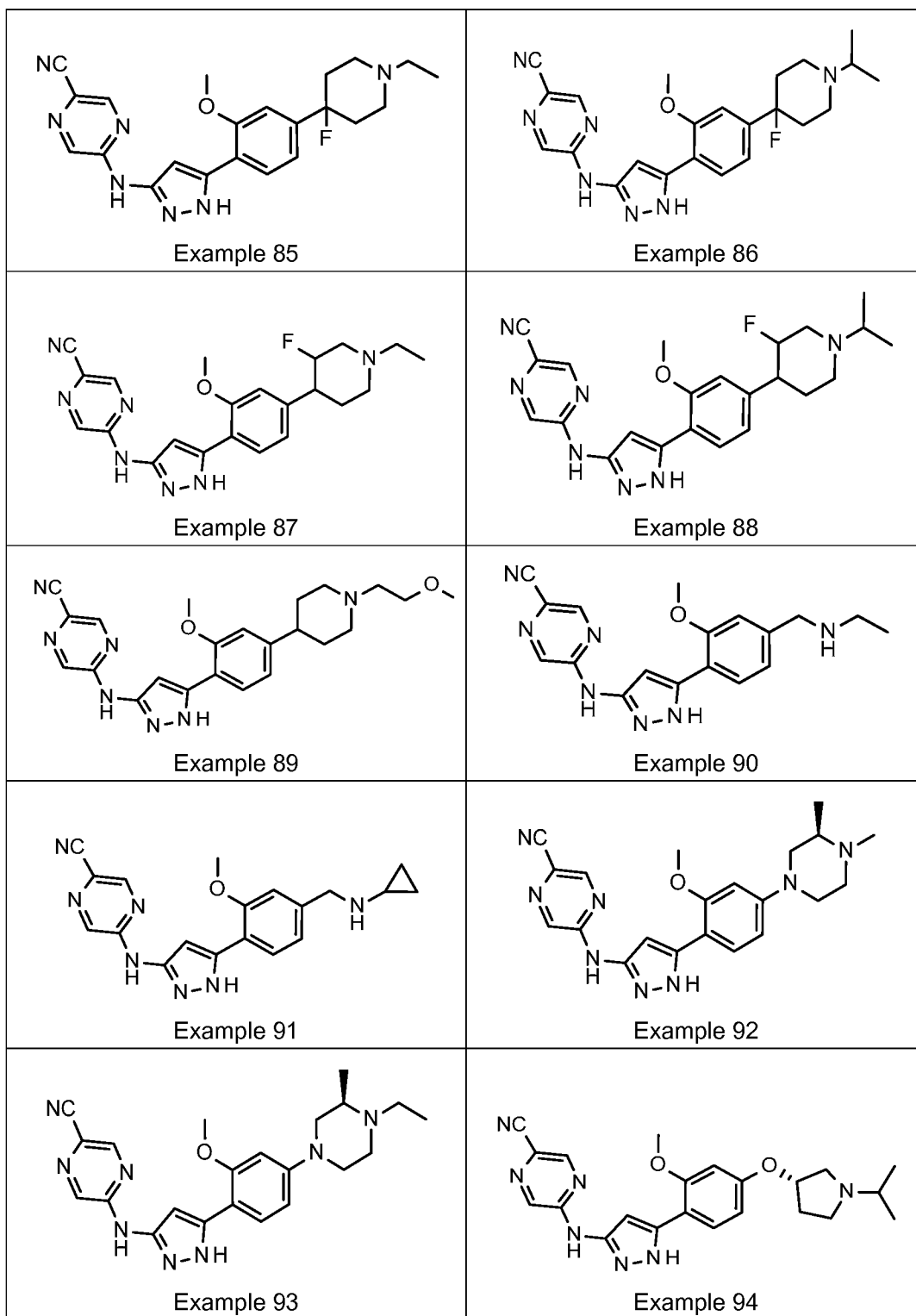


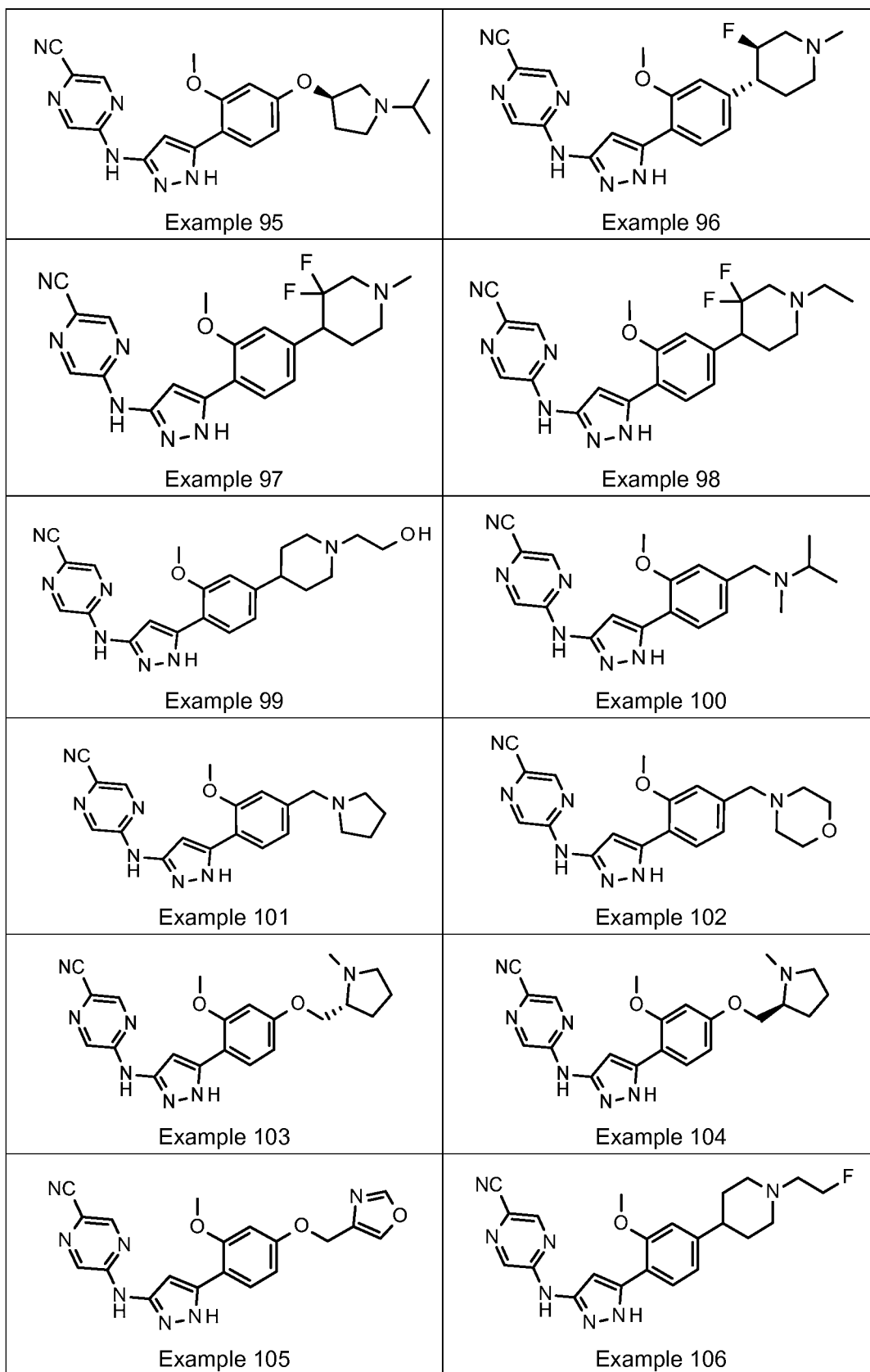


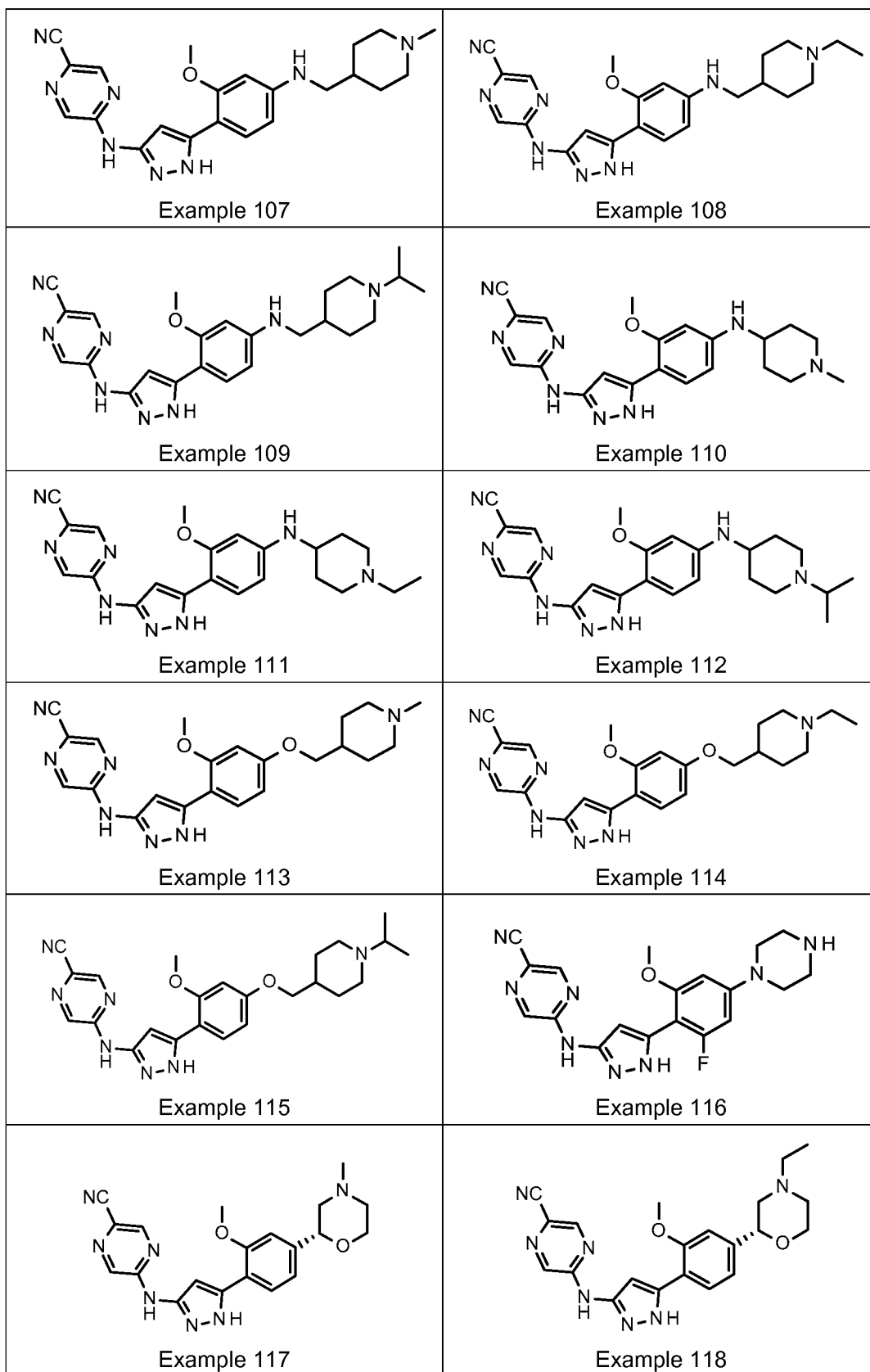


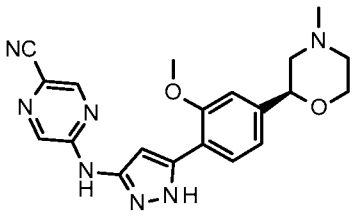
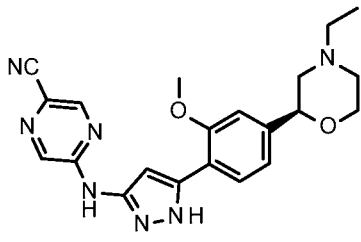
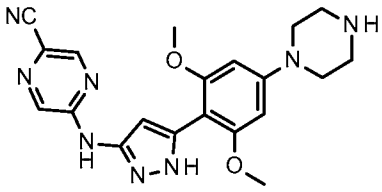
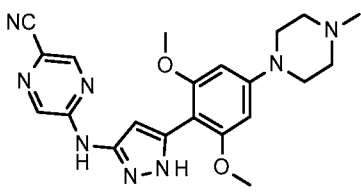
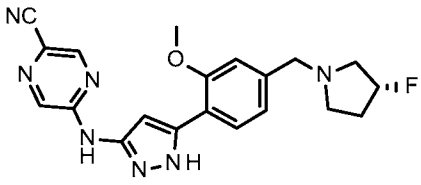
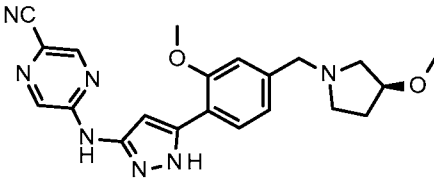
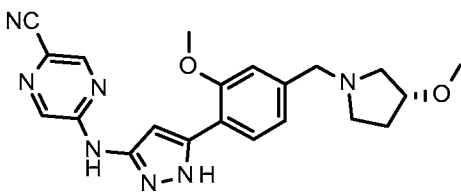
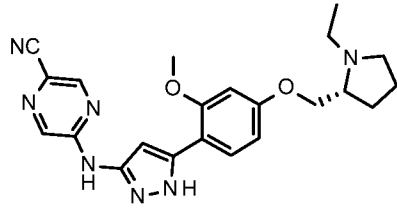
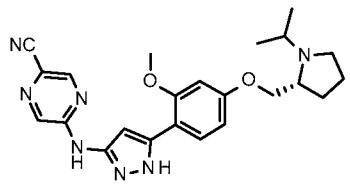
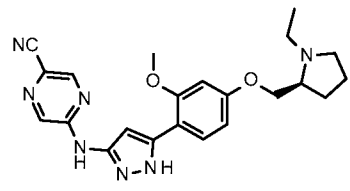
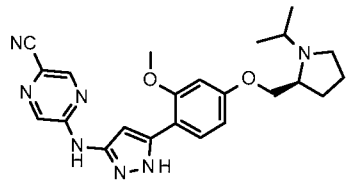
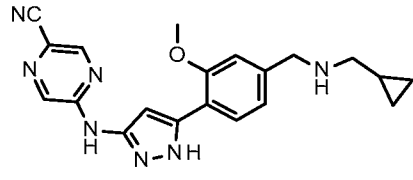
 <p>Example 63</p>	 <p>Example 64</p>
 <p>Example 65</p>	 <p>Example 66</p>
 <p>Example 67</p>	 <p>Example 68</p>
 <p>Example 69</p>	 <p>Example 70</p>
 <p>Example 71</p>	 <p>Example 72</p>
 <p>Example 73</p>	 <p>Example 74</p>

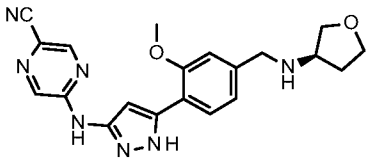
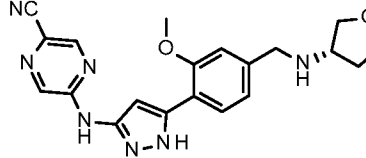
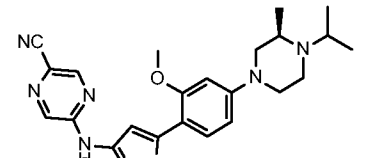
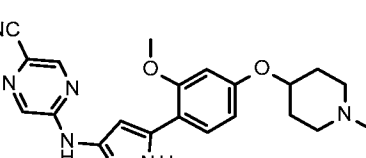
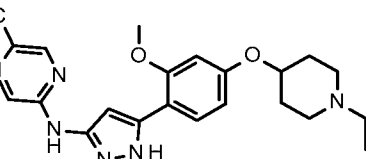
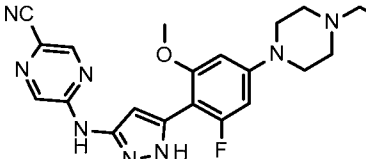
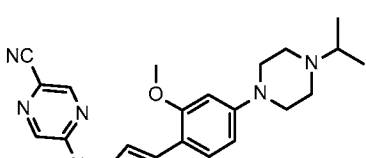
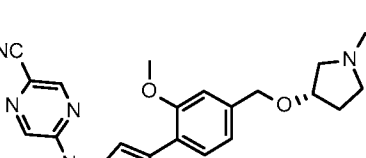
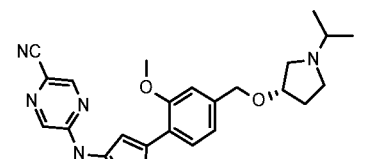
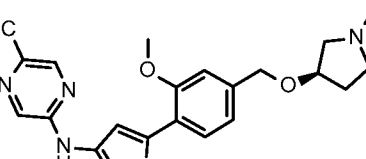
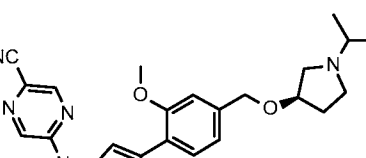
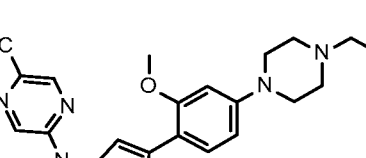
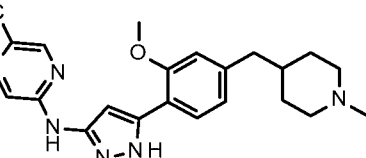
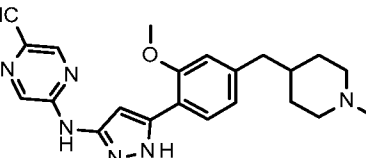




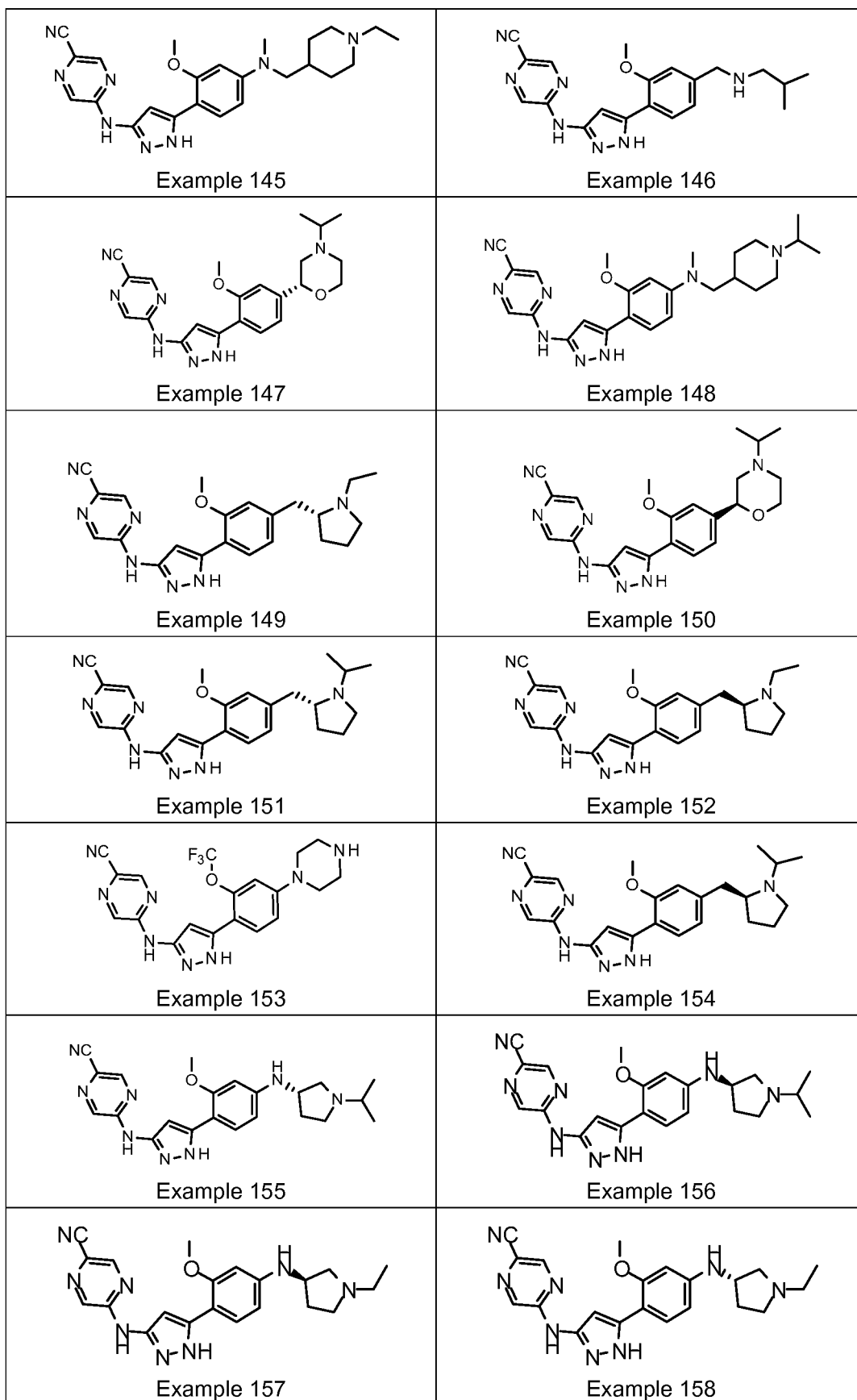


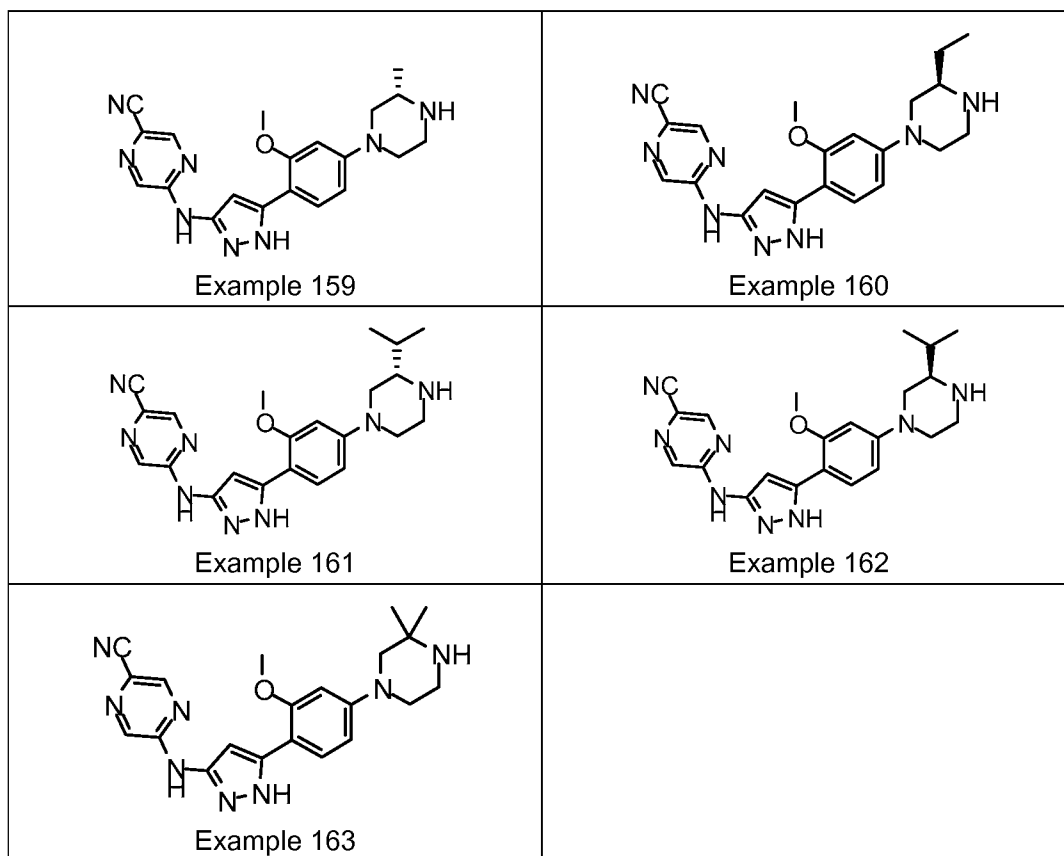


 <p>Example 119</p>	 <p>Example 120</p>
 <p>Example 121</p>	 <p>Example 122</p>
 <p>Example 123</p>	 <p>Example 124</p>
 <p>Example 125</p>	 <p>Example 126</p>
 <p>Example 127***</p>	 <p>Example 128</p>
 <p>Example 129</p>	 <p>Example 130</p>

 <p>Example 131</p>	 <p>Example 132</p>
 <p>Example 133</p>	 <p>Example 134</p>
 <p>Example 135</p>	 <p>Example 136</p>
 <p>Example 137</p>	 <p>Example 138</p>
 <p>Example 139</p>	 <p>Example 140</p>
 <p>Example 141</p>	 <p>Example 142</p>
 <p>Example 143</p>	 <p>Example 144</p>



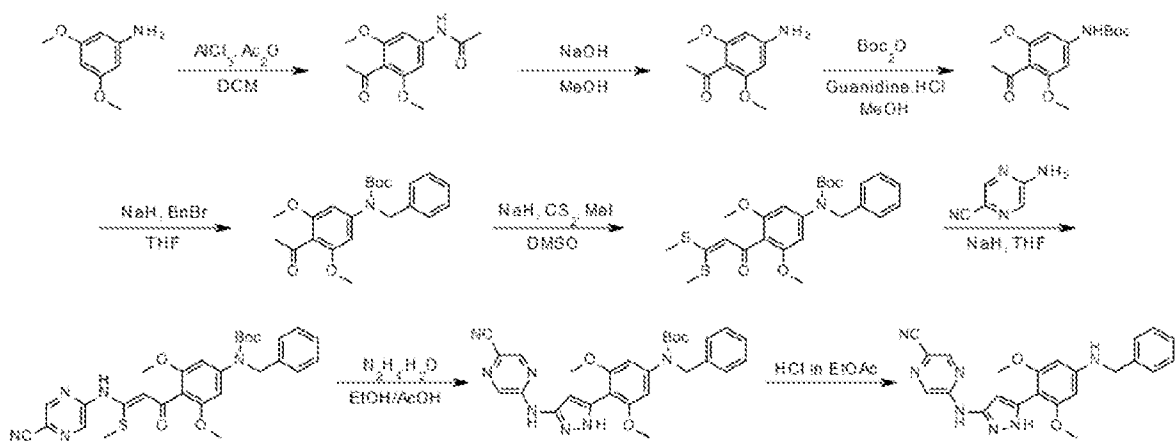




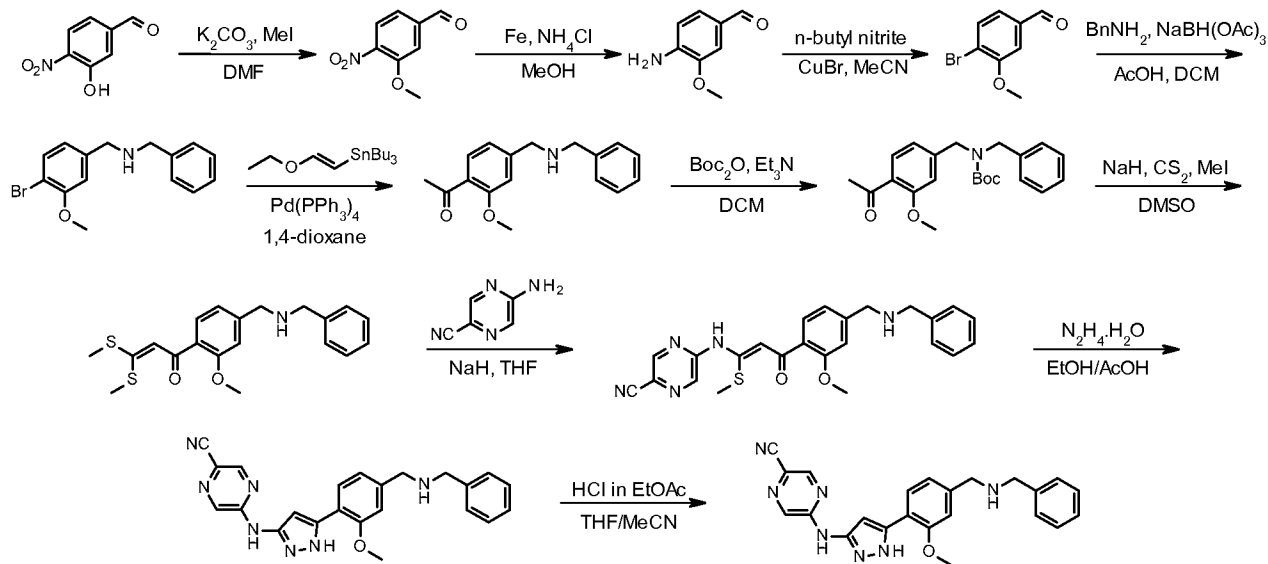
### SYNTHETIC METHODS

Synthetic methods A to T were used to prepare the compounds of Examples 1 to 163. The reaction schemes for synthetic methods A to T are shown below.

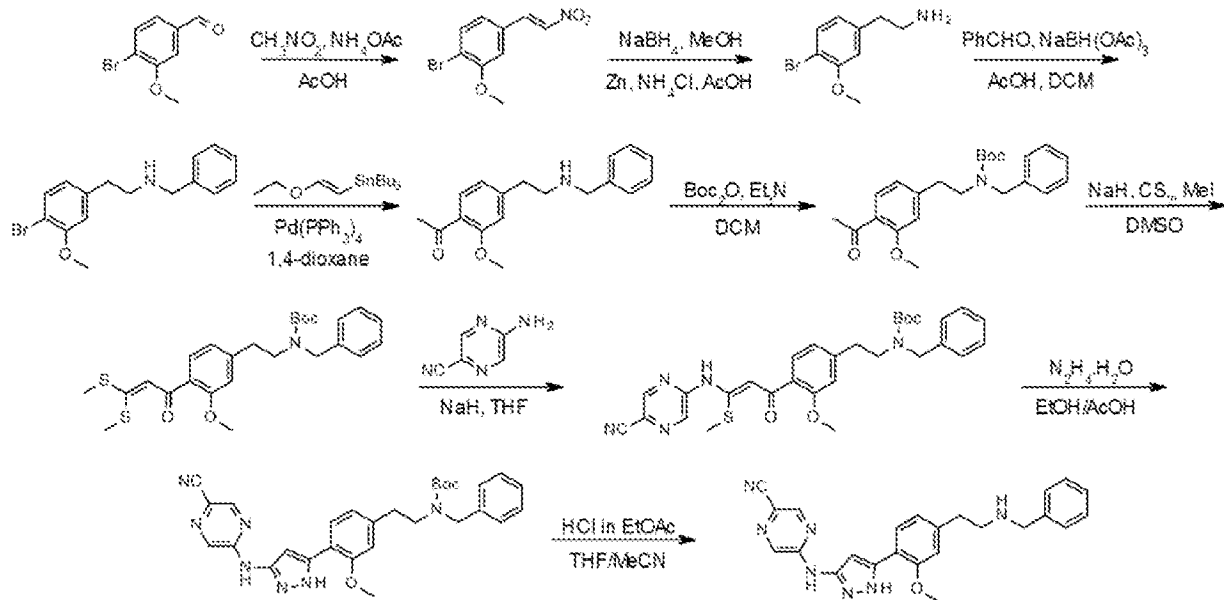
#### Synthetic Method A



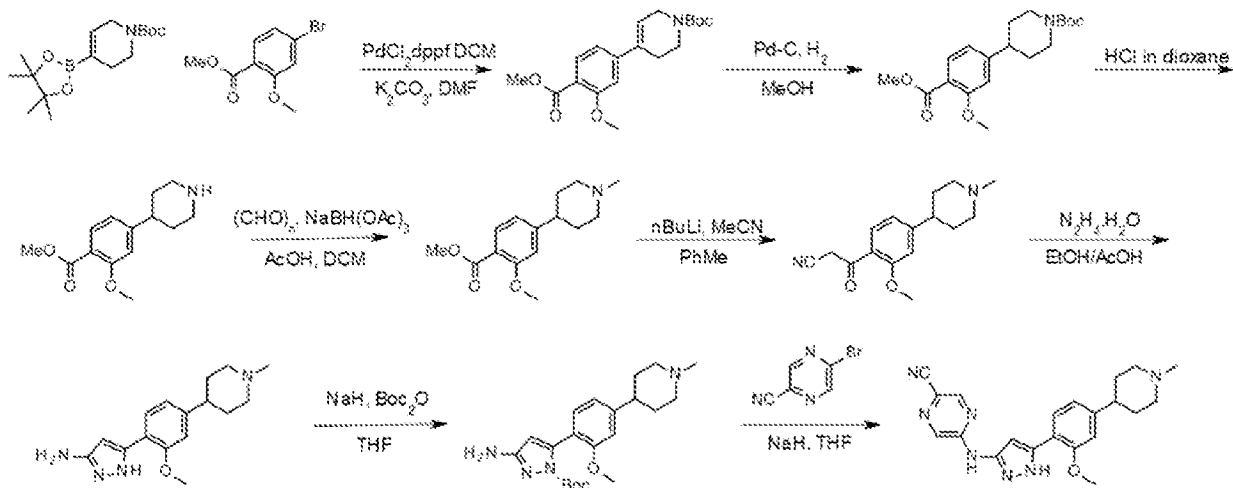
Synthetic Method B



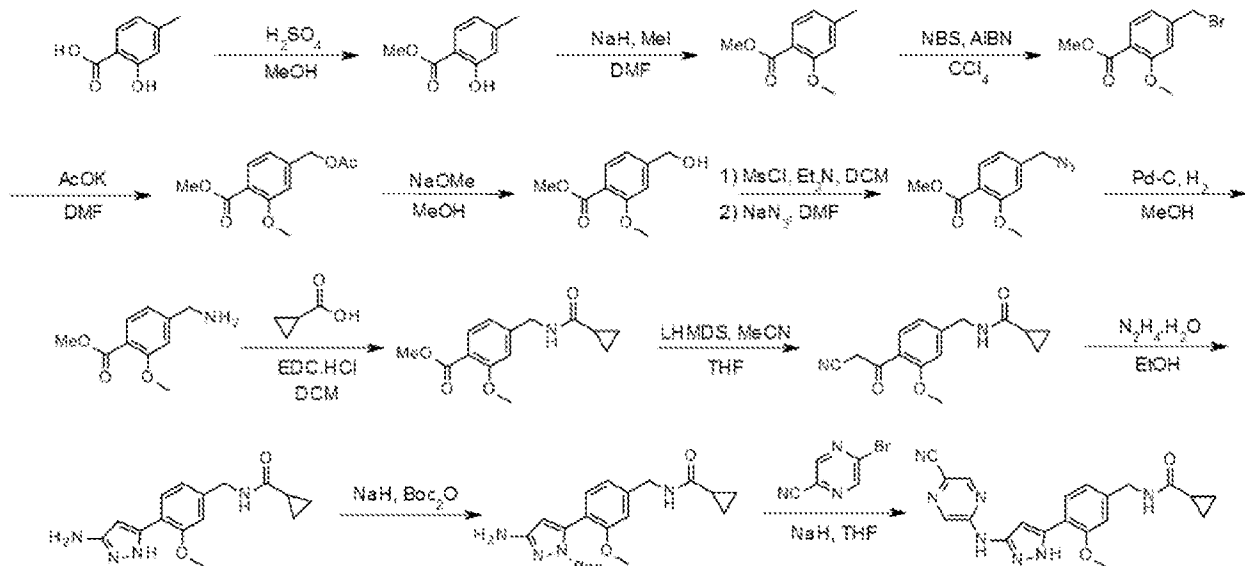
Synthetic Method C



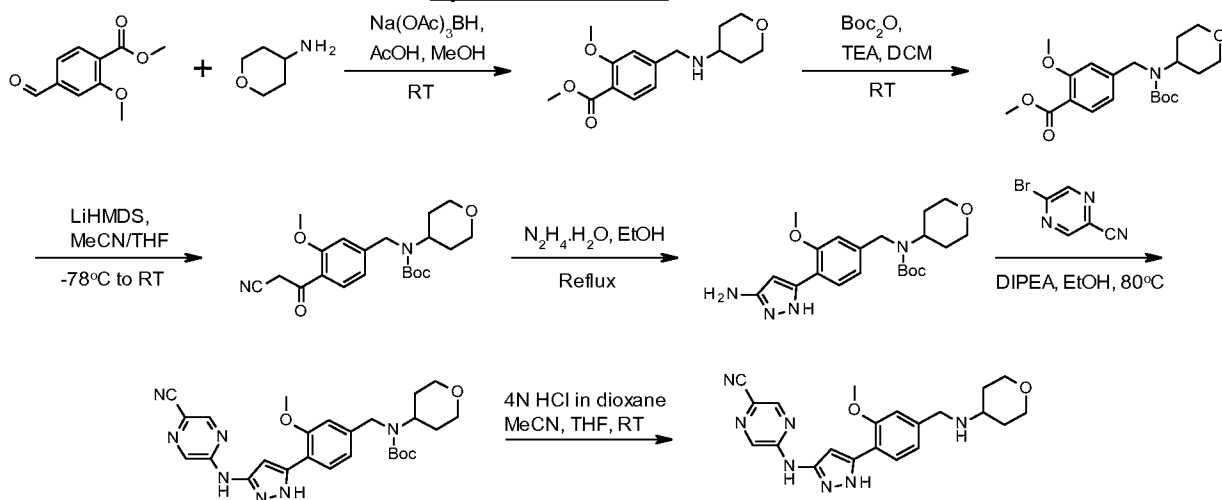
**Synthetic Method D**



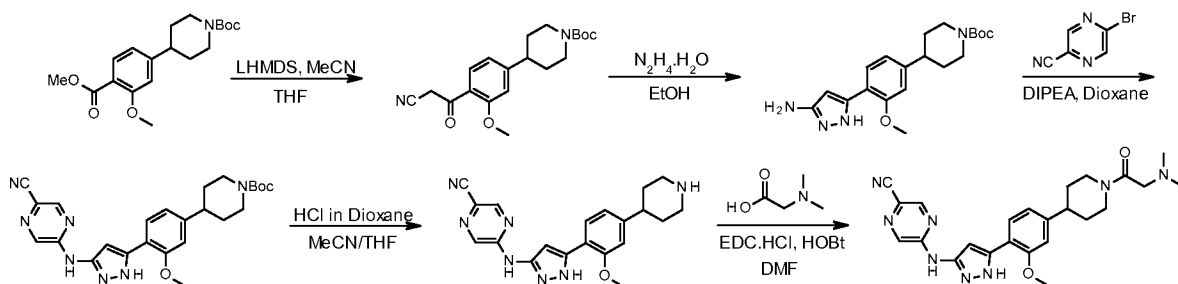
**Synthetic Method E**



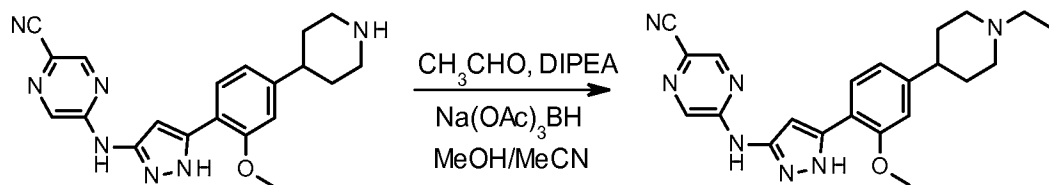
**Synthetic Method F**



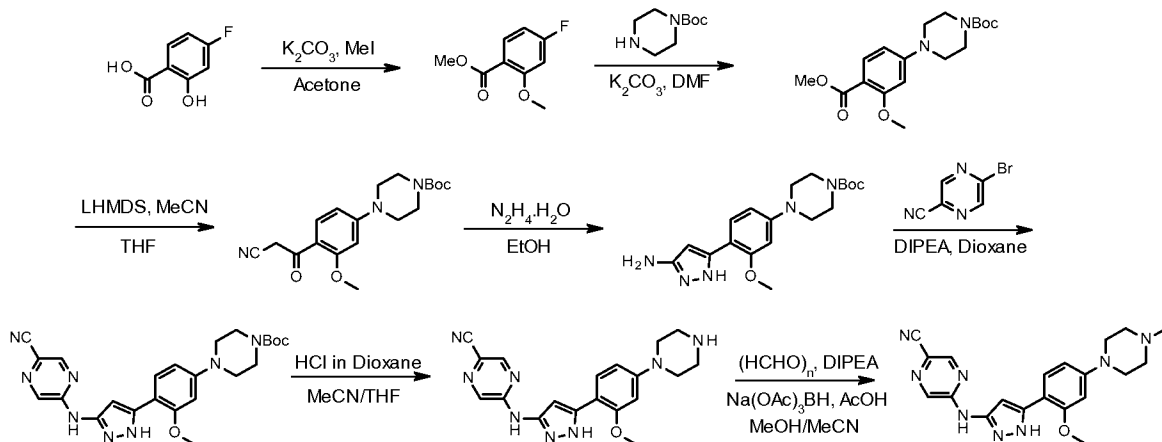
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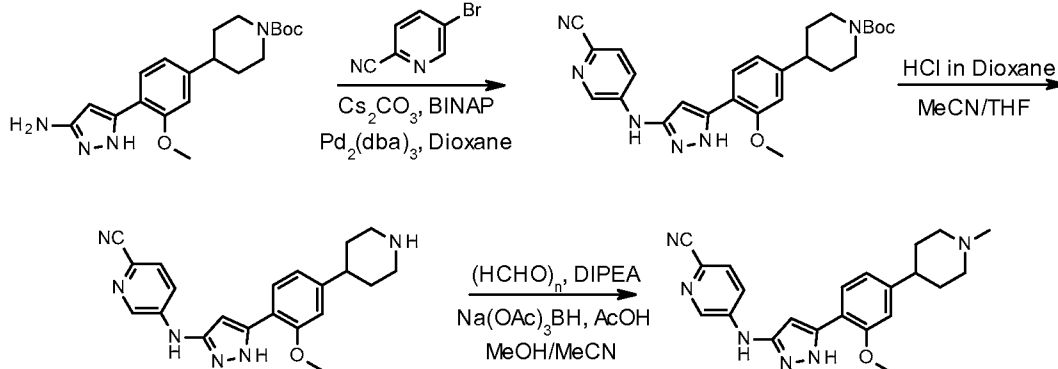
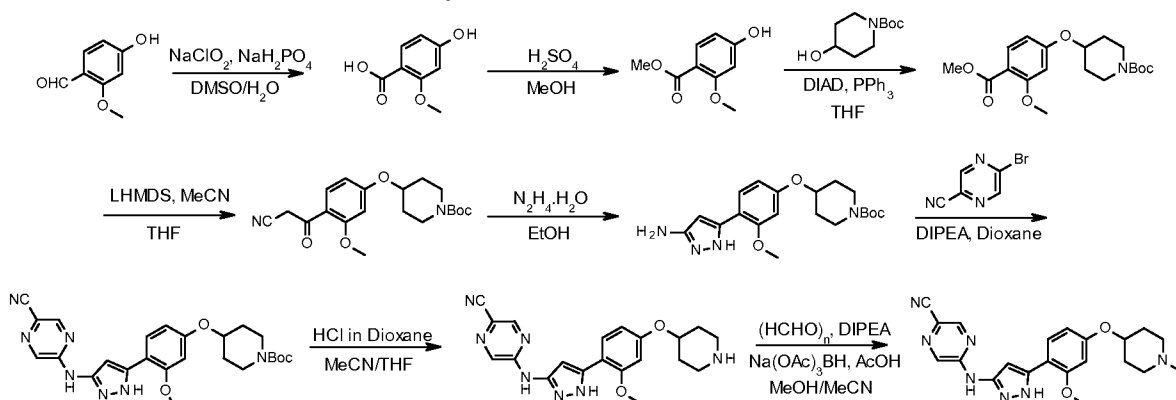
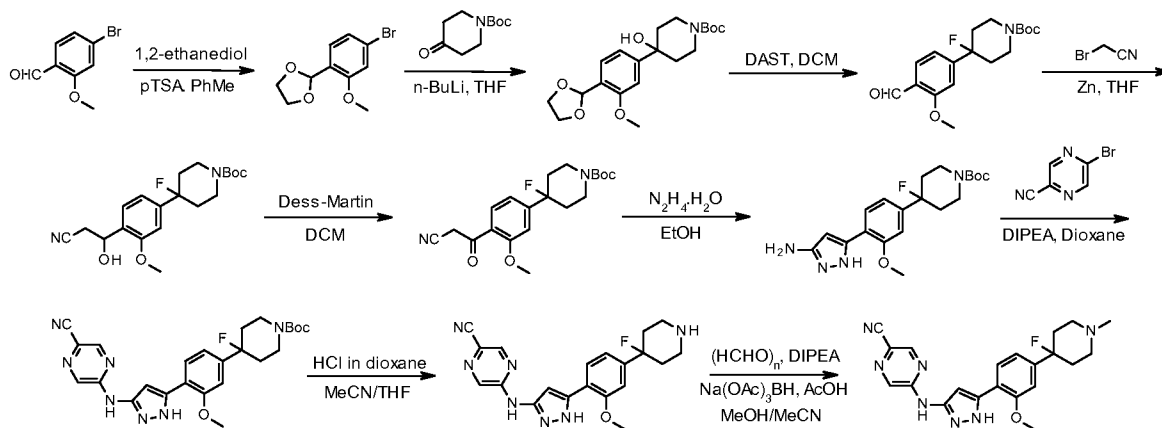


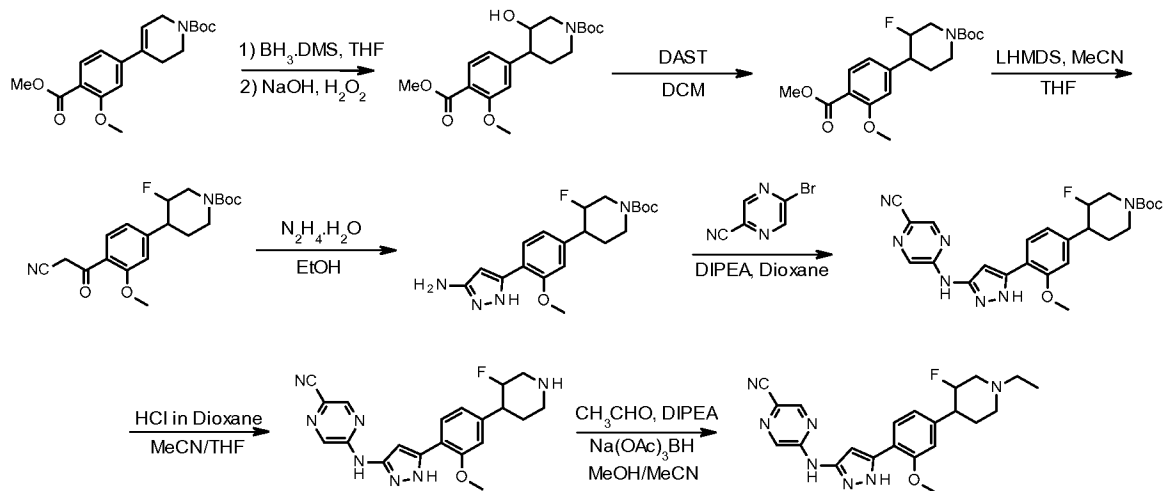
**Synthetic Method H**



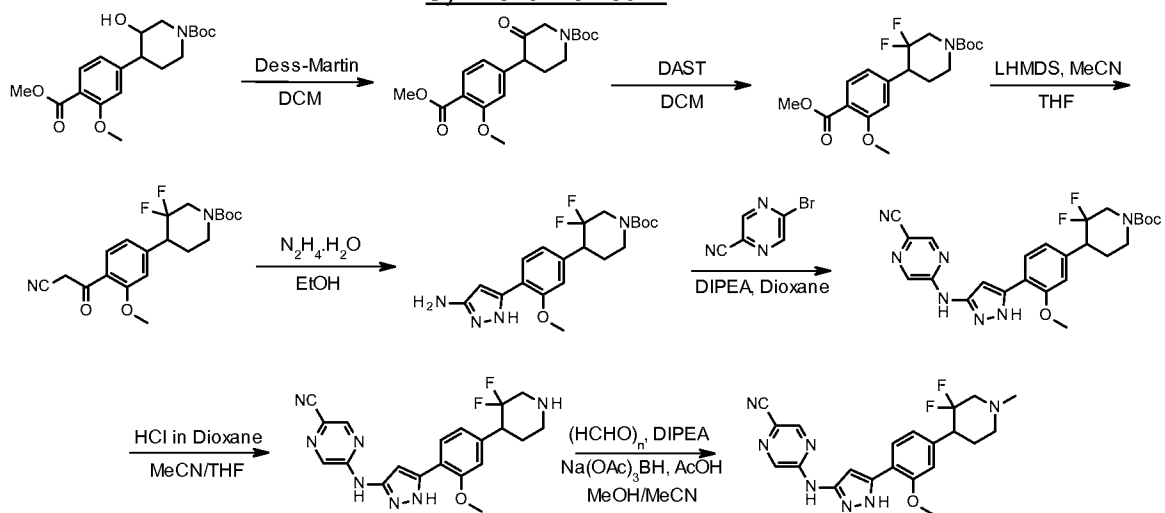
**Synthetic Method I**



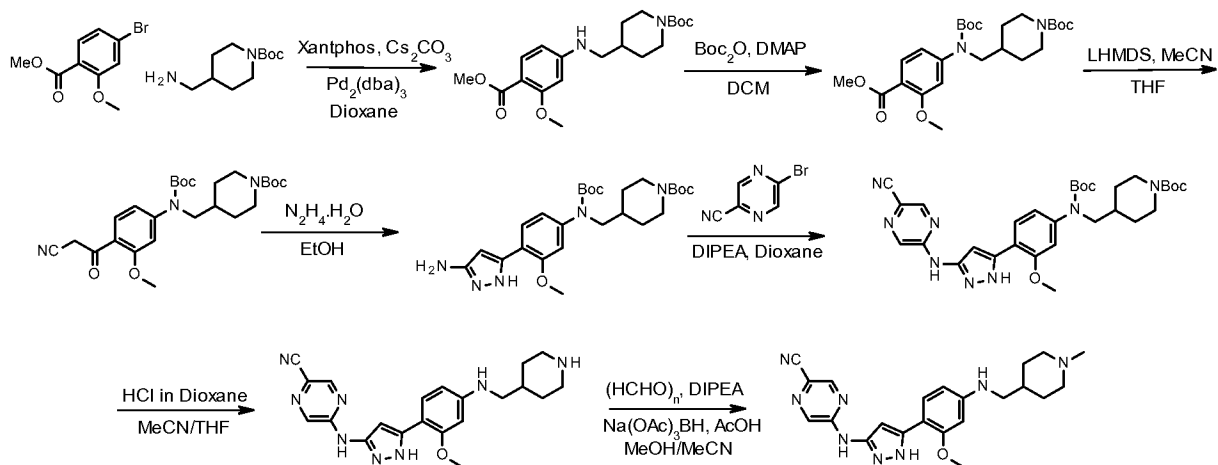
Synthetic Method JSynthetic Method KSynthetic Method LSynthetic Method M



**Synthetic Method N**

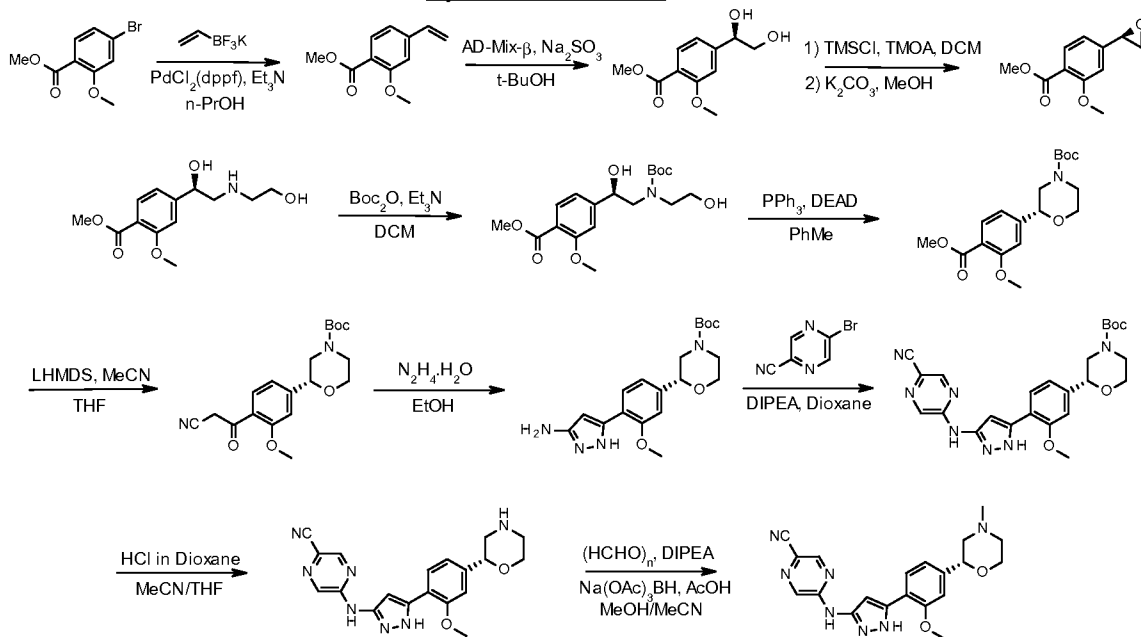


**Synthetic Method O**

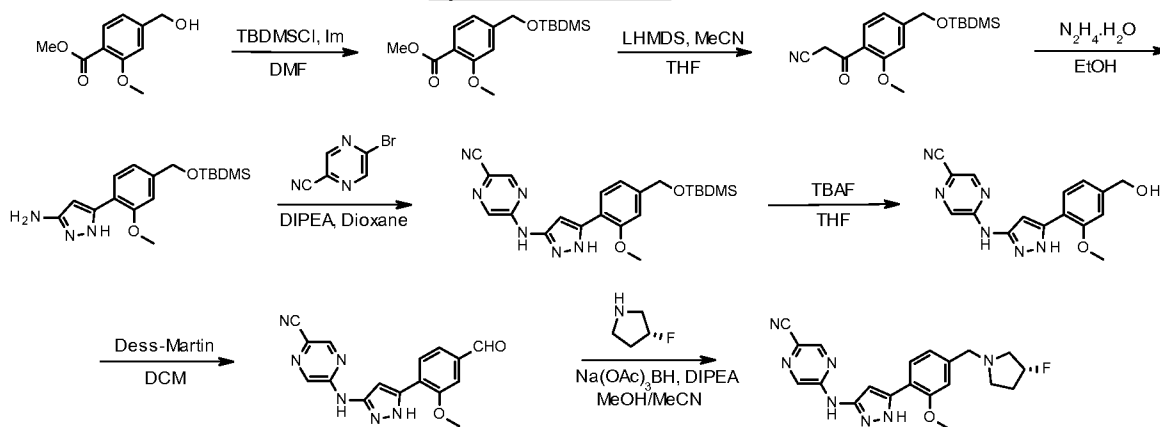




**Synthetic Method P**



**Synthetic Method Q**



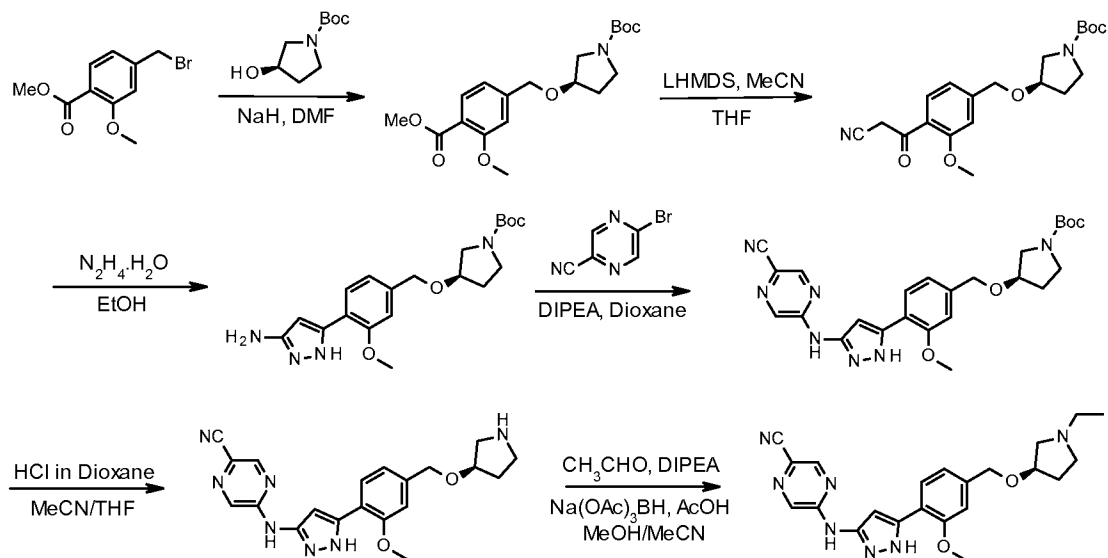
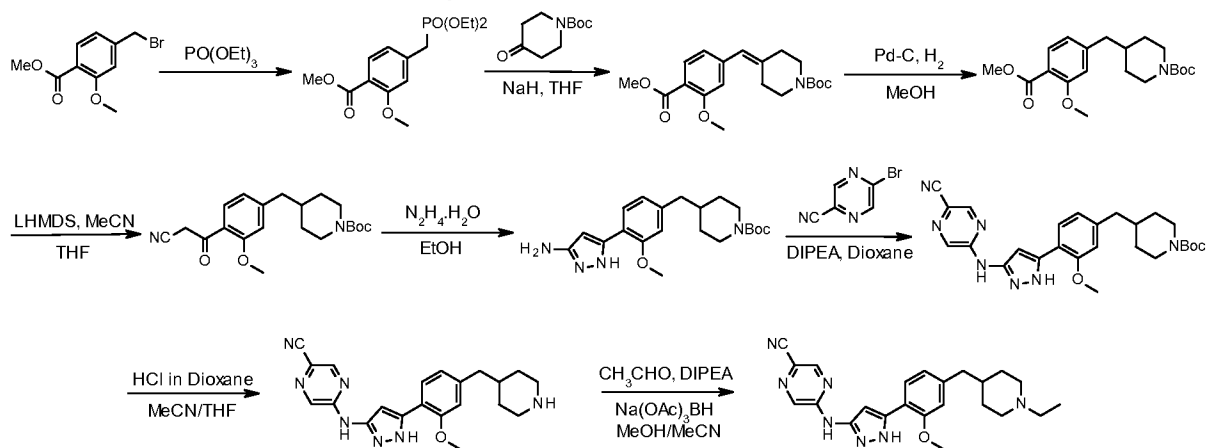
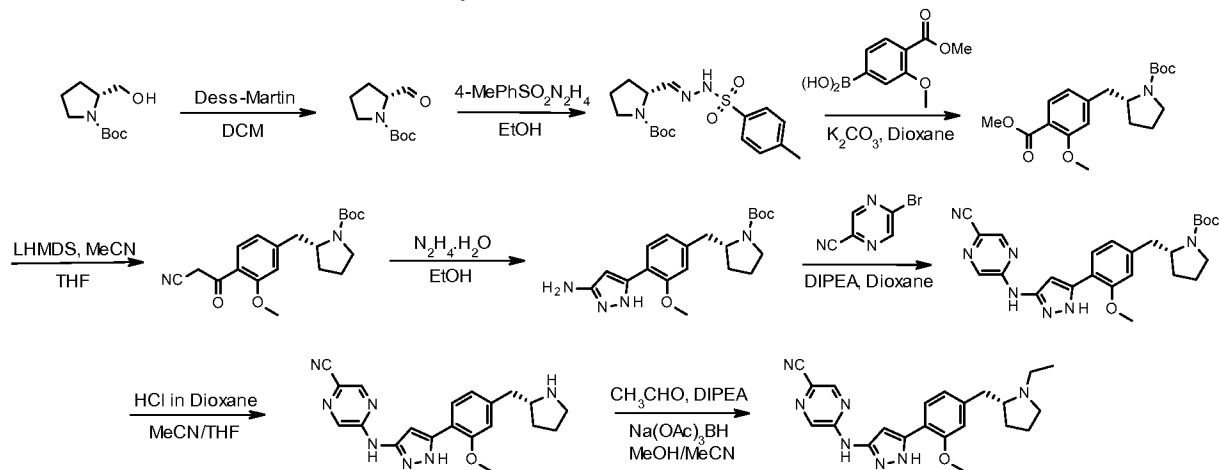
Synthetic Method RSynthetic Method SSynthetic Method T

Table 2

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
1	5-[5-(4-benzylamino-2,6-dimethoxy-phenyl)-1H-pyrazol-3-ylamino]pyrazine-2-carbonitrile	A	(DMSO-d <sub>6</sub> ) δ 11.99 (s, 1H), 10.58 (s, 1H), 8.63 (s, 1H), 7.39 (t, 2H) 7.33 (s, 2H), 7.25 (t, 1H), 6.62 (d, 2H), 5.99 (s, 2H), 4.35 (s, 2H) and 3.38 (s, 6H).	2.28	428	A
2	5-[5-(4-benzylamino-2-methoxy-phenyl)-1H-pyrazol-3-ylamino]pyrazine-2-carbonitrile	A	(DMSO-d <sub>6</sub> ) δ 12.20 (br s, 1H), 10.68 (s, 1H), 8.67 (s, 1H), 8.50 (bs, 1H), 7.40-7.07 (m, 7H), 6.70 (s, 1H), 6.37 (s, 1H), 6.27 (d, 1H), 4.34 (s, 2H) and 3.78 (s, 3H).	2.31	398	A
3	5-[5-[4-(benzylamino-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]pyrazine-2-carbonitrile hydrochloride	B	(DMSO-d <sub>6</sub> ) δ 12.70 (s, 1H), 10.80 (s, 1H), 9.56 (s, 2H), 8.67 (s, 1H), 8.53 (s, 1H), 7.85 (d, 1H), 7.56 (t, 2H), 7.45 (q, 3H), 7.18 (d, 1H), 7.01 (s, 1H), 4.20 (d, 4H) and 3.93 (d, 3H).	1.79	412	A
4	5-[5-[4-(2-benzylamino-ethyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]pyrazine-2-carbonitrile hydrochloride	C	(DMSO-d <sub>6</sub> ) δ 10.79 (s, 1H), 9.44 (s, 2H), 8.67 (s, 1H), 8.53 (br s, 1H), 7.64 (d, 1H), 7.58 (d, 2H), 7.48-7.42 (m, 3H), 7.05 (s, 1H), 6.93 (dd, 2H), 4.18 (s, 2H), 3.91 (s, 3H), 3.20 (d, 2H) and 3.05 (d, 2H).	1.85	426	A
5	5-[5-[4-(benzylamino-methyl)-phenyl]-1H-pyrazol-3-ylamino]pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 10.89 (s, 1H), 9.74 (br s, 2H), 8.67 (s, 1H), 8.50 (br s, 1H), 7.82 (d, 1H), 7.66 (s, 1H), 7.57 (dd, 2H), 7.46-7.40 (m, 3H), 6.99 (br s, 1H) and 4.22 (d, 4H).	1.79	382	A
6	5-[5-(4-[(S)-1-(4-fluoro-phenyl)-ethylamino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 10.81 (s, 1H), 10.14 (br s, 1H), 9.78 (d, 1H), 8.67 (s, 1H), 8.52 (br s, 1H), 7.72-7.67 (m, 3H), 7.46 (s, 1H), 7.33 (t, 2H), 7.10 (dd, 1H), 7.00 (s, 1H), 4.44-4.39 (m, 1H), 4.05 (d, 1H), 3.91 (s, 3H), 3.86-3.81 (m, 1H) and 1.65 (d, 3H).	1.91	444	A

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
7	5-[5-(4-[(R)-1-(4-fluoro-phenyl)-ethylamino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 10.10 (br s, 1H), 9.76 (br s, 1H), 8.67 (s, 1H), 8.52 (br s, 1H), 7.72-7.67 (m, 3H), 7.45 (s, 1H), 7.33 (t, 2H), 7.11 (cd, 1H), 6.99 (s, 1H), 4.44-4.39 (m, 1H), 4.08-4.04 (m, 1H), 3.93 (s, 3H), 3.86-3.81 (m, 1H) and 1.65 (d, 3H).	1.91	444	A
8	5-(5-[4-[(4-fluoro-benzylamino)-methyl]-2-methoxy-phenyl]-1H-pyrazol-3-ylamino)-pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 12.69 (s, 1H), 10.82 (s, 1H), 9.73 (s, 2H), 8.67 (d, 1H), 8.53 (s, 1H), 7.75 (d, 1H), 7.63 (q, 2H), 7.46 (s, 1H), 7.30 (t, 2H), 7.18 (d, 1H), 7.01 (s, 1H), 4.18 (d, 4H) and 3.94 (s, 3H).	1.85	430	A
9	5-(5-[2-methoxy-4-[(2-morpholin-4-yl-ethylamino)-methyl]-phenyl]-1H-pyrazol-3-ylamino)-pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 12.75 (d, 1H), 11.10 (t, 1H), 10.81 (s, 1H), 9.66-9.56 (m, 1H), 8.66 (s, 1H), 8.49 (d, 1H), 7.75 (dd, 1H), 7.50 (s, 1H), 7.21 (s, 1H), 7.15 (s, 1H), 4.25 (s, 2H), 4.05 (s, 3H), 3.82 (d, 2H), 3.56 (d, 2H), 3.50 (s, 4H), 3.16-3.08 (m, 2H) and 1.20 (t, 1H).	1.70	435	A
10	(5-[2-methoxy-4-[(2-morpholin-4-yl-ethylamino)-methyl]-phenyl]-1H-pyrazol-3-yl)-pyrazin-2-yl-amine hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 12.39 (br s, 1H), 11.19 (br s, 1H), 9.84 (s, 1H), 9.69 (br s, 2H), 8.56 (s, 1H), 8.14 (s, 1H), 7.92 (d, 1H), 7.76 (d, 1H), 7.50 (s, 1H), 7.22 (d, 1H), 6.89 (s, 1H), 4.25 (t, 2H), 4.03 (t, 2H), 4.01 (s, 3H), 3.83 (s, 2H), 3.62-3.50 (m, 6H) and 3.15 (d, 2H).	1.52	410	A
11	5-[5-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile hydrochloride	D	(DMSO-d <sub>6</sub> ) δ 12.39 (br s, 1H), 10.77 (s, 1H), 10.49 (br s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.65 (d, 1H), 7.01 (s, 1H), 6.92 (d, 2H), 3.93 (s, 3H), 3.49 (d, 2H), 3.12-3.01 (m, 2H), 2.90-2.77 (m, 4H) and 2.08-2.03 (m, 4H).	1.70	390	A

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
12	5-[5-(4-[(1-cyclopropane-carbonyl)piperidin-4-ylmethyl]-amino)-methyl]-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 12.71 (s, 1H), 10.80 (br s, 1H), 9.27 (br s, 2H), 8.67 (s, 1H), 8.53 (br s, 1H), 7.74 (d, 1H), 7.50 (s, 1H), 7.20 (d, 2H), 7.07 (dd, 1H), 4.33 (m, 2H), 4.35-4.28 (m, 2H), 4.17 (s, 3H), 3.95 (s, 3H), 3.41-3.36 (m, 1H), 3.09-3.06 (m, 1H), 2.83 (d, 2H), 2.03-1.97 (m, 2H), 1.85-1.75 (m, 2H), 1.67-1.07 (m, 3H) and 0.69-0.67 (d, 4H).	1.72	487	A
13	N-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]cyclopropanecarboxamide	E	(DMSO-d <sub>6</sub> ) δ 12.58 (s, 1H), 10.71 (s, 1H), 8.64 (s, 1H), 8.57 (s, 1H), 8.48 (s, 1H), 7.61 (s, 1H), 7.03 (s, 1H), 6.91 (s, 2H), 4.29 (s, 2H), 3.87 (s, 3H), 1.60 (s, 1H) and 0.68 (br s, 4H).	4.44	320	B
14	5-[5-[2-methoxy-4-[(tetrahydropyran-4-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.77 (s, 1H), 9.58 (br s, 2H), 8.64 (s, 1H), 8.51 (s, 1H), 7.72 (d, 1H), 7.58 (s, 1H), 7.22 (d, 1H), 6.98 (s, 1H), 4.17 (s, 2H), 3.94 (s, 3H), 3.94-3.86 (m, 2H), 3.32-3.28 (m, 2H), 3.28-3.24 (m, 1H), 2.04 (t, 2H) and 1.72 (t, 2H).	3.61	406	B
15	5-[5-[2-methoxy-4-[methyl(2-morpholinoethyl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 11.53 (br s, 1H), 11.35 (br s, 1H), 10.77 (s, 1H), 8.63 (s, 1H), 8.51 (s, 1H), 7.73 (s, 1H), 7.57 (s, 1H), 7.24 (d, 1H), 6.98 (s, 1H), 4.40 (s, 2H), 3.92 (s, 4H), 3.62 (s, 4H), 3.29 (br s, 4H) and 2.47 (s, 3H).	3.57	449	B
16	5-[5-[2-methoxy-4-(2-morpholinoethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	A	(DMSO-d <sub>6</sub> ) δ 11.40 (s, 1H), 10.68 (s, 1H), 8.62 (s, 1H), 8.52 (s, 1H), 7.39 (d, 1H), 6.71 (s, 1H), 6.35 (s, 1H), 6.32 (d, 1H), 4.00 (br s, 4H), 3.91 (s, 3H), 3.55 (t, 2H), 3.44 (br s, 2H), 3.24 (t, 2H) and 3.13 (br s, 2H).	3.56	421	B
17	5-[5-[4-[1-[2-(dimethylamino)acetyl]-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	G	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 9.72 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.63 (d, 1H), 7.02 (s, 1H), 6.93 (d, 2H), 4.54 (d, 1H), 4.43-4.29 (m, 2H), 3.91 (s, 3H), 3.74 (d, 1H), 3.21-3.15 (m, 1H), 2.89-2.75 (m, 8H), 1.91-1.87 (m, 2H), 1.71-1.68 (m, 1H) and 1.58-1.54 (m, 1H).	3.90	461	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
18	5-[[5-[2-methoxy-4-[[[(1R)-1-methyl-2-morpholino-ethyl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 11.42 (s, 1H), 10.82 (s, 1H), 10.05 (d, 1H), 9.78 (d, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.75 (d, 1H), 7.64 (s, 1H), 7.28 (d, 2H), 7.01 (s, 1H), 4.36-4.24 (m, 2H), 3.97-3.89 (m, 7H), 3.79-3.76 (m, 2H), 3.57 (br s, 2H), 3.45-3.42 (m, 1H), 3.17 (br s, 2H) and 1.53-1.52 (d, 3H).	3.69	449	B
19	5-[[5-[4-[[[(1,1-dimethyl-2-morpholino-ethyl)amino]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.73 (s, 1H), 10.09 (s, 1H), 8.63 (s, 1H), 8.51 (s, 1H), 7.71 (d, 1H), 7.58 (s, 1H), 7.25 (d, 1H), 6.96 (s, 1H), 4.22 (br s, 2H), 3.75 (s, 3H), 3.69 (br m, 2H), 3.32 (br m, 8H), 1.82 (br m, 2H) and 1.61 (s, 6H).	3.79	463	B
20	5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	G	(DMSO-d <sub>6</sub> ) δ 10.78 (s, 1H), 9.13 (d, 1H), 8.95 (d, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.65 (d, 1H), 6.99 (s, 1H), 6.92 (s, 2H), 6.87 (s, 1H), 3.92 (s, 3H), 3.36 (d, 2H), 3.03-2.92 (m, 2H), 2.90-2.87 (m, 1H) and 1.99-1.90 (m, 4H).	3.72	376	B
21	5-[[5-[2-fluoro-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.90 (s, 1H), 8.70 (s, 1H), 8.51 (s, 1H), 7.84 (d, 1H), 7.26-7.21 (m, 2H), 6.95 (s, 1H), 3.57-3.51 (m, 2H), 3.10-3.04 (m, 2H), 2.89-2.85 (m, 1H), 2.78 (d, 3H) and 2.06-1.97 (m, 4H).	3.64	378	B
22	5-[[5-[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.56 (s, 1H), 11.17 (s, 1H), 10.77 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.57 (d, 1H), 6.84 (s, 1H), 6.70-6.66 (m, 2H), 3.98 (d, 2H), 3.91 (s, 3H), 3.49 (d, 2H), 3.24-3.10 (m, 4H) and 2.81 (d, 3H).	3.53	391	B
23	5-[[5-[2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.38 (s, 1H), 10.73 (s, 1H), 10.66 (s, 1H), 8.67 (s, 1H), 8.55 (d, 1H), 7.50 (d, 1H), 6.79 (s, 1H), 6.45 (dd, 1H), 6.40 (s, 1H), 3.94 (s, 1H), 3.91 (s, 3H), 3.77-3.70 (m, 1H), 3.54-3.42 (m, 4H), 3.24-3.07 (m, 2H), 2.82-2.80 (d, 3H), 2.36-2.32 (m, 1H) and 2.20 (m, 1H).	3.71	405	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
24	5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.58 (s, 1H), 9.68 (s, 1H), 8.67 (s, 1H), 8.02-8.00 (m, 1H), 7.81 (d, 1H), 7.69-7.67 (m, 1H), 7.02 (s, 1H), 6.92 (d, 1H), 6.38 (d, 1H), 3.92 (s, 3H), 3.49 (d, 1H), 3.07-3.04 (m, 2H), 2.90-2.84 (m, 1H), 2.78 (d, 3H) and 2.04-1.99 (m, 4H).	3.64	389	B
25	6-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.59 (s, 1H), 10.23 (s, 1H), 8.58 (s, 1H), 7.95-7.92 (m, 1H), 7.65 (d, 1H), 7.32-7.28 (m, 1H), 7.01 (s, 1H), 6.92 (d, 1H), 6.80 (s, 1H), 3.92 (s, 3H), 3.49 (d, 1H), 3.11-3.04 (m, 2H), 2.90-2.82 (m, 1H), 2.78 (d, 3H) and 2.08-2.02 (m, 4H).	3.80	389	B
26	N-[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]-5-methyl-pyrazin-2-amine hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.92 (s, 1H), 10.31 (s, 1H), 8.61 (s, 1H), 8.21 (s, 1H), 7.69 (d, 1H), 7.03 (s, 1H), 6.93 (d, 1H), 6.71 (s, 1H), 3.92 (s, 3H), 3.61-3.49 (br d, 2H), 3.06 (d, 2H), 2.88-2.85 (br d, 1H), 2.76 (d, 3H), 2.42 (s, 3H) and 2.11-2.03 (m, 4H).	3.55	379	B
27	5-[[5-[4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.88 (s, 1H), 10.61 (s, 1H), 8.69 (s, 1H), 8.50 (s, 1H), 7.73 (d, 2H), 7.34 (d, 2H), 6.92 (d, 2H), 3.49 (t, 2H), 3.06 (t, 2H), 2.89-2.87 (m, 1H), 2.68 (s, 3H), 2.18-2.07 (m, 2H) and 1.99-1.92 (m, 2H).	3.62	360	B
28	5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)oxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 12.55 (br s, 1H), 10.92 (br s, 1H), 10.77 (br s, 1H), 8.66 (s, 1H), 8.55 (s, 1H), 7.62-7.60 (m, 1H), 6.86 (s, 1H), 6.79-6.71 (m, 2H), 4.65 (br s, 1H), 3.89 (s, 3H), 3.47 (d, 1H), 3.29 (d, 1H), 3.18-3.08 (m, 2H), 2.77-2.74 (m, 3H), 2.34-2.14 (m, 2H), 2.06 (d, 1H) and 1.94 (d, 1H).	3.75	406	B
29	5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.79 (br s, 1H), 10.58 (br s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.59 (d, 1H), 6.85 (s, 1H), 6.68 (d, 1H), 6.65 (d, 1H), 3.93 (d, 2H), 3.90 (s, 3H), 3.42 (d, 2H), 3.01-2.92 (m, 2H), 2.71 (d, 3H), 1.99-1.91 (m, 3H) and 1.69-1.60 (m, 2H).	3.80	420	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
30	2-fluoro-4-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]benzotrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 12.45 (s, 1H), 10.35 (s, 1H), 9.70 (s, 1H), 7.69-7.59 (m, 3H), 7.14 (d, 1H), 7.05 (s, 1H), 6.92 (d, 1H), 6.37 (s, 1H), 3.92 (s, 3H), 3.53 (d, 2H), 3.11-3.02 (m, 2H), 2.86-2.82 (m, 1H), 2.68 (d, 3H) and 2.08-1.92 (m, 4H).	3.95	406	B
31	5-[[5-[2-methoxy-4-[(2-pyridylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	F	(DMSO-d <sub>6</sub> ) δ 14.30 (br s, 1H), 10.82 (s, 1H), 9.51 (br s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.96-7.92 (m, 2H), 7.69 (d, 1H), 7.35 (s, 1H), 7.19 (d, 1H), 7.11 (d, 1H), 6.96 (s, 1H), 6.89 (t, 1H), 4.72 (d, 2H) and 3.93 (s, 3H).	3.72	399	B
32	5-[[5-[5-fluoro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.81 (s, 1H), 10.69 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.59-7.55 (m, 1H), 7.01 (s, 1H), 6.98 (d, 1H), 3.92 (s, 3H), 3.49 (d, 2H), 3.15-3.07 (m, 3H), 2.77 (d, 3H), 2.21-2.12 (m, 2H) and 1.99-1.96 (m, 2H).	3.74	408	B
33	5-[[5-[2-methoxy-4-[(3S)-pyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.76 (s, 1H), 9.60 (s, 1H), 9.46 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.63 (d, 1H), 6.87 (s, 1H), 6.69 (t, 2H), 5.30 (q, 1H), 3.90 (s, 3H), 3.50 (q, 1H), 3.36-3.27 (m, 3H) and 2.24-2.18 (m, 2H).	3.68	378	B
34	5-[[5-[2-methoxy-4-(pyrrolidin-2-yl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.76 (s, 1H), 9.67 (s, 1H), 9.08 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.64 (d, 1H), 6.88 (s, 1H), 6.74 (s, 1H), 6.70 (d, 1H), 4.39-4.31 (m, 1H), 4.25-4.20 (m, 1H), 3.91 (s, 3H), 3.93-3.90 (m, 1H), 3.66 (t, 1H), 3.22 (s, 3H) and 2.33-2.23 (m, 2H).	3.90	392	B
35	5-[[5-[2-methoxy-4-[(1-methylpyrrolidin-2-yl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 10.67 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.64 (d, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 6.79 (d, 1H), 6.71 (q, 1H), 4.42 (d, 2H), 3.91 (s, 3H), 3.85-3.81 (m, 1H), 3.62-3.59 (m, 1H), 3.15 (t, 1H), 2.97 (d, 3H), 2.34-2.24 (m, 1H), 2.08-2.05 (m, 1H), 2.02-1.99 (m, 1H) and 1.88-1.79 (m, 1H).	3.71	406	B



Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
36	5-[[5-[2-methoxy-4-(4-piperidylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 13.00-12.00 (br s, 1H), 10.77 (br s, 1H), 9.08 (d, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.59 (d, 1H), 6.85 (s, 1H), 6.67-6.63 (m, 2H), 3.93 (d, 2H), 3.89 (s, 3H), 3.29 (d, 2H), 2.95-2.86 (m, 2H), 2.08 (s, 1H), 1.93 (d, 2H) and 1.56-1.48 (m, 2H).	3.86	406	B
37	5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.85 (s, 1H), 10.77 (s, 1H), 9.91 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.62 (s, 1H), 7.26 (d, 1H), 7.01 (s, 1H), 4.22 (d, 2H), 3.96 (s, 3H), 3.50 (d, 2H), 3.25 (br s, 1H), 3.15 (d, 1H), 3.00 (q, 2H), 2.69 (d, 3H), 2.36 (t, 2H) and 2.08 (q, 2H).	3.01	419	B
38	5-[[5-[2-isopropoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 12.63 (s, 1H), 10.78 (s, 1H), 10.45 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 7.67 (d, 1H), 7.06 (s, 1H), 7.01 (s, 1H), 6.89 (d, 1H), 4.76-4.73 (m, 1H), 3.49 (d, 2H), 3.06 (br s, 2H), 2.90 (d, 1H), 2.78 (d, 3H), 2.01 (br d, 4H) and 1.37 (d, 6H).	3.94	418	B
39	5-[[5-[2-methoxy-4-(3-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.82 (s, 1H), 9.39 (s, 1H), 9.17 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.64 (t, 1H), 7.08 (d, 1H), 6.95 (d, 2H), 3.92 (s, 3H), 3.44-3.39 (m, 2H), 3.07 (t, 2H), 2.90 (s, 1H) and 1.89-1.76 (m, 4H).	3.72	376	B
40	5-[[5-[2-methoxy-4-(1-methyl-3-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.86 (s, 1H), 10.82 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.67 (d, 1H), 7.05 (s, 1H), 6.95 (d, 2H), 3.93 (s, 3H), 3.47-3.37 (m, 2H), 3.24-3.14 (m, 2H), 2.99-2.93 (m, 1H), 2.75 (d, 3H), 1.94 (d, 3H) and 1.66 (d, 1H).	3.75	390	B
41	5-[[5-[2-methoxy-4-(1-methyl-2-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.82 (s, 1H), 9.70 (d, 1H), 9.29 (d, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.56 (s, 1H), 7.21 (d, 1H), 6.99 (s, 1H), 4.28-4.25 (m, 1H), 3.97 (s, 3H), 3.35 (d, 2H), 3.06-3.01 (m, 1H), 1.94-1.77 (m, 5H) and 1.66-1.64 (m, 1H).	3.83	376	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
42	5-[[5-[2-methoxy-4-[(3S)-1-methylpyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.77 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.63 (s, 1H), 6.87 (s, 1H), 6.70 (q, 2H), 5.25 (d, 1H), 3.90 (s, 3H), 3.65-3.38 (m, 2H), 3.44-3.38 (m, 1H), 3.24-3.12 (m, 2H), 2.88 (q, 3H) and 2.36-2.14 (m, 2H).	3.70	392	B
43	5-chloro-N-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]pyrazin-2-amine hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.03 (s, 1H), 9.22 (d, 1H), 9.05 (d, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 7.64 (d, 1H), 6.99 (s, 1H), 6.90 (d, 1H), 6.73 (s, 1H), 3.91 (s, 3H), 3.36 (d, 2H), 2.98 (d, 1H), 2.93-2.88 (m, 2H) and 1.95-1.89 (m, 4H).	3.98	385	B
44	5-chloro-N-[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]pyrazin-2-amine hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.70 (s, 1H), 10.04 (s, 1H), 8.48 (s, 1H), 8.27 (s, 1H), 7.65 (d, 1H), 7.04 (d, 1H), 6.91 (d, 1H), 6.74 (s, 1H), 3.91 (s, 3H), 3.49 (d, 2H), 3.10-3.04 (m, 2H), 2.89 (d, 1H), 2.77 (d, 3H) and 2.11-2.03 (m, 4H).	3.95	399	B
45	5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carboxylic acid hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 9.30 (d, 1H), 9.12 (br d, 1H), 8.98 (d, 1H), 8.89 (br d, 1H), 7.96 (d, 1H), 6.97 (s, 1H), 6.91 (d, 1H), 5.60 (s, 1H), 3.89 (s, 3H), 3.37 (d, 2H), 3.04-2.96 (m, 2H), 2.91-2.87 (br m, 1H) and 1.99-1.90 (m, 4H).	3.60	395	B
46	5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.56 (s, 1H), 10.75 (s, 1H), 9.22 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.55 (d, 1H), 6.84 (s, 1H), 6.68-6.64 (m, 2H), 3.91 (s, 3H), 3.50-3.47 (m, 4H) and 3.23 (br s, 4H).	3.54	377	B
47	5-[[5-[4-[(2S,6S)-2,6-dimethyl-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.78 (s, 1H), 9.04 (s, 1H), 9.04 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.65 (d, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 6.90 (s, 1H), 3.92 (s, 3H), 3.82-3.78 (m, 1H), 3.47-3.43 (m, 1H), 3.17-3.12 (m, 1H), 2.08-1.99 (m, 2H), 1.80 (d, 1H), 1.69-1.59 (m, 1H), 1.44 (d, 3H) and 1.30 (d, 3H).	3.90	404	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
48	5-[[5-(2-methoxy-4-tetrahydropyran-4-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.77 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.60 (d, 1H), 7.03 (d, 1H), 6.94 (dd, 2H), 3.98-3.95 (m, 2H), 3.92 (s, 3H), 3.48-3.42 (m, 2H), 2.84-2.80 (m, 1H) and 1.76-1.70 (m, 4H).	4.85	377	B
49	2-fluoro-4-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]benzonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 12.42 (br s, 1H), 9.76 (s, 1H), 9.15 (br s, 1H), 8.98 (br s, 1H), 7.69-7.60 (m, 3H), 7.16 (d, 1H), 7.04 (s, 1H), 6.90 (d, 1H), 6.34 (s, 1H), 3.91 (s, 3H), 3.41-3.35 (m, 2H), 3.00 (t, 2H), 2.91-2.85 (m, 1H) and 2.01-1.88 (m, 4H).	4.02	392	B
50	6-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.19 (s, 1H), 8.94 (d, 1H), 8.76 (d, 1H), 8.57 (s, 1H), 7.93 (d, 1H), 7.64 (d, 1H), 7.32 (s, 1H), 6.98 (s, 1H), 6.90 (d, 1H), 6.80 (s, 1H), 3.91 (s, 3H), 3.38 (d, 2H), 3.00-2.95 (m, 2H), 2.95-2.89 (m, 1H) and 1.99-1.84 (m, 4H).	3.73	375	B
51	5-[[5-[2-fluoro-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.91 (s, 1H), 9.10 (s, 1H), 8.69 (s, 1H), 8.51 (s, 1H), 7.85 (d, 1H), 7.23-7.21 (m, 2H), 6.95 (s, 1H), 3.36 (d, 2H), 3.02-2.97 (m, 2H), 2.94-2.90 (m, 1H) and 1.99-1.88 (m, 4H).	3.72	364	B
52	5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.51 (s, 1H), 9.69 (s, 1H), 9.06 (d, 1H), 8.87 (d, 1H), 8.67 (d, 1H), 8.03-8.00 (m, 1H), 7.81 (d, 1H), 7.68 (d, 1H), 6.99 (s, 1H), 6.90 (s, 1H), 6.37 (s, 1H), 3.92 (s, 3H), 3.37 (d, 2H), 3.03-2.87 (m, 3H) and 1.98-1.89 (m, 4H).	3.65	375	B
53	5-[[5-[2-isopropoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 9.11 (d, 1H), 8.97 (d, 1H), 8.66 (s, 1H), 8.57 (s, 1H), 7.67 (d, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 6.88 (d, 1H), 4.77-4.71 (m, 1H), 3.36 (d, 2H), 2.98 (d, 2H), 2.90-2.84 (m, 1H), 1.99-1.86 (m, 4H) and 1.37 (d, 6H).	4.00	404	B
54	5-[[5-[4-(1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 9.30 (s, 1H), 8.67 (d, 1H), 7.51 (d, 1H), 6.79 (s, 1H), 6.48 (d, 1H), 6.41 (s, 1H), 3.91 (s, 3H), 3.81 (d, 2H), 3.65-3.57 (m, 2H), 3.23 (s, 2H), 3.10 (s, 2H) and 2.14 (d, 2H).	3.70	391	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
55	N-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]-5-methyl-pyrazin-2-amine hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.26 (s, 1H), 9.18 (d, 1H), 9.03 (d, 1H), 8.60 (s, 1H), 8.20 (s, 1H), 7.68 (d, 1H), 7.01 (s, 1H), 6.92 (d, 1H), 6.71 (s, 1H), 3.92 (s, 3H), 3.37 (d, 2H), 2.99 (d, 2H), 2.91-2.88 (m, 1H), 2.42 (s, 3H) and 1.97-1.89 (br m, 4H).	3.62	365	B
56	5-[5-[4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.87 (s, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 8.50 (s, 1H), 7.72 (d, 2H), 7.32 (d, 2H), 6.92 (s, 1H), 3.41-3.34 (m, 2H), 3.04-2.96 (m, 2H), 2.91-2.85 (m, 1H) and 1.92 (br s, 4H).	3.63	346	B
57	5-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 12.54 (br s, 1H), 10.76 (br s, 1H), 8.98 (s, 2H), 8.58 (s, 1H), 7.57 (s, 1H), 6.73-6.70 (m, 3H), 4.75-4.71 (m, 1H), 3.83 (s, 3H), 3.21 (s, 2H), 3.07 (s, 2H), 2.10 (s, 2H) and 1.84 (s, 2H).	3.77	392	B
58	5-[5-[5-fluoro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.82 (s, 1H), 9.21 (d, 1H), 8.99-8.96 (m, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.57 (d, 1H), 7.01 (s, 1H), 6.97 (d, 1H), 3.92 (s, 3H), 3.36 (d, 2H), 3.18-3.12 (m, 1H), 3.07-2.99 (m, 2H), 2.09-1.99 (m, 2H) and 1.92 (d, 2H).	3.83	394	B
59	5-[5-[4-[(isopropylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.83 (s, 1H), 9.45 (s, 2H), 8.67 (d, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.62 (d, 1H), 7.25 (dd, 1H), 7.00 (s, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.31-3.24 (m, 1H) and 1.34 (d, 6H).	3.66	364	B
60	5-[5-[4-(1-ethyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.79 (s, 1H), 10.67 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.66 (d, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 3.92 (s, 3H), 3.55 (d, 2H), 3.13-3.10 (m, 2H), 3.03-2.95 (m, 2H), 2.91-2.85 (m, 1H), 2.18-2.09 (m, 2H), 2.02 (d, 2H) and 1.30 (t, 3H).	3.70	404	B
61	5-[5-[4-(1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 10.65 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.66 (d, 1H), 7.031 (s, 1H), 6.93 (d, 2H), 3.92 (s, 3H), 3.45-3.42 (m, 3H), 3.10-3.02 (m, 2H), 2.93-2.87 (m, 1H), 2.34-2.22 (m, 2H), 2.02-1.99 (m, 2H) and 1.33-1.31 (m, 6H).	3.74	418	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
62	2-[4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-1-piperidyl]acetamide hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 12.61 (br s, 1H), 10.79 (s, 1H), 9.83 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 8.10 (s, 1H), 7.73 (s, 1H), 7.66 (d, 1H), 7.01 (s, 1H), 6.92 (d, 2H), 3.95 (s, 2H), 3.93 (s, 3H), 3.59-3.57 (m, 2H), 3.25-3.17 (m, 2H), 2.89-2.83 (m, 1H), 2.15 (t, 2H) and 2.09-2.03 (m, 2H).	3.65	433	B
63	5-[[5-[2-methoxy-4-[[methyl(tetrahydropyran-4-yl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 12.68 (s, 1H), 11.09 (s, 1H), 10.82 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.76 (d, 1H), 7.64 (s, 1H), 7.26 (d, 1H), 7.02 (s, 1H), 4.52-4.48 (m, 1H), 4.20-4.15 (m, 1H), 4.00 (d, 2H), 3.97 (s, 3H), 3.50-3.43 (m, 1H), 3.32 (q, 2H), 2.58 (d, 3H), 2.17 (d, 1H), 2.08 (d, 1H) and 1.91-1.81 (m, 2H).	3.54	420	B
64	5-[[5-[4-(4-fluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	L	(DMSO-d <sub>6</sub> ) δ 11.13 (br s, 1H), 10.81 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.76 (d, 1H), 7.17 (s, 1H), 7.06 (d, 1H), 6.99 (s, 1H), 3.95 (s, 3H), 3.49 (d, 2H), 3.29-3.26 (m, 2H), 2.85 (d, 3H), 2.68-2.59 (m, 2H) and 2.28-2.22 (m, 2H).	3.79	408	B
65	5-[[5-[2-methoxy-4-(1-methylazetidin-3-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 12.86 (br s, 1H), 10.79 (br s, 2H), 8.67 (s, 1H), 8.53 (s, 1H), 7.69 (d, 1H), 7.17 (s, 1H), 7.11 (d, 1H), 6.97 (s, 1H), 4.47-4.01 (m, 5H), 3.91 (s, 3H), 2.94 (s, 1H) and 2.87 (d, 2H).	3.53	362	B
66	5-[[5-[4-(3-fluoro-1-methyl-azetidin-3-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	L	(DMSO-d <sub>6</sub> ) δ 11.53 (br s, 1H), 10.83 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.82 (t, 1H), 7.45 (s, 1H), 7.29-7.23 (m, 2H), 7.03 (s, 1H), 4.92-4.83 (m, 1H), 4.75-4.68 (m, 2H), 4.63-4.55 (m, 1H), 3.99 (s, 3H) and 2.95 (d, 3H).	3.64	380	B
67	5-[[5-[5-chloro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 11.00 (s, 1H), 10.83 (s, 1H), 8.68 (s, 1H), 8.53 (s, 1H), 7.80 (s, 1H), 7.03 (s, 2H), 3.94 (s, 3H), 3.50 (d, 2H), 3.25-3.11 (m, 3H), 2.77 (d, 3H), 2.21-2.12 (m, 2H) and 1.97 (d, 2H).	3.97	424	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
68	5-[[5-[5-chloro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.85 (s, 1H), 9.18 (s, 1H), 9.09 (d, 1H), 8.68 (d, 1H), 8.53 (s, 1H), 7.79 (s, 1H), 7.02 (s, 2H), 3.94 (s, 3H), 3.43-3.36 (m, 2H), 3.30-3.25 (m, 1H), 3.11-3.02 (m, 2H), 2.09-1.99 (m, 2H) and 1.94-1.91 (m, 2H).	4.04	410	B
69	5-[[5-[3-chloro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.88 (s, 1H), 10.66 (s, 1H), 8.69 (s, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.21 (d, 1H), 7.04 (s, 1H), 3.70 (s, 3H), 3.51 (d, 2H), 3.30-3.24 (m, 1H), 3.20-3.12 (m, 2H), 2.77 (d, 3H) and 2.09-1.96 (m, 4H).	3.83	424	B
70	5-[[5-[3-chloro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.90 (s, 1H), 9.14 (s, 2H), 8.69 (d, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.21 (d, 1H), 7.04 (s, 1H), 3.69 (s, 3H), 3.39-3.30 (m, 3H), 3.11-3.02 (m, 2H) and 2.01-1.91 (m, 4H).	3.90	410	B
71	methyl 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carboxylate hydrochloride	J	(DMSO-d <sub>6</sub> ) δ 9.31 (s, 1H), 9.04 (br s, 1H), 9.00 (s, 1H), 8.81 (br s, 1H), 7.96 (d, 1H), 6.97 (s, 1H), 6.91 (d, 1H), 5.60 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.38 (d, 2H), 3.00 (d, 2H), 2.94-2.85 (br m, 1H), 2.03-1.97 (m, 2H) and 1.89-1.83 (m, 2H).	3.90	409	B
72	5-[[5-[2-methoxy-4-[(tetrahydrofuran-3-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.83 (s, 1H), 9.79 (s, 2H), 8.67 (d, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.57 (d, 1H), 7.24 (dd, 1H), 7.01 (s, 1H), 4.23-4.15 (m, 2H), 4.01-3.91 (m, 5H), 3.84-3.81 (m, 2H), 3.70-3.65 (m, 1H) and 2.25-2.13 (m, 2H).			
73	5-[[5-[2-methoxy-4-[[methyl(tetrahydrofuran-3-yl)amino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 11.50 (br s, 1H), 10.83 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.76 (d, 1H), 7.63 (s, 1H), 7.26 (d, 1H), 7.02 (s, 1H), 4.48-4.15 (m, 6H), 4.01-3.99 (m, 2H), 3.96 (s, 3H), 3.78-3.73 (m, 1H), 3.66-3.60 (m, 1H), 2.56 (d, 3H), 2.44-2.30 (m, 1H) and 2.25-2.21 (m, 1H).	3.57	406	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
74	5-[[5-[2-methoxy-4-(tetrahydropyran-4-ylmethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 10.86 (s, 1H), 8.68 (s, 1H), 8.55 (s, 1H), 7.50 (d, 1H), 6.80 (s, 1H), 6.59 (s, 1H), 6.52 (d, 1H), 3.86 (br s, 5H), 3.28 (t, 2H), 3.05 (d, 2H), 1.87-1.84 (m, 1H), 1.71 (d, 2H) and 1.27-1.23 (m, 2H).	4.67	406	B
75	5-[[5-[2-methoxy-4-(tetrahydropyran-4-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	K	(DMSO-d <sub>6</sub> ) δ 12.65 (br s, 1H), 10.75 (s, 1H), 8.67 (d, 1H), 8.53 (s, 1H), 7.57 (d, 1H), 6.85 (s, 1H), 6.68 (d, 1H), 6.64 (dd, 1H), 3.91-3.88 (m, 7H), 3.37-3.31 (m, 2H), 2.03-2.01 (m, 1H), 1.71 (d, 2H) and 1.40-1.30 (m, 2H).	4.97	407	B
76	5-[[5-[4-(4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	L	(DMSO-d <sub>6</sub> ) δ 10.82 (s, 1H), 9.29 (br s, 1H), 9.19 (br s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.76 (d, 1H), 7.15 (s, 1H), 7.06 (d, 1H), 6.99 (s, 1H), 3.95 (s, 3H), 3.38-3.36 (m, 2H), 3.19-3.10 (m, 2H), 2.60-2.57 (m, 1H), 2.50-2.45 (m, 1H) and 2.19-2.13 (m, 2H).	3.85	394	B
77	5-[[5-[4-(3-fluoroazetidin-3-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	L	(DMSO-d <sub>6</sub> ) δ 10.85 (s, 1H), 10.05 (br s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.81-7.80 (d, 1H), 7.45-7.42 (d, 1H), 7.33-7.20 (m, 2H), 7.03 (s, 1H), 4.65-4.52 (m, 4H) and 4.00 (s, 3H).	3.69	366	B
78	5-[[5-[2-methoxy-4-[(3R)-1-methylpyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 11.51 (s, 1H), 11.05 (s, 1H), 10.81 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.63 (d, 1H), 6.87 (s, 1H), 6.72 (s, 1H), 6.68 (d, 1H), 5.25 (d, 1H), 3.90 (s, 3H), 3.42 (s, 1H), 3.22-3.19 (m, 2H), 2.88-2.85 (d, 3H), 2.33-2.24 (m, 2H) and 2.12 (m, 1H).	3.69	392	B
79	5-[[5-(2-methoxy-4-morpholino-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	I	(DMSO-d <sub>6</sub> ) δ 12.40 (s, 1H), 10.69 (s, 1H), 8.66 (d, 1H), 8.55 (s, 1H), 7.51 (d, 1H), 6.82 (d, 1H), 6.62 (d, 1H), 6.59 (d, 1H), 3.90 (s, 3H), 3.77-3.74 (m, 4H) and 3.22-3.17 (m, 4H).	4.66	378	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
80	5-[[5-[4-(4-ethylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.49 (s, 1H), 10.98 (s, 1H), 10.75 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.57 (d, 1H), 6.84 (s, 1H), 6.69 (d, 1H), 6.66 (d, 1H), 3.98 (d, 2H), 3.91 (s, 3H), 3.56 (d, 2H), 3.26-3.14 (m, 4H), 3.08 (q, 2H) and 1.30 (t, 3H).	3.56	405	B
81	5-[[5-[4-(4-isopropylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 11.03 (s, 1H), 10.78 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.56 (d, 1H), 6.84 (s, 1H), 6.69 (d, 1H), 6.66 (d, 1H), 3.98 (d, 2H), 3.91 (s, 3H), 3.55 (d, 1H), 3.49 (d, 2H), 3.30 (t, 2H), 3.12 (q, 2H) and 1.33 (d, 6H).	3.66	419	B
82	5-[[5-[2-methoxy-4-[(3R)-3-methylpiperazin-1-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 10.83 (s, 1H), 9.71 (s, 1H), 9.50 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.54 (s, 1H), 6.84 (s, 1H), 6.69 (s, 1H), 6.65 (s, 1H), 3.90 (s, 5H), 3.33 (s, 2H), 3.16-3.10 (m, 2H), 2.92-2.87 (m, 1H) and 1.34 (d, 3H).	3.72	391	B
83	5-[[5-[4-(4-ethyl-1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.44 (s, 1H), 10.81 (s, 1H), 10.75 (s, 1H), 8.67 (d, 1H), 8.56 (s, 1H), 7.51 (d, 1H), 6.78 (s, 1H), 6.46 (dd, 1H), 6.41 (d, 1H), 3.98 (d, 2H), 3.91 (s, 3H), 3.83-3.77 (m, 1H), 3.57-3.52 (m, 4H), 3.19-3.10 (m, 2H), 3.05-3.01 (m, 1H), 2.42-2.34 (m, 1H), 2.22-2.17 (m, 1H) and 1.28 (t, 3H).	3.85	419	B
84	5-[[5-[4-(4-isopropyl-1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.50 (s, 1H), 10.74 (s, 1H), 10.55 (s, 1H), 8.67 (d, 1H), 8.56 (s, 1H), 7.51 (d, 1H), 6.78 (s, 1H), 6.46 (dd, 1H), 6.41 (d, 1H), 3.98-3.82 (m, 5H), 3.58-3.55 (m, 3H), 3.45 (d, 2H), 3.16 (q, 1H), 2.98 (q, 1H), 2.41-2.38 (m, 1H), 2.23-2.19 (m, 1H) and 1.27 (d, 6H).	3.90	433	B
85	5-[[5-[4-(1-ethyl-4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	L	(DMSO-d <sub>6</sub> ) δ 11.22 (s, 1H), 10.82 (s, 1H), 8.69 (s, 1H), 8.54 (s, 1H), 7.76 (d, 1H), 7.18 (s, 1H), 7.07 (d, 1H), 6.99 (s, 1H), 3.95 (s, 3H), 3.57-3.54 (m, 2H), 3.22-3.15 (m, 4H), 2.79-2.65 (m, 2H), 2.26-2.21 (m, 2H) and 1.33 (t, 3H).	3.91	422	B



Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
86	5-[[5-[4-(4-fluoro-1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	L	(DMSO-d <sub>6</sub> ) δ 11.22 (br s, 1H), 10.81 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.76 (d, 1H), 7.21 (s, 1H), 7.09 (d, 1H), 6.98 (s, 1H), 3.95 (s, 3H), 3.57 (m, 1H), 3.47 (d, 2H), 3.24-3.16 (m, 2H), 2.96-2.89 (m, 1H), 2.85-2.79 (m, 1H), 2.26-2.20 (m, 2H) and 1.36 (d, 6H).	4.05	436	B
87	5-[[5-[4-(1-ethyl-3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	M	(DMSO-d <sub>6</sub> ) δ 11.49 (br s, 1H), 10.82 (s, 1H), 8.68 (d, 1H), 8.54 (s, 1H), 7.69 (d, 1H), 7.08 (s, 1H), 6.99 (d, 1H), 6.95 (s, 1H), 5.38-5.25 (m, 1H), 3.92 (s, 3H), 3.86 (d, 1H), 3.55 (d, 1H), 3.24-3.21 (m, 2H), 3.15-3.03 (m, 3H), 2.29-2.26 (m, 1H), 2.11-2.08 (m, 1H) and 1.34 (t, 3H).	3.78	422	B
88	5-[[5-[4-(3-fluoro-1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	M	(DMSO-d <sub>6</sub> ) δ 11.45 (br s, 1H), 10.80 (s, 1H), 8.68 (s, 1H), 8.55 (s, 1H), 7.69 (d, 1H), 7.10 (s, 1H), 6.99 (d, 1H), 6.95 (s, 1H), 5.54-5.36 (m, 1H), 3.92 (s, 3H), 3.75-3.72 (m, 1H), 3.62-3.61 (m, 1H), 3.44-3.41 (m, 1H), 3.17-3.11 (m, 3H), 2.42-2.34 (m, 2H), 2.10 (m, 1H) and 1.35 (d, 6H).	3.82	436	B
89	5-[[5-[2-methoxy-4-[1-(2-methoxyethyl)-4-piperidyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.85 (s, 1H), 10.80 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.66 (d, 1H), 7.02 (s, 1H), 6.92 (d, 2H), 3.91 (s, 3H), 3.78 (br s, 2H), 3.58 (d, 2H), 3.32 (br s, 5H), 3.10 (d, 2H), 2.85 (br s, 1H), 2.18-2.12 (m, 2H) and 1.99 (d, 2H).	3.85	434	B
90	5-[[5-[4-(ethylaminomethyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.83 (s, 1H), 9.55 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.73 (d, 1H), 7.56 (s, 1H), 7.21 (d, 1H), 6.99 (s, 1H), 4.13 (s, 2H), 3.95 (s, 3H), 3.01-2.95 (m, 2H) and 1.27 (t, 3H).	3.67	350	B
91	5-[[5-[4-[(cyclopropylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.85 (s, 1H), 9.56 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.72 (d, 1H), 7.55 (s, 1H), 7.22 (d, 1H), 7.01 (s, 1H), 4.23 (s, 2H), 3.95 (s, 3H), 2.65 (br s, 1H), 0.96 (d, 2H) and 0.73 (d, 2H).	3.73	362	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
92	5-[[5-[4-[(3R)-3,4-dimethylpiperazin-1-yl]-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 11.44 (s, 1H), 10.89 (s, 1H), 9.69 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.57 (s, 1H), 6.84 (s, 1H), 6.71-6.68 (m, 2H), 4.03-3.99 (m, 2H), 3.91 (s, 3H), 3.31-3.00 (m, 5H), 2.79 (s, 3H) and 1.21 (d, 3H).	3.69	405	B
93	5-[[5-[4-[(3R)-4-ethyl-3-methylpiperazin-1-yl]-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 11.18 (s, 1H), 10.78 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.54 (s, 1H), 6.84 (s, 1H), 6.69 (s, 1H), 6.66 (s, 1H), 4.01-3.94 (m, 2H), 3.91 (s, 3H), 3.76 (s, 1H), 3.55-3.52 (m, 2H), 3.39-3.26 (m, 2H), 3.15-3.04 (m, 3H), 1.41 (d, 3H) and 1.34-1.23 (m, 3H).	3.69	419	B
94	5-[[5-[4-[(3S)-1-isopropylpyrrolidin-3-yl]oxy-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 11.89 (s, 1H), 11.32 (s, 1H), 10.81 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 7.63 (d, 1H), 6.87 (s, 1H), 6.74-6.67 (m, 2H), 5.24 (s, 1H), 3.90 (s, 3H), 3.60-3.45 (m, 4H), 3.23-3.16 (m, 1H), 2.21-2.12 (m, 2H) and 1.32-1.30 (d, 6H).	3.81	420	B
95	5-[[5-[4-[(3R)-1-isopropylpyrrolidin-3-yl]oxy-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 11.70 (s, 1H), 11.04 (s, 1H), 10.83 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.63 (d, 1H), 6.87 (s, 1H), 6.73 (s, 1H), 6.70 (s, 1H), 5.23 (s, 1H), 3.90 (s, 3H), 3.55-3.23 (m, 5H), 2.21-1.98 (m, 2H) and 1.30 (d, 6H).	3.80	420	B
96	5-[[5-[4-[(3R,S),4(R,S)]-3-fluoro-1-methyl-4-piperidyl]-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	M	(DMSO-d <sub>6</sub> ) δ 11.55 (br s, 1H), 10.80 (s, 1H), 8.68 (d, 1H), 8.55 (s, 1H), 7.69 (d, 1H), 7.08 (d, 1H), 6.98 (d, 1H), 6.95 (s, 1H), 5.31-5.18 (m, 1H), 3.92 (s, 3H), 3.82 (d, 1H), 3.49 (d, 1H), 3.21-2.94 (m, 3H), 2.87 (d, 3H), 2.23-2.20 (m, 1H) and 2.11-2.08 (m, 1H).	3.74	408	B
97	5-[[5-[4-(3,3-difluoro-1-methyl-4-piperidyl)-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	N	(DMSO-d <sub>6</sub> ) δ 11.28 (br s, 1H), 10.82 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.71 (d, 1H), 7.01 (s, 1H), 6.99 (d, 2H), 4.08 (t, 1H), 3.92 (s, 3H), 3.77-3.69 (m, 1H), 3.54-3.49 (m, 2H), 3.25 (m, 1H), 2.89 (d, 3H), 2.45-2.34 (m, 1H) and 2.21-2.19 (m, 1H).	3.79	426	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
98	5-[[5-[4-(1-ethyl-3,3-difluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	N	(DMSO-d <sub>6</sub> ) δ 11.09 (br s, 1H), 10.84 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.71 (d, 1H), 7.00 (s, 1H), 6.99 (d, 2H), 4.06 (t, 1H), 3.92 (s, 3H), 3.71-3.43 (m, 4H), 3.27-3.25 (m, 2H), 2.44-2.38 (m, 1H), 2.22-2.18 (m, 1H) and 1.32 (t, 3H).	3.84	440	B
99	5-[[5-[4-[1-(2-hydroxyethyl)-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 10.82 (s, 1H), 10.32 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.65 (d, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 6.91 (s, 1H), 3.92 (s, 3H), 3.83-3.81 (m, 2H), 3.64-3.61 (m, 2H), 3.19-3.06 (m, 4H), 2.90-2.84 (m, 1H), 2.19-2.10 (m, 2H) and 2.02-1.99 (m, 2H).	3.70	420	B
100	5-[[5-[4-[[isopropyl(methyl)amino]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.84 (s, 1H), 10.72 (s, 1H), 8.68 (d, 1H), 8.55 (s, 1H), 7.73 (s, 1H), 7.66 (s, 1H), 7.28 (d, 1H), 7.01 (s, 1H), 4.36 (m, 1H), 4.21-4.19 (m, 1H), 3.95 (s, 3H), 3.56 (s, 1H), 2.54 (d, 3H) and 1.34 (d, 6H).	3.64	378	B
101	5-[[5-[2-methoxy-4-(pyrrolidin-1-yl)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 11.26 (s, 1H), 10.84 (s, 1H), 8.68 (d, 1H), 8.53 (s, 1H), 7.74 (d, 1H), 7.58 (s, 1H), 7.23 (d, 1H), 7.01 (s, 1H), 4.36 (d, 2H), 3.96 (s, 3H), 3.36-3.34 (m, 2H), 3.07-3.01 (m, 2H), 2.06-1.95 (m, 2H) and 1.92-1.89 (m, 2H).	3.63	376	B
102	5-[[5-[2-methoxy-4-(morpholinomethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 11.79 (s, 1H), 10.84 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.75 (d, 1H), 7.65 (s, 1H), 7.23 (d, 1H), 7.01 (s, 1H), 4.35 (d, 2H), 3.97 (s, 3H), 3.92-3.85 (m, 4H), 3.23 (d, 2H) and 3.11-3.08 (m, 2H).	3.54	392	B
103	5-[[5-[2-methoxy-4-[(2R)-1-methylpyrrolidin-2-yl]methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 12.68 (s, 1H), 10.78 (br s, 2H), 8.67 (s, 1H), 8.54 (s, 1H), 7.64 (d, 1H), 6.89 (s, 1H), 6.79 (s, 1H), 6.71 (dd, 1H), 4.39 (dd, 1H), 4.27 (dd, 1H), 3.86 (s, 3H), 3.85-3.79 (m, 1H), 3.60-3.59 (m, 1H), 3.14-3.10 (m, 1H), 2.96 (s, 3H), 2.33-2.23 (m, 1H), 2.08-1.91 (m, 2H) and 1.88-1.81 (m, 1H).	3.67	406	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
104	5-[[5-[2-methoxy-4-[(2S)-1-methylpyrrolidin-2-yl]methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.91 (s, 1H), 10.80 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.64 (d, 1H), 6.88 (s, 1H), 6.79 (d, 1H), 6.71 (cd, 1H), 4.46-4.38 (m, 2H), 3.91 (s, 3H), 3.83-3.79 (m, 1H), 3.60-3.57 (m, 1H), 3.14-3.09 (m, 1H), 2.95 (d, 3H), 2.30-2.25 (m, 1H), 2.08-1.94 (m, 2H) and 1.87-1.81 (m, 1H).	3.74	406	B
105	5-[[5-[2-methoxy-4-(oxazol-4-yl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	K	(DMSO-d <sub>6</sub> ) δ 12.49 (br s, 1H), 10.71 (s, 1H), 8.66 (s, 1H), 8.54 (s, 1H), 8.43 (s, 1H), 8.27 (s, 1H), 7.58 (d, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 6.75 (d, 1H), 5.09 (s, 2H) and 3.90 (s, 3H).	4.54	390	B
106	5-[[5-[4-[1-(2-fluoroethyl)-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	H	(DMSO-d <sub>6</sub> ) δ 11.14 (s, 1H), 10.83-10.81 (d, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.67 (d, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 6.91 (s, 1H), 4.96 (d, 2H), 3.92 (s, 3H), 3.60-3.49 (m, 4H), 3.17-3.15 (m, 2H), 2.88-2.84 (m, 1H) and 2.18-2.02 (m, 4H).	3.78	422	B
107	5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)methylamino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 10.83 (s, 1H), 10.56 (br s, 1H), 8.67 (d, 1H), 8.60 (s, 1H), 7.46 (d, 1H), 6.77 (s, 1H), 6.46 (s, 1H), 6.41 (d, 1H), 3.85 (s, 3H), 3.39 (d, 2H), 3.04 (d, 2H), 2.94-2.86 (m, 2H), 2.68 (dd, 3H), 1.98-1.94 (m, 3H) and 1.56-1.48 (m, 2H).	3.75	419	B
108	5-[[5-[4-[(1-ethyl-4-piperidyl)methylamino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 12.49 (s, 1H), 10.85 (s, 1H), 10.46 (br s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.46 (d, 1H), 6.77 (s, 1H), 6.48 (s, 1H), 6.42 (d, 1H), 3.86 (s, 3H), 3.46 (d, 2H), 3.17-3.14 (m, 2H), 3.05-3.01 (m, 2H), 2.87-2.79 (m, 2H), 1.99-1.96 (m, 2H), 1.89-1.84 (m, 1H), 1.61-1.52 (m, 2H) and 1.26 (t, 3H).	3.80	433	B
109	5-[[5-[4-[(1-isopropyl-4-piperidyl)methylamino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 12.59 (s, 1H), 10.89 (s, 1H), 10.38 (br s, 1H), 8.68 (s, 1H), 8.56 (s, 1H), 7.49 (d, 1H), 6.79 (s, 1H), 6.52 (s, 1H), 6.46 (d, 1H), 3.86 (s, 3H), 3.37-3.34 (m, 3H), 3.05 (d, 2H), 2.90-2.87 (m, 2H), 1.99-1.91 (m, 3H), 1.72-1.66 (m, 2H) and 1.27 (d, 6H).	3.78	447	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
110	5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)amino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 12.38 (s, 1H), 10.87 (s, 1H), 10.75 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 7.43 (d, 1H), 6.75 (s, 1H), 6.41 (s, 1H), 6.37 (d, 1H), 3.84 (s, 3H), 3.57 (t, 1H), 3.44 (d, 2H), 3.10-3.02 (m, 2H), 2.72 (d, 3H), 2.12 (d, 2H), 1.89 (d, 2H) and 1.83-1.77 (m, 2H).	3.66	405	B
111	5-[[5-[4-[(1-ethyl-4-piperidyl)amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 12.56 (s, 1H), 10.78 (s, 1H), 10.63 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.46 (d, 1H), 6.77 (s, 1H), 6.47 (s, 1H), 6.42 (d, 2H), 3.85 (s, 3H), 3.58 (t, 1H), 3.50 (d, 2H), 3.11-2.95 (m, 4H), 2.13 (d, 2H), 1.91-1.81 (m, 2H) and 1.29-1.26 (m, 3H).	3.67	419	B
112	5-[[5-[4-[(1-isopropyl-4-piperidyl)amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 12.38 (s, 1H), 10.73 (s, 1H), 10.16 (s, 1H), 8.66 (s, 1H), 8.55 (s, 1H), 7.42 (d, 1H), 6.75 (s, 1H), 6.40 (s, 1H), 6.36 (d, 1H), 3.85 (s, 3H), 3.60 (d, 1H) 3.46-3.35 (m, 1H), 3.40-3.37 (m, 2H), 3.24 (m, 1H), 2.14-2.11 (m, 2H), 1.93-1.81 (m, 2H) and 1.29 (d, 6H).	3.72	433	B
113	5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)oxymethyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.96 (br s, 1H), 10.86 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.68 (dd, 1H), 7.12-6.96 (m, 3H), 4.56 (d, 2H), 3.92 (d, 3H), 3.58-3.55 (m, 1H), 3.39 (d, 1H), 3.23 (d, 1H), 3.01 (d, 1H), 2.72-2.67 (m, 3H), 2.17 (d, 1H), 2.03 (br s, 2H) and 1.82-1.75 (m, 1H).	3.94	420	B
114	5-[[5-[4-[(1-ethyl-4-piperidyl)oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.81 (br s, 1H), 10.53 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.67 (dd, 1H), 7.12 (d, 1H), 7.04 (dd, 1H), 6.96 (s, 1H), 4.57 (d, 2H), 3.92 (s, 3H), 3.62-3.57 (m, 1H), 3.46 (d, 1H), 3.30 (d, 1H), 3.12-3.02 (m, 3H), 2.89 (q, 1H), 2.18 (d, 1H), 2.04 (br s, 2H), 1.85-1.76 (m, 1H) and 1.27-1.22 (m, 3H).	3.90	434	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
115	5-[[5-[4-[(1-isopropyl-4-piperidyl)oxymethyl]-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.81 (s, 1H), 10.46 (d, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.67 (dd, 1H), 7.12 (d, 1H), 7.03 (dd, 1H), 6.96 (s, 1H), 4.57 (d, 2H), 3.92 (s, 3H), 3.61 (m, 1H), 3.43-3.34 (m, 2H), 3.22 (d, 1H), 3.07-2.93 (m, 2H), 2.19-2.04 (m, 3H), 1.91-1.88 (m, 1H) and 1.29-1.24 (m, 6H).	3.95	448	B
116	5-[[5-(2-fluoro-6-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.52 (s, 1H), 10.82 (s, 1H), 9.50 (s, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 6.78 (s, 1H), 6.58 (d, 1H), 6.51 (s, 1H), 3.88 (s, 3H), 3.55 (br s, 4H) and 3.19 (br s, 4H).	3.73	395	B
117	5-[[5-[2-methoxy-4-[(2R)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	P	(DMSO-d <sub>6</sub> ) δ 11.44 (s, 1H), 10.81 (s, 1H), 8.67 (d, 1H), 8.53 (s, 1H), 7.73 (d, 1H), 7.13 (s, 1H), 7.05 (dd, 1H), 6.99 (s, 1H), 4.91 (d, 1H), 4.20 (dd, 1H), 4.06-4.02 (m, 1H), 3.94 (s, 3H), 3.67 (d, 1H), 3.45 (d, 1H), 3.16-3.11 (m, 2H) and 2.80 (d, 3H).	3.69	392	B
118	5-[[5-[2-methoxy-4-[(2R)-4-ethylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	P	(DMSO-d <sub>6</sub> ) δ 11.41 (s, 1H), 10.81 (s, 1H), 8.67 (d, 1H), 8.53 (s, 1H), 7.73 (d, 1H), 7.15 (s, 1H), 7.07 (d, 1H), 6.98 (s, 1H), 4.96 (d, 1H), 4.20 (dd, 1H), 4.09 (d, 1H), 3.94 (s, 3H), 3.68 (d, 1H), 3.50 (d, 1H), 3.19-3.05 (m, 4H) and 1.31 (t, 3H).	3.69	406	B
119	5-[[5-[2-methoxy-4-[(2S)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	P	(DMSO-d <sub>6</sub> ) δ 11.57 (s, 1H), 10.81 (s, 1H), 8.67 (d, 1H), 8.53 (s, 1H), 7.73 (d, 1H), 7.13 (d, 1H), 7.05 (d, 1H), 6.98 (s, 1H), 4.20 (dd, 1H), 4.04 (t, 1H), 3.94 (s, 3H), 3.66 (d, 1H), 3.45 (d, 1H), 3.19-3.08 (m, 2H) and 2.80 (d, 3H).	3.65	392	B
120	5-[[5-[2-methoxy-4-[(2S)-4-ethylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	P	(DMSO-d <sub>6</sub> ) δ 10.93 (s, 1H), 10.79 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.72 (d, 1H), 7.18 (s, 1H), 7.10 (d, 1H), 6.98 (s, 1H), 5.04 (d, 1H), 4.22-4.12 (m, 2H), 3.95 (s, 3H), 3.62-3.47 (m, 5H), 3.25-3.08 (m, 3H) and 1.34 (d, 3H).	3.68	406	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
121	5-[[5-(2,6-dimethoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.29 (s, 1H), 10.72 (s, 1H), 9.32 (s, 2H), 8.65 (s, 1H), 8.58 (s, 1H), 6.71 (s, 1H), 6.32 (s, 2H), 3.81 (s, 6H), 3.53-3.51 (m, 4H) and 3.22-3.17 (m, 4H).	3.61	407	B
122	5-[[5-[2,6-dimethoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.28 (s, 1H), 11.25 (s, 1H), 10.75 (s, 1H), 8.65 (s, 1H), 8.58 (s, 1H), 6.71 (s, 1H), 6.33 (s, 2H), 4.02 (d, 2H), 3.82 (s, 6H), 3.49 (d, 2H), 3.25-3.09 (m, 4H) and 2.81 (d, 3H).	3.57	421	B
123	5-[[5-[4-[(3R)-3-fluoropyrrolidin-1-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	Q	(DMSO-d <sub>6</sub> ) δ 11.85 (s, 1H), 11.51 (s, 1H), 10.84 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.75 (t, 1H), 7.59 (d, 1H), 7.27 (dd, 1H), 7.02 (s, 1H), 5.53-5.39 (m, 1H), 4.54-4.40 (m, 2H), 3.96 (s, 3H), 3.62-3.53 (m, 2H), 3.41-3.39 (m, 1H), 3.30-3.29 (m, 1H) and 2.33-2.22 (m, 2H).	3.56	394	B
124	5-[[5-[2-methoxy-4-[(3S)-3-methoxypyrrolidin-1-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	Q	(DMSO-d <sub>6</sub> ) δ 11.63 (s, 1H), 11.07 (s, 1H), 10.83 (s, 1H), 8.68 (d, 1H), 8.54 (s, 1H), 7.76-7.73 (t, 1H), 7.57 (d, 1H), 7.24 (t, 1H), 7.01 (s, 1H), 4.40-4.36 (m, 2H), 4.15-4.09 (m, 1H), 3.96 (s, 3H), 3.63-3.57 (m, 1H), 3.45-3.36 (m, 2H), 3.27 (d, 3H), 3.29-3.24 (m, 2H), 2.34-2.30 (m, 1H), 2.13-2.11 (m, 1H) and 2.05-1.99 (m, 1H).	3.77	406	B
125	5-[[5-[2-methoxy-4-[(3R)-3-methoxypyrrolidin-1-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	Q	(DMSO-d <sub>6</sub> ) δ 11.56 (s, 1H), 11.01 (s, 1H), 10.83 (s, 1H), 8.68 (s, 1H), 8.53 (s, 1H), 7.76-7.73 (t, 1H), 7.56 (d, 1H), 7.24 (t, 1H), 7.02 (s, 1H), 4.40-4.37 (m, 2H), 4.15-4.11 (m, 1H), 3.95 (s, 3H), 3.63-3.60 (m, 1H), 3.58-3.46 (m, 1H), 3.44-3.41 (d, 3H), 2.39-2.17 (m, 1H) and 2.13-2.01 (m, 2H).	3.72	406	B
126	5-[[5-[4-[(2R)-1-ethylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.80 (s, 1H), 10.63 (br s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.65-7.63 (d, 1H), 6.88 (s, 1H), 6.77 (d, 1H), 6.71-6.68 (dd, 1H), 4.49-4.36 (m, 2H), 3.91 (s, 3H), 3.20-3.10 (m, 2H), 2.28-2.21 (m, 2H), 2.08-1.93 (m, 2H), 1.88-1.82 (m, 1H) and 1.31 (t, 3H).	3.78	420	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
127	5-[[5-[4-[[[(2R)-1-isopropylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.77 (s, 1H), 10.52 (br s, 2H), 8.67 (s, 1H), 8.54 (s, 1H), 7.64 (d, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 6.68 (d, 1H), 4.47 (t, 1H), 4.34 (d, 1H), 4.05 (br s, 1H), 3.91 (s, 3H), 3.77 (s, 1H), 3.43-3.40 (m, 1H), 3.28-3.26 (m, 1H), 2.23-2.18 (m, 1H), 1.99-1.87 (m, 3H), 1.36 (d, 3H) and 1.29 (d, 3H).	3.86	434	B
128	5-[[5-[4-[[[(2S)-1-ethylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.82 (s, 2H), 8.67 (s, 1H), 8.55 (s, 1H), 7.64 (d, 1H), 6.88 (s, 1H), 6.77 (d, 1H), 6.70 (dd, 1H), 4.51 (dd, 1H), 4.38 (dd, 1H), 3.91 (s, 3H), 3.87-3.82 (m, 1H), 3.62-3.52 (m, 2H), 3.19-3.11 (m, 2H), 2.28-2.23 (m, 1H), 2.05-1.95 (m, 2H), 1.86-1.81 (m, 1H) and 1.32-1.29 (t, 3H).	3.76	420	B
129	5-[[5-[4-[[[(2S)-1-isopropylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.78 (s, 1H), 10.60 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.64 (d, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 6.68 (d, 1H), 4.51-4.46 (m, 1H), 4.36-4.34 (m, 1H), 4.04 (s, 1H), 3.91 (s, 3H), 3.77 (s, 1H), 3.45-3.37 (m, 1H), 3.27-3.25 (m, 1H), 2.23-2.18 (m, 1H), 1.98 (m, 2H), 1.91-1.85 (m, 1H), 1.36 (d, 3H) and 1.29 (d, 3H).	3.88	434	B
130	5-[[5-[4-[(cyclopropylmethylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.84 (s, 1H), 9.50 (s, 2H), 8.67 (d, 1H), 8.53 (s, 1H), 7.74 (d, 1H), 7.53 (d, 1H), 7.20 (dd, 1H), 7.01 (s, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 2.81 (q, 2H), 1.17-1.13 (m, 1H), 0.61-0.56 (m, 2H) and 0.40-0.37 (m, 2H).	3.81	376	B
131	5-[[5-[2-methoxy-4-[[[(3R)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.83 (s, 1H), 9.72 (s, 2H), 8.67 (d, 1H), 8.53 (s, 1H), 7.74 (d, 1H), 7.56 (s, 1H), 7.23 (d, 1H), 7.01 (s, 1H), 4.19 (m, 2H), 4.00-3.91 (m, 5H), 3.82-3.81 (m, 2H), 3.70-3.65 (m, 1H) and 2.24-2.13 (m, 2H).	3.64	392	B



Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
132	5-[[5-[2-methoxy-4-[[[(3S)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.85 (s, 1H), 9.84 (br s, 2H), 8.67 (d, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.59 (d, 1H), 7.24 (d, 1H), 7.01 (s, 1H), 4.19-4.18 (m, 2H), 3.99-3.91 (m, 5H), 3.84-3.81 (m, 2H), 3.70-3.64 (m, 1H) and 2.24-2.15 (m, 2H).	3.64	392	B
133	5-[[5-[4-[(3R)-4-isopropyl-3-methylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 10.91 (s, 1H), 10.76 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.56 (d, 1H), 6.84 (s, 1H), 6.70-6.66 (m, 2H), 4.04-3.85 (m, 3H), 3.92 (s, 3H), 3.50-3.27 (m, 3H), 3.19-3.04 (m, 2H), 1.41 (t, 6H) and 1.18 (d, 3H).	3.77	433	B
134	5-[[5-[4-[(1-ethyl-4-piperidyl)oxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.77 (s, 1H), 10.67 (br s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.61 (dd, 1H), 6.86 (s, 1H), 6.79-6.71 (m, 2H), 4.88 (br s, 1H), 3.89 (s, 3H), 3.54 (d, 1H), 3.37 (d, 1H), 3.17-3.02 (m, 4H), 2.27-2.16 (m, 2H), 2.09-2.05 (m, 1H), 1.98-1.95 (m, 1H) and 1.28 (t, 3H).	3.84	420	B
135	5-[[5-[4-[(1-isopropyl-4-piperidyl)oxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	K	(DMSO-d <sub>6</sub> ) δ 10.76 (s, 1H), 10.03 (br s, 1H), 8.67 (d, 1H), 8.53 (s, 1H), 7.62-7.59 (m, 1H), 6.86 (s, 1H), 6.79-6.71 (m, 2H), 4.88 (br s, 1H), 4.74-4.68 (m, 1H), 3.90 (s, 3H), 3.53-3.43 (d, 2H), 3.31 (d, 1H), 3.19-3.08 (m, 2H), 2.29-2.18 (m, 2H), 2.11 (d, 1H), 2.01-1.92 (m, 1H) and 1.29 (d, 6H).	3.91	434	B
136	5-[[5-[4-(4-ethylpiperazin-1-yl)-2-fluoro-6-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 11.13 (s, 1H), 10.78 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 6.77 (s, 1H), 6.61 (dd, 1H), 6.54 (s, 1H), 4.04 (d, 2H), 3.90 (s, 3H), 3.54 (d, 2H), 3.28 (t, 2H), 3.20-3.13 (m, 2H), 3.10-3.02 (m, 2H) and 1.30 (t, 3H).	3.66	423	B
137	5-[[5-[4-(4-isopropylpiperazin-1-yl)-2-fluoro-6-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 10.98 (s, 1H), 10.79 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 6.78 (s, 1H), 6.61 (dd, 1H), 6.54 (s, 1H), 4.04 (d, 2H), 3.90 (s, 3H), 3.54-3.46 (m, 3H), 3.33 (t, 2H), 3.15-3.07 (m, 2H), 3.10-3.02 (m, 2H) and 1.33 (d, 6H).	3.77	437	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
138	5-[[5-[4-[[[(3S)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	R	(DMSO-d <sub>6</sub> ) δ 11.32 (s, 1H), 10.82 (s, 1H), 8.67 (d, 1H), 8.57 (s, 1H), 7.68 (dd, 1H), 7.19 (d, 1H), 7.05 (t, 1H), 6.97 (s, 1H), 4.55-4.53 (m, 2H), 4.38-4.30 (m, 1H), 3.93 (d, 3H), 3.65-3.60 (m, 1H), 3.57-3.43 (m, 1H), 3.18-3.13 (m, 4H), 2.31-2.23 (m, 1H), 2.05-2.01 (m, 1H) and 1.28-1.24 (m, 3H).	3.84	420	B
139	5-[[5-[4-[[[(3S)-1-isopropylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	R	(DMSO-d <sub>6</sub> ) δ 11.15 (s, 1H), 10.81 (s, 1H), 10.52 (s, 1H), 8.68 (s, 1H), 8.53 (s, 1H), 7.68 (dd, 1H), 7.15 (d, 1H), 7.07-7.02 (m, 1H), 6.97 (s, 1H), 4.60-4.52 (m, 2H), 4.34-4.30 (m, 1H), 3.93 (d, 3H), 3.67-3.37 (m, 3H), 3.25-3.14 (m, 2H), 2.30-2.18 (m, 1H), 2.08-1.95 (m, 1H) and 1.30-1.28 (m, 6H).	3.89	434	B
140	5-[[5-[4-[[[(3R)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	R	(DMSO-d <sub>6</sub> ) δ 12.91 (s, 1H), 10.82 (s, 1H), 8.68 (s, 1H), 8.54 (s, 1H), 7.68 (d, 1H), 7.16 (d, 1H), 7.05 (t, 1H), 6.97 (s, 1H), 4.58-4.53 (m, 2H), 4.35-4.31 (m, 1H), 3.93 (d, 3H), 3.70-3.67 (m, 1H), 3.59-3.54 (m, 1H), 3.20-3.09 (m, 4H), 2.34-2.31 (m, 1H), 2.07-2.02 (m, 1H) and 1.27-1.24 (m, 3H).	3.84	420	B
141	5-[[5-[4-[[[(3R)-1-isopropylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	R	(DMSO-d <sub>6</sub> ) δ 11.39 (d, 1H), 10.83 (s, 1H), 10.78 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.68 (d, 1H), 7.16 (d, 1H), 7.07-7.02 (m, 1H), 6.96 (s, 1H), 4.56-4.51 (m, 2H), 4.33-4.30 (m, 1H), 3.92 (d, 3H), 3.68-3.35 (m, 3H), 3.27-3.14 (m, 2H), 2.29-2.17 (m, 1H), 2.07-1.96 (m, 1H) and 1.31-1.28 (m, 6H).	3.89	434	B
142	5-[[5-[4-(4-isobutylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 10.87 (s, 1H), 10.79 (s, 1H), 8.67 (d, 1H), 8.56 (s, 1H), 7.56 (d, 1H), 6.84 (s, 1H), 6.69 (s, 1H), 6.66 (d, 1H), 3.91 (br s, 5H), 3.56-3.42 (m, 4H), 3.15-3.08 (m, 2H), 2.99 (t, 2H), 2.19-2.12 (m, 1H) and 1.03 (d, 6H).	3.88	433	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
143	5-[[5-[4-[(1-ethyl-4-piperidyl)methyl]-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	S	(DMSO-d <sub>6</sub> ) δ 10.81 (s, 1H), 10.29 (s, 1H), 8.67 (d, 1H), 8.55 (s, 1H), 7.61 (d, 1H), 7.00-6.99 (m, 1H), 6.93 (s, 1H), 6.90-6.89 (m, 1H), 3.90 (s, 3H), 3.42-3.39 (m, 2H), 3.04-2.98 (m, 2H), 2.83-2.72 (m, 2H), 2.58-2.56 (d, 2H), 1.82-1.81 (m, 1H), 1.78-1.75 (m, 2H), 1.60-1.51 (m, 2H) and 1.25-1.21 (m, 3H).	3.95	418	B
144	5-[[5-[4-[(1-isopropyl-4-piperidyl)methyl]-2-methoxyphenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	S	(DMSO-d <sub>6</sub> ) δ 10.79 (s, 1H), 10.16 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.61 (d, 1H), 6.98 (s, 1H), 6.93 (s, 1H), 6.88-6.86 (m, 1H), 3.91 (s, 3H), 3.39-3.34 (m, 1H), 3.31-3.28 (m, 2H), 2.91-2.83 (m, 2H), 2.57 (d, 2H), 1.86-1.84 (m, 1H), 1.78-1.75 (m, 2H), 1.69-1.63 (m, 2H) and 1.25-1.24 (m, 6H).	4.02	432	B
145	5-[[5-[4-[(1-ethyl-4-piperidyl)methyl-methyl-amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 10.77 (s, 1H), 10.31 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.49 (d, 1H), 6.77 (s, 1H), 6.40 (d, 2H), 3.90 (s, 3H), 3.44 (d, 2H), 3.33 (d, 2H), 3.02-2.97 (m, 5H), 2.80 (q, 2H), 1.98 (br s, 1H), 1.82 (d, 2H), 1.63-1.54 (q, 2H) and 1.23 (t, 3H).	4.02	447	B
146	5-[[5-[4-[(isobutylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	F	(DMSO-d <sub>6</sub> ) δ 10.84 (s, 1H), 9.41 (s, 2H), 8.67 (d, 1H), 8.54 (s, 1H), 7.74 (d, 1H), 7.59 (s, 1H), 7.23 (d, 1H), 7.00 (s, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 2.71 (q, 2H), 2.11-2.04 (m, 1H) and 0.95 (d, 6H).	3.90	378	B
147	5-[[5-[4-[(2R)-4-isopropylmorpholin-2-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	P	(DMSO-d <sub>6</sub> ) δ 11.36 (s, 1H), 10.80 (s, 1H), 8.67 (d, 1H), 8.53 (s, 1H), 7.73 (d, 1H), 7.17 (s, 1H), 7.09 (d, 1H), 6.98 (s, 1H), 5.05 (d, 1H), 4.22-4.14 (m, 2H), 3.95 (s, 3H), 3.60-3.39 (m, 3H), 3.17-3.02 (m, 2H) and 1.34 (d, 6H).	3.76	420	B
148	5-[[5-[4-[(1-isopropyl-4-piperidyl)methyl-methyl-amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 10.76 (s, 1H), 10.17 (s, 1H), 8.67 (s, 1H), 8.56 (s, 1H), 7.49 (d, 1H), 6.77 (s, 1H), 6.40 (d, 2H), 3.91 (s, 3H), 3.39-3.32 (m, 5H), 3.02 (s, 3H), 2.92-2.84 (m, 2H), 2.02-1.98 (m, 1H), 1.83-1.80 (m, 2H), 1.73-1.67 (m, 2H) and 1.24 (d, 6H).	4.04	461	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
149	5-[[5-[4-[(2R)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	T	(DMSO-d <sub>6</sub> ) δ 10.79 (s, 1H), 10.72 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.65 (d, 1H), 7.17 (d, 1H), 7.01 (dd, 1H), 6.95 (s, 1H), 3.93 (s, 3H), 3.63-3.58 (m, 2H), 3.39-3.30 (m, 2H), 3.09-3.04 (m, 1H), 3.02-2.93 (m, 2H), 2.01-1.90 (m, 3H), 1.78-1.72 (m, 1H) and 1.27 (t, 3H).	3.78	404	B
150	5-[[5-[4-[(2S)-4-isopropylmorpholin-2-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	P	(DMSO-d <sub>6</sub> ) δ 12.74 (br s, 1H), 10.99 (s, 1H), 10.80 (s, 1H), 8.68 (d, 1H), 8.52 (s, 1H), 7.72 (d, 1H), 7.17 (s, 1H), 7.09 (d, 1H), 6.98 (s, 1H), 5.00 (d, 1H), 4.22 (dd, 1H), 4.12 (td, 1H), 3.95 (s, 3H), 3.58 (d, 1H), 3.50 (q, 1H), 3.43 (d, 1H), 3.18-3.03 (m, 2H) and 1.33 (d, 6H).	3.75	420	B
151	5-[[5-[4-[(2R)-1-isopropylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	T	(DMSO-d <sub>6</sub> ) δ 10.79 (s, 1H), 10.58 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.65 (d, 1H), 7.16 (s, 1H), 7.01 (d, 1H), 6.95 (s, 1H), 3.93 (s, 3H), 3.78 (br s, 1H), 3.55 (br s, 1H), 3.39-3.31 (m, 2H), 3.20 (br s, 1H), 3.02-2.99 (m, 1H), 1.94 (br s, 3H), 1.75 (br s, 1H), 1.35 (d, 3H) and 1.24 (d, 3H).	3.84	418	B
152	5-[[5-[4-[(2S)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	T	(DMSO-d <sub>6</sub> ) δ 10.79 (s, 1H), 10.68 (s, 1H), 8.67 (d, 1H), 8.54 (s, 1H), 7.65 (d, 1H), 7.17 (s, 1H), 7.01 (d, 1H), 6.95 (s, 1H), 3.93 (s, 3H), 3.63-3.57 (m, 2H), 3.39-3.31 (m, 2H), 3.09-2.93 (m, 3H), 1.99-1.91 (m, 3H), 1.78-1.72 (m, 1H) and 1.28 (t, 3H).	3.76	404	B
153	5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	(DMSO-d <sub>6</sub> ) δ 12.98 (s, 1H), 10.84 (s, 1H), 9.32 (s, 2H), 8.66 (d, 1H), 8.53 (s, 1H), 7.74 (d, 1H), 7.16-7.13 (m, 1H), 7.03 (s, 1H), 6.83 (s, 1H), 3.57-3.51 (m, 4H) and 3.22-3.17 (m, 4H).	3.92	431	B
154	5-[[5-[4-[(2S)-1-isopropylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	T	(DMSO-d <sub>6</sub> ) δ 10.78 (s, 1H), 10.56 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.65 (d, 1H), 7.17 (s, 1H), 7.02 (d, 1H), 6.95 (s, 1H), 3.94 (s, 3H), 3.79 (br s, 1H), 3.36-3.30 (m, 2H), 3.22-3.17 (m, 1H), 3.02-2.97 (m, 1H), 1.96-1.86 (m, 3H), 1.80-1.75 (m, 1H), 1.35 (d, 3H) and 1.25 (d, 3H).	3.81	418	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
155	5-[5-[4-[(3S)-1-isopropylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 11.33 (d, 1H), 10.76 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 7.44 (d, 1H), 6.75 (s, 1H), 6.34 (s, 1H), 6.30 (d, 1H), 4.30-4.20 (m, 1H), 3.85 (d, 3H), 3.60-3.59 (m, 1H), 3.50-3.40 (m, 2H), 3.32-3.25 (m, 1H), 3.17-2.91 (m, 1H), 2.46-2.42 (m, 1H), 2.27-2.22 (m, 1H), 1.99-1.89 (m, 1H) and 1.31 (d, 6H).	3.73	419	B
156	5-[5-[4-[(3R)-1-isopropylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 11.15 (br s, 1H), 11.00 (br s, 1H), 10.72 (s, 1H), 8.66 (d, 1H), 8.56 (br s, 1H), 7.44 (d, 1H), 6.75 (s, 1H), 6.33 (s, 1H), 6.29 (dd, 1H), 4.32-4.17 (m, 1H), 3.86 (s, 3H), 3.65-3.37 (m, 3H), 3.35-3.23 (m, 1H), 3.21-3.11 (m, 1H), 2.97-2.88 (m, 1H), 2.30-2.20 (m, 1H) and 1.31 (d, 6H).	3.78	419	B
157	5-[5-[4-[(3R)-1-ethylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	ND	3.71	405	B
158	5-[5-[4-[(3S)-1-ethylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	O	(DMSO-d <sub>6</sub> ) δ 11.08 (br s, 1H), 10.98 (br s, 1H), 10.72 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 7.44 (d, 1H), 6.75 (s, 1H), 6.33 (s, 1H), 6.29 (d, 1H), 4.38-4.17 (m, 2H), 3.94-3.86 (m, 1H), 3.85 (s, 3H), 3.61-3.52 (m, 1H), 3.42-3.33 (m, 1H), 3.28-3.15 (m, 2H), 3.14-3.03 (m, 1H), 2.92-2.85 (m, 1H), 2.32-2.20 (m, 1H), 2.03-1.87 (m, 2H) and 1.26 (t, 3H).	3.66	405	B
159	5-[5-[2-methoxy-4-[(3S)-3-methylpiperazin-1-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	ND	3.68	391	B
160	5-[5-[4-[(3R)-3-ethylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	ND	3.83	405	B

Ex. No.	Name	Synthetic Method	<sup>1</sup> H NMR	LC (RT)	MS(MH <sup>+</sup> )	LCMS Method
161	5-[[5-[4-[(3S)-3-isopropylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	ND	3.97	419	B
162	5-[[5-[4-[(3R)-3-isopropylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	ND	3.94	419	B
163	5-[[5-[4-(3,3-dimethylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride	I	ND	3.85	405	B

ND = Not determined

Synthetic Route A

(Illustrated with reference to Example 1:

Example 1

5 5-[5-(4-Benzylamino-2,6-dimethoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile)

1A. N-(4-Acetyl-3,5-dimethoxy-phenyl)-acetamide

AlCl<sub>3</sub> (36.0 g, 27.5 mmol) was added in portions to a stirred solution of 3,5-dimethoxy-phenylamine (12.0 g, 78.4 mmol) and Ac<sub>2</sub>O (20.0 g, 19.6 mmol) in DCM (120 mL) at 0°C. The mixture was stirred for 15 minutes then allowed to warm to room  
10 temperature and stirring continued for a further one hour. The reaction mixture was poured onto ice and the resulting precipitate collected by filtration. The collected solid was dried under reduced pressure to give the title compound (5.0 g, 27%) as a white solid.

1B. 1-(4-Amino-2,6-dimethoxy-phenyl)-ethanone

15 A mixture of N-(4-acetyl-3,5-dimethoxy-phenyl)-acetamide (5.0 g, 21.1 mmol) in MeOH (50 mL) and 5N aq. NaOH (50 mL) was heated to reflux for 4 hours. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was partitioned between water (100 mL) and EtOAc (50 mL) then the separated aqueous phase was extracted with EtOAc (3 x 50 mL). The combined  
20 organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title compound (3.8 g, 92%).

1C. (4-Acetyl-3,5-dimethoxy-phenyl)-carbamic acid tert-butyl ester

Boc<sub>2</sub>O (6.37 g, 29.2 mmol) was added to a stirred solution of 1-(4-amino-2,6-dimethoxy-phenyl)-ethanone (6.37 g, 29.2 mmol) and guanidine hydrochloride (1.85 g,  
25 19.5 mmol) in EtOH (38 mL). The mixture was heated to reflux for 12 hours and then allowed to cool to room temperature. DCM (200 mL) was added then the mixture washed with water (2 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-10% EtOAc/hexanes as the eluent to give the title compound  
30 (3.5 g, 61%).

1D. (4-Acetyl-3,5-dimethoxy-phenyl)-benzyl-carbamic acid tert-butyl ester

NaH (60% in mineral oil, 0.57 g, 14.2 mmol) was added in portions to a stirred solution of (4-acetyl-3,5-dimethoxy-phenyl)-carbamic acid tert-butyl ester (3.5 g, 11.9 mmol) in THF (18 mL) at 0°C and the resulting mixture stirred for 30 minutes. Benzyl bromide  
5 (3.04 g, 17.8 mmol) was added dropwise over 10 minutes then the mixture was heated to 70°C for 3 hours. The solution was allowed to cool to room temperature then water (40 mL) was carefully added and the mixture extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral  
10 silica gel (60-120 mesh size) using 0-5% EtOAc/hexanes as the eluent to give the title compound (3.0 g, 66%).

1E. Benzyl-[4-(3,3-bis-methylsulfanyl-acryloyl)-3,5-dimethoxy-phenyl]-carbamic acid tert-butyl ester

A solution of (4-acetyl-3,5-dimethoxy-phenyl)-benzyl-carbamic acid tert-butyl ester (3.0  
15 g, 7.8 mmol) in DMSO (15 mL) was added slowly to a stirred slurry of NaH (0.78 g, 19.5 mmol) in DMSO (15 mL) maintaining the internal temperature at 10-15°C. After stirring at 10°C for 10 minutes, carbon disulfide (1.18 g, 15.6 mmol) was added and stirring continued for a further 10 minutes. Methyl iodide (2.19 g, 15.6 mmol) was  
20 added at 10°C then the mixture was allowed to warm to room temperature and stirring continued for 10 minutes. The reaction mixture was carefully poured onto ice then extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120  
25 mesh size) using 0-17% EtOAc/hexanes as the eluent to give the title compound (1.7 g, 45%).

1F. Benzyl-[4-[(Z)-3-(5-cyano-pyrazin-2-ylamino)-3-methylsulfanyl-acryloyl]-3,5-dimethoxy-phenyl]-carbamic acid tert-butyl ester

A solution of 2-amino-5-cyanopyrazine (1.25 g, 5.2 mmol) in THF (10 mL) was added slowly to a stirred slurry of NaH (60% in mineral oil) (0.21 g, 5.2 mmol) in THF (17 mL)  
30 at 0°C. The mixture was stirred for 30 minutes at 0°C then a solution of benzyl-[4-(3,3-bis-methylsulfanyl-acryloyl)-3,5-dimethoxy-phenyl]-carbamic acid tert-butyl ester (1.7 g, 3.48 mmol) in THF (7 mL) was added dropwise and the reaction mixture was heated to 80°C for 12 hours. The solution was allowed to cool to room temperature then



water (40 mL) was carefully added and the mixture extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh size) using 0-70% EtOAc/hexanes as the eluent to give the  
5 title compound (0.9 g, 46%).

1G. Benzyl-{4-[5-(5-cyano-pyrazin-2-ylamino)-2H-pyrazol-3-yl]-3,5-dimethoxy-phenyl}-  
carbamic acid tert-butyl ester

A stirred solution of hydrazine monohydrate (0.077 g, 2.40 mmol), benzyl-{4-[(Z)-3-(5-  
10 cyano-pyrazin-2-ylamino)-3-methylsulfanyl-acryloyl]-3,5-dimethoxy-phenyl}-carbamic  
acid tert-butyl ester (0.90 g, 1.6 mmol) and acetic acid (2 drops) in EtOH (0.7 mL) was  
heated to 60°C for 15 minutes. The mixture was allowed to cool to room temperature  
and the precipitated solid collected by filtration. The solid was washed with Et<sub>2</sub>O (2 x 5  
mL) and dried under reduced pressure to give the title compound (0.10 g, 12%).

15 1H. 5-[5-(4-Benzylamino-2,6-dimethoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-  
carbonitrile

Trifluoroacetic acid (1 mL) was added dropwise to a stirred solution of benzyl-{4-[5-(5-  
20 cyano-pyrazin-2-ylamino)-2H-pyrazol-3-yl]-3,5-dimethoxy-phenyl}-carbamic acid tert-  
butyl ester (0.10 g, 0.19 mmol) in DCM (2 mL) at room temperature. The mixture was  
stirred at room temperature for 3 hours then heated to 40°C for a further 2 hours. The  
solvents were evaporated under reduced pressure to leave a residue which was  
purified by preparative HPLC to give the title compound (0.025 g, 34%) as an off-white  
solid.

Synthetic Route B

(Illustrated with reference to Example 3:

25 Example 3

5-[5-[4-(Benzylamino-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-  
carbonitrile hydrochloride)

3A. 3-Methoxy-4-nitro-benzaldehyde

A mixture of 2-hydroxy-4-nitro-benzaldehyde (8.0 g, 47.9 mmol), methyl iodide (10.2 g,  
30 71.9 mmol) and potassium carbonate (6.61 g, 47.9 mmol) in DMF (80 mL) was stirred

at 60°C for 3 hours. The cooled reaction mixture was diluted with EtOAc (100 mL), washed with water (200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title compound (6.5 g, 75%) which was used without further purification.

### 3B. 4-Amino-3-methoxy-benzaldehyde

5 A stirred mixture of 3-methoxy-4-nitro-benzaldehyde (6.5 g, 35.9 mmol), iron powder (4.51 g, 80.8 mmol) and NH<sub>4</sub>Cl (3.87 g, 71.8 mmol) in MeOH (50 mL) and water (50 mL) was heated to reflux for 3 hours. The cooled reaction mixture was filtered through a pad of celite and diluted with EtOAc (100 ml). The separated organic phase was washed with water (2 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced  
10 pressure to give the title compound (4.5 g, 83%) which was used without further purification.

### 3C. 4-Bromo-3-methoxy-benzaldehyde

A mixture of 4-amino-3-methoxy-benzaldehyde (4.5 g, 29.8 mmol), n-butyl nitrite (4.6 g, 35.8 mmol) and copper bromide (6.83 g, 47.7 mmol) in MeCN (45 mL) was stirred at  
15 room temperature for 12 hours. The reaction mixture was diluted with EtOAc (100 mL), washed with water (200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-70% EtOAc/hexanes as the eluent to give the title compound (4.2 g, 66%).

### 20 3D. Benzyl-(4-bromo-3-methoxy-benzyl)-amine

NaBH(OAc)<sub>3</sub> (6.24 g, 29.4 mmol) was added in portions to a stirred solution of 4-bromo-3-methoxy-benzaldehyde (4.2 g, 19.6 mmol), benzylamine (2.51 g, 23.6 mmol) and acetic acid (2.35 g, 39.3 mmol) in DCM (42 mL) at room temperature. The resulting solution was stirred for 12 hours then diluted with EtOAc (40 mL), washed  
25 with water (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-2% MeOH/DCM as the eluent to give the title compound (3.8 g, 64%).

### 3E. 1-[4-(Benzylamino-methyl)-2-methoxy-phenyl]-ethanone

A stirred solution of benzyl-(4-bromo-3-methoxy-benzyl)-amine (3.8 g, 12.5 mmol) and tributyl(1-ethoxyvinyl)tin (5.39 g, 15.0 mmol) in 1,4-dioxane (40 mL) was degassed with nitrogen for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.72 g, 0.62 mmol) was added to the mixture and the resulting solution heated to 130°C for 16  
30

hours. The mixture was allowed to cool to room temperature then diluted with EtOAc (60 mL), washed with water (40 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-2% MeOH/DCM as the eluent to give the title  
5 compound (1.5 g, 45%).

3F. (4-Acetyl-3-methoxy-benzyl)-benzyl-carbamic acid tert-butyl ester

Boc<sub>2</sub>O (1.45 g, 6.69 mmol) was added to a stirred solution of 1-[4-(benzylamino-methyl)-2-methoxy-phenyl]-ethanone (1.5 g, 5.57 mmol) and Et<sub>3</sub>N (1.69 g, 16.7 mmol) in DCM (5 mL) and the resulting mixture stirred at room temperature for 3 hours. The  
10 mixture was diluted with DCM (20 mL), washed with water (2 x 20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-2% MeOH/DCM as the eluent to give the title compound (1.5 g, 73%).

3G. Benzyl-[4-(3,3-bis-methylsulfanyl-acryloyl)-3-methoxy-benzyl]-carbamic acid tert-butyl ester  
15

A solution of (4-acetyl-3-methoxy-benzyl)-benzyl-carbamic acid tert-butyl ester (1.5 g, 4.1 mmol) in DMSO (15 mL) was added slowly to a stirred slurry of NaH (60% in mineral oil, 0.41 g, 10.2 mmol) in DMSO (20 mL) maintaining the internal temperature at 10-15°C. After stirring at 10°C for 10 minutes, carbon disulfide (0.62 g, 8.1 mmol)  
20 was added and stirring continued for a further 10 minutes. Methyl iodide (1.15 g, 8.1 mmol) was added at 10°C then the mixture was allowed to warm to room temperature and stirring continued for 10 minutes. The reaction mixture was carefully poured onto ice then extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to  
25 leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-30% EtOAc/hexanes as the eluent to give the title compound (0.75 g, 39%).

3H. Benzyl-[4-[(Z)-3-(5-cyano-pyrazin-2-ylamino)-3-methylsulfanyl-acryloyl]-3-methoxy-benzyl]-carbamic acid tert-butyl ester

30 A solution of 2-amino-5-cyanopyrazine (0.29 g, 2.4 mmol) in THF (8 mL) was added slowly to a stirred slurry of NaH (60% in mineral oil, 0.095 g, 2.4 mmol) in THF (8 mL) at 0°C. The mixture was stirred for 30 minutes at 0°C then a solution of benzyl-[4-(3,3-bis-methylsulfanyl-acryloyl)-3-methoxy-benzyl]-carbamic acid tert-butyl ester (0.75 g,

1.58 mmol) in THF (7 mL) was added dropwise and the reaction mixture was then heated to 80°C for 12 hours. The solution was allowed to cool to room temperature then water (40 mL) was carefully added and the mixture extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-80% EtOAc/hexanes as the eluent to give the title compound (0.28 g, 32%).

3I. Benzyl-{4-[5-(5-cyano-pyrazin-2-ylamino)-2H-pyrazol-3-yl]-3-methoxy-benzyl}-carbamic acid tert-butyl ester

10 A stirred solution of hydrazine monohydrate (0.024 g, 0.77 mmol), benzyl-{4-[(Z)-3-(5-cyano-pyrazin-2-ylamino)-3-methylsulfanyl-acryloyl]-3-methoxy-benzyl}-carbamic acid tert-butyl ester (0.28 g, 0.51 mmol) and acetic acid (2 drops) in EtOH (0.7 mL) was heated to 60°C for 15 minutes. The solution was allowed to cool to room temperature then water (10 mL) was added and the mixture extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh) using 0-10% MeOH/DCM as the eluent to give the title compound (0.035 g, 13%).

20 3J. 5-{5-[4-(Benzylamino-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile hydrochloride

A 4N solution of HCl in Et<sub>2</sub>O (1 mL) was added dropwise to a stirred solution of benzyl-{4-[5-(5-cyano-pyrazin-2-ylamino)-2H-pyrazol-3-yl]-3-methoxy-benzyl}-carbamic acid tert-butyl ester (0.035 g, 0.06 mmol) in DCM (2 mL) at room temperature. The mixture was stirred for 18 hours at room temperature and then the solvents were evaporated under reduced pressure to leave a solid which was washed with Et<sub>2</sub>O (2 x 5 mL) and dried to give the title compound (0.012 g, 43%) as a white solid.

Synthetic Route C

(Illustrated with reference to Example 4:

Example 4

30 5-{5-[4-(2-Benzylamino-ethyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile hydrochloride)

4A. 1-Bromo-2-methoxy-4-((E)-2-nitro-vinyl)-benzene

A stirred solution of 4-bromo-3-methoxy-benzaldehyde (5.0 g, 23.3 mmol), ammonium acetate (2.4 g, 30.2 mmol) and nitromethane (6.3 mL, 116 mmol) in glacial acetic acid (20 mL) was heated to 80°C for 12 hours. The mixture was allowed to cool to room temperature then poured into water (100 mL). The resulting solid was collected by filtration and then dissolved in DCM (80 mL). The solution was washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using DCM as the eluent to give the title compound (4.2 g, 40%).

10 4B. 2-(4-Bromo-3-methoxy-phenyl)-ethylamine

Sodium borohydride (2.9 g, 77.5 mmol) was added in portions to a stirred solution of 1-bromo-2-methoxy-4-((E)-2-nitro-vinyl)-benzene (4.0 g, 15.5 mmol) in MeOH (50 mL) at 0°C. The resulting solution was allowed to warm to room temperature and stirring continued for one hour. Water (2 mL) was carefully added followed by the careful addition of 50% aqueous acetic acid solution (5 mL) whilst maintaining the temperature below 30°C. Zinc powder (5.1 g, 77.5 mmol) and saturated aqueous NH<sub>4</sub>Cl solution (20 mL) were added and the resulting mixture heated to 50°C for one hour. The cooled mixture was diluted with DCM (50 mL) and filtered through a cotton wool plug. Water (40 mL) was added to the filtrate and the separated aqueous phase was extracted with DCM (2 x 50 mL). The combined organic extracts were washed with brine (20 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh) using 8-10% MeOH/DCM as the eluent to give the title compound (2.0 g, 56%).

4C. Benzyl-[2-(4-bromo-3-methoxy-phenyl)-ethyl]-amine

25 Benzaldehyde (0.83 g, 7.9 mmol) was added dropwise to a stirred solution of 2-(4-bromo-3-methoxy-phenyl)-ethylamine (2.0 g, 8.7 mmol) and glacial acetic acid (0.94 mL, 15.8 mmol) in EtOH (40 mL) at room temperature. The mixture was stirred for one hour then NaBH(OAc)<sub>3</sub> (3.35 g, 15.8 mmol) was added in portions and the resulting mixture stirred for a further 4 hours. Saturated aq. NaHCO<sub>3</sub> (50 mL) was added and the mixture extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (20 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-

120 mesh) using 2-3.5% MeOH/DCM as the eluent to give the title compound (1.5 g, 59%).

#### 4D. 1-[4-(2-Benzylamino-ethyl)-2-methoxy-phenyl]-ethanone

A stirred solution of benzyl-[2-(4-bromo-3-methoxy-phenyl)-ethyl]-amine (1.5 g, 4.68 mmol) and tributyl(1-ethoxyvinyl)tin (2.1 g, 5.6 mmol) in 1,4-dioxane (20 mL) was degassed with nitrogen for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.27 g, 0.23 mmol) was added to the mixture and the resulting solution heated to 100°C for 12 hours. The solution was allowed to cool to room temperature and 1N aq. HCl solution (6 mL) was added and the mixture stirred for a further 2 hours. Saturated aq. NaHCO<sub>3</sub> solution was carefully added to attain pH10 and the mixture extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and 3N HCl in dioxane (2 mL) added. The solution was stirred for 30 minutes then the solvents were removed under reduced pressure. The resulting solid was triturated with Et<sub>2</sub>O (4 x 50 mL) and dried to give the title compound (1.4 g, 93%) as its hydrochloride salt.

#### 4E. [2-(4-Acetyl-3-methoxy-phenyl)-ethyl]-benzyl-carbamic acid tert-butyl ester

Boc<sub>2</sub>O (1.51 g, 6.58 mmol) was added to a stirred solution of 1-[4-(2-benzylamino-ethyl)-2-methoxy-phenyl]-ethanone (1.40 g, 4.38 mmol) and Et<sub>3</sub>N (1.23 mL, 8.76 mmol) in DCM (30 mL) and the resulting mixture stirred at room temperature for 6 hours. The mixture was partitioned between DCM (30 mL) and water (50 mL) then the separated aqueous phase was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh) using 10-20% EtOAc/hexanes as the eluent to give the title compound (1.2 g, 71%).

#### 4F. Benzyl-[2-[4-(3,3-bis-methylsulfanyl-acryloyl)-3-methoxy-phenyl]-ethyl]-carbamic acid tert-butyl ester

A solution of [2-(4-acetyl-3-methoxy-phenyl)-ethyl]-benzyl-carbamic acid tert-butyl ester (1.0 g, 2.60 mmol) in DMSO (3 mL) was added slowly to a stirred slurry of NaH (60% in mineral oil, 0.26 g, 6.5 mmol) in DMSO (6 mL) maintaining the internal temperature at 10-15°C. After stirring at 10°C for 30 minutes, carbon disulfide (0.32 mL, 5.20 mmol) was added and stirring continued for a further 20 minutes. Methyl

iodide (0.35 mL, 5.72 mmol) was added at 10°C then the mixture was allowed to warm to room temperature and stirring continued for 30 minutes. Water (50 mL) was carefully added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh size) using 0-30% EtOAc/hexanes as the eluent to give the title compound (0.60 g, 47%).

4G. Benzyl-(2-{4-[(Z)-3-(5-cyano-pyrazin-2-ylamino)-3-methylsulfanyl-acryloyl]-3-methoxy-phenyl}-ethyl)-carbamic acid tert-butyl ester

10 A solution of 2-amino-5-cyanopyrazine (0.12 g, 0.92 mmol) was added in portions to a stirred slurry of NaH (60% in mineral oil) (0.040 g, 0.92 mmol) in THF (3 mL) at room temperature. The mixture was stirred for 30 minutes then benzyl-{2-[4-(3,3-bis-methylsulfanyl-acryloyl)-3-methoxy-phenyl]-ethyl}-carbamic acid tert-butyl ester (0.30 g, 0.62 mmol) was added and the reaction mixture was then heated to 65°C for 12  
15 hours. The solution was allowed to cool to room temperature then water (10 mL) was carefully added and the mixture extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh) using 15-30% EtOAc/hexanes as  
20 the eluent to give the title compound (0.17 g, 49%).

4H. Benzyl-(2-{4-[5-(5-cyano-pyrazin-2-ylamino)-2H-pyrazol-3-yl]-3-methoxy-phenyl}-ethyl)-carbamic acid tert-butyl ester

A stirred solution of hydrazine monohydrate (0.03 mL, 0.60 mmol), benzyl-(2-{4-[(Z)-3-(5-cyano-pyrazin-2-ylamino)-3-methylsulfanyl-acryloyl]-3-methoxy-phenyl}-ethyl)-carbamic acid tert-butyl ester (0.17 g, 0.30 mmol) and acetic acid (0.05 mL, 0.9 mmol) in EtOH (2 mL) was heated to 65°C for 3 hours. The solution was allowed to cool to room temperature then water (20 mL) was added and the mixture extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was  
25 purified by column chromatography on neutral silica gel (60-120 mesh) using 1.5% MeOH/DCM as the eluent to give the title compound (0.095 g, 60%).  
30

4I. 5-{5-[4-(2-Benzylamino-ethyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile hydrochloride

3N HCl in dioxane (0.5 mL) was added dropwise to a stirred solution of benzyl-(2-{4-[5-(5-cyano-pyrazin-2-ylamino)-2H-pyrazol-3-yl]-3-methoxy-phenyl}-ethyl)-carbamic acid tert-butyl ester (0.090 g, 0.17 mmol) in MeCN (2 mL) and THF (2 mL) at room temperature. The mixture was stirred for 30 minutes at room temperature then the mixture heated to 50°C for 3 hours. The mixture was allowed to cool to room temperature and the precipitated solid was collected by filtration. The collected solid was washed with THF/MeCN (1:1, 1.5 mL) and Et<sub>2</sub>O (10 mL) and dried to give the title compound (0.055 g, 70%) as a white solid.

Synthetic Route D

(Illustrated with reference to Example 11:

Example 11

5-{5-[2-Methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile hydrochloride)

11A. 4-(3-Methoxy-4-methoxycarbonyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

A solution of 4-bromo-2-methoxy-benzoic acid methyl ester (4.0 g, 16.5 mmol), 1-Boc-piperidine-4-boronic acid pinacol ester (5.1 g, 16.5 mmol) and K<sub>2</sub>CO<sub>3</sub> (6.6 g, 49.5 mmol) in DMF (25 mL) was degassed with nitrogen for 15 minutes. PdCl<sub>2</sub>(dppf).DCM (1.0 g, 0.6 mmol) was added at room temperature then the mixture was heated to 90°C and stirring continued for 5 hours. Water (100 mL) was added and the mixture extracted with EtOAc (2 x 50 mL) then the combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 10-15% EtOAc/hexanes as the eluent to give the title compound (5.0 g, 87%).

11B. 4-(3-Methoxy-4-methoxycarbonyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 4-(3-methoxy-4-methoxycarbonyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (5.0 g, 14.4 mmol) and 10% Pd/C (0.5 g) was stirred under a hydrogen atmosphere at room temperature for 6 hours. The mixture was



filtered through a pad of celite and the solvents evaporated under reduced pressure to give the title compound (4.5 g, 90%) which was used without further purification.

11C. 2-Methoxy-4-piperidin-4-yl-benzoic acid methyl ester

3N HCl in dioxane (15 mL) was added to a stirred solution of 4-(3-methoxy-4-  
5 methoxycarbonyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (4.5 g, 12.8  
mmol) in DCM (50 mL) at 0°C. The mixture was allowed to warm to room temperature  
and stirring continued for 5 hours then the solvents were removed under reduced  
pressure. The residue was triturated with Et<sub>2</sub>O (2 x 10 mL) then partitioned between  
DCM (50 mL) and saturated NaHCO<sub>3</sub> solution (50 mL). The separated aqueous phase  
10 was extracted with DCM (2 x 50 mL) then the combined organic extracts were dried  
(Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title compound (2.5 g,  
78%) which was used without further purification.

11D. 2-Methoxy-4-(1-methyl-piperidin-4-yl)-benzoic acid methyl ester

Formalin (37% formaldehyde in water) (5.0 mL, 50 mmol) was added to a stirred  
15 solution of 2-methoxy-4-piperidin-4-yl-benzoic acid methyl ester (0.3 g, 1.1 mmol) in  
MeOH (15 mL) and the mixture stirred for 30 minutes. The solution was cooled to 0°C  
and NaBH(AcO)<sub>3</sub> (3.20 g, 15 mmol) was added and the resulting solution stirred for 3  
hours at room temperature. Saturated NaHCO<sub>3</sub> solution (100 mL) was added and the  
mixture extracted with DCM (3 x 75 mL). The combined organic extracts were washed  
20 with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the  
title compound (2.5 g, 95%) which was used without further purification.

11E. 3-[2-Methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-3-oxo-propionitrile

LHMDS (1M in hexane) (24 mL, 24 mmol) was added dropwise to MeCN (1.78 mmol,  
34.2 mmol) in dry toluene (50 mL) at -78°C under a nitrogen atmosphere and the  
25 resulting yellow solution stirred for 30 minutes at -78°C. A solution of 2-methoxy-4-(1-  
methyl-piperidin-4-yl)-benzoic acid methyl ester (1.8 g, 6.84 mmol) in dry toluene (50  
mL) was added dropwise maintaining the temperature at -78°C, then the mixture was  
allowed to warm to room temperature and stirring continued for 30 minutes. The  
mixture was cooled to 0°C and water (150 mL) was carefully added then the separated  
30 aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts  
were washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced  
pressure to leave a residue that was purified by column chromatography on neutral

silica gel (60-120 mesh) using 2-3% MeOH/DCM as the eluent to give the title compound (1.40 g, 75%).

11F. 5-[2-Methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamine

A stirred solution of hydrazine monohydrate (0.22 g, 4.44 mmol) and 3-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-3-oxo-propionitrile (1.0 g, 3.67 mmol) in EtOH (2 mL) was heated to 85°C for 10 hours. The solution was allowed to cool to room temperature and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel (60-120 mesh size) using 10% MeOH/DCM as the eluent to give the title compound (0.60 g, 57%).

10 11G. 3-Amino-5-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-pyrazole-1-carboxylic acid tert-butyl ester

NaH (60% in mineral oil) (0.031 g, 0.77 mmol) was added in portions to a stirred solution of 5-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamine (0.20 g, 0.69 mmol) in a mixture of THF (15 mL) and DMF (5 mL) at 0°C. The mixture was stirred for 30 minutes then Boc<sub>2</sub>O (0.17 g, 0.77 mmol) was added and then the mixture allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a solid that was washed with Et<sub>2</sub>O (8 mL) to give the title compound (0.23 g, 84%).

11H. 5-{5-[2-Methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile hydrochloride

NaH (60% in mineral oil) (0.016 g, 0.38 mmol) was added in portions to a stirred solution of 3-amino-5-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-pyrazole-1-carboxylic acid tert-butyl ester (0.75 g, 0.19 mmol) in THF (3 mL) at 0°C. The mixture was stirred for 10 minutes then 5-bromopyrazine-2-carbonitrile (0.036 g, 0.19 mmol) was added and then the mixture allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a solid that was purified by preparative HPLC to give the title compound (0.03 g, 40%) as its free base. This material was dissolved in MeCN (1 mL) and THF (1 mL) then 3N HCl in dioxane (0.2 mL) was added. The mixture was stirred at room temperature for 30 minutes then

the solvents were removed under reduced pressure to leave a solid which was washed with Et<sub>2</sub>O (5 mL) and dried to give the title compound (0.032 g, 98%) as a white solid.

#### Synthetic Route E

(Illustrated with reference to Example 13:

#### 5 Example 13

N-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]cyclopropanecarboxamide)

#### 13A. Methyl 2-hydroxy-4-methyl-benzoate

Concentrated H<sub>2</sub>SO<sub>4</sub> (200 mL) was added dropwise over 30 minutes to a stirred  
10 solution of 2-hydroxy-4-methyl-benzoic acid (100 g, 657 mmol) in MeOH (500 mL) at room temperature. The mixture was heated to reflux for 5 hours then allowed to cool to room temperature and carefully poured into ice cold saturated NaHCO<sub>3</sub> solution (300 mL). The mixture was extracted with DCM (4 x 500 mL) and the combined organic extracts dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the  
15 title compound (100 g, 94%) which was used without further purification.

#### 13B. Methyl 2-methoxy-4-methyl-benzoate

A solution of methyl 2-hydroxy-4-methyl-benzoate (100 g, 602 mmol) in DMF (170 mL) was added dropwise over 30 minutes to a stirred slurry of NaH (33.8 g, 1.41 mol) in dry DMF (330 mL) at 0°C under a nitrogen atmosphere. The resulting mixture was  
20 stirred at 0°C for a further 30 minutes then iodomethane (255 g, 1.81 mol) was added dropwise over 20 minutes. The mixture was heated to 70°C for 3 hours then allowed to cool and carefully poured into ice-cold 1N HCl solution (1500 mL). The mixture was extracted with DCM (2 x 1000 mL) and the combined organic extracts dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column  
25 chromatography on neutral silica gel using 15%EtOAc/hexanes as the eluent to give the title compound (102 g, 94%).

#### 13C. Methyl 4-(bromomethyl)-2-methoxy-benzoate

A stirred solution of methyl 2-methoxy-4-methyl-benzoate (100 g, 555 mmol) and N-bromosuccinimide (108.6 g, 610 mmol) in carbon tetrachloride (1300 mL) was  
30 degassed with nitrogen for 15 minutes.  $\alpha,\alpha'$ -Azoisobutyronitrile (18.2 g, 111 mmol)

was added in one portion and the resulting mixture heated to 70°C for 15 hours then allowed to cool to room temperature. The mixture was poured into water (600 mL) and then the separated aqueous phase extracted with DCM (2 x 800 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title compound (144 g) which was used without further purification.

13D. Methyl 4-(acetoxymethyl)-2-methoxy-benzoate

A stirred mixture of methyl 4-(bromomethyl)-2-methoxy-benzoate (144 g, 558 mmol) and potassium acetate (285 g, 2.9 mol) in dry DMF (1440 mL) was heated to 80°C for one hour then the cooled mixture was poured into ice-water (5000 mL). The mixture was extracted with DCM (2 x 1000 mL) and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 15%EtOAc/hexanes as the eluent to give the title compound (63.0 g, 48% over two steps).

13E. Methyl 4-(hydroxymethyl)-2-methoxy-benzoate

A solution of methyl 4-(acetoxymethyl)-2-methoxy-benzoate (63.0 g, 265 mmol) in MeOH (500 mL) was added dropwise to a stirred solution of sodium methoxide (2.86 g, 52.9 mmol) in MeOH (280 mL) at room temperature. The mixture was stirred for two hours then poured into 2N HCl solution (1000 mL) and extracted with DCM (3 x 1000 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) to afford the title compound (49.0 g, 94%) which was used without further purification.

13F. Methyl 2-methoxy-4-(methylsulfonyloxymethyl)benzoate

Methanesulfonyl chloride (2.1 mL, 26.8 mmol) was added dropwise to a stirred solution of methyl 4-(hydroxymethyl)-2-methoxy-benzoate (5.0 g, 25.5 mmol) and triethylamine (7.1 mL, 51.0 mmol) in DCM (120 mL) at 0°C under a nitrogen atmosphere. The resulting mixture was stirred at 0°C for two hours then partitioned between DCM (100 mL) and 1N HCl (100 mL). The separated organic phase was washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title compound (7.6 g, 100%) which was used without further purification.

13G. Methyl 4-(azidomethyl)-2-methoxy-benzoate

A solution of sodium azide (9.0 g, 138 mmol) and methyl 2-methoxy-4-(methylsulfonyloxymethyl)benzoate (7.6 g, 27.7 mmol) in dry DMF (60 mL) was heated to 70°C for 3 hours. The cooled reaction mixture was poured into cold water (500 mL)

and the resulting mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give the title compound (7.8 g, 100%) which was used without further purification.

5 13H. Methyl 4-(aminomethyl)-2-methoxy-benzoate

A mixture of methyl 4-(azidomethyl)-2-methoxy-benzoate (7.8 g, 27.7 mmol) and 10% Pd on carbon (0.78 g) in MeOH (80 mL) was stirred at room temperature under a hydrogen atmosphere for 3 hours. The mixture was filtered through celite and the filtrate evaporated under reduced pressure to leave a residue which was purified by  
10 column chromatography on neutral silica gel using 6-7% MeOH/chloroform to give the title compound (3.1 g, 45% over two steps).

13I. Methyl 4-[(cyclopropanecarbonylamino)methyl]-2-methoxy-benzoate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.75g, 11.3 mmol) and hydroxybenzotriazole (0.14g, 1.0 mmol) were added to a stirred solution of methyl 4-  
15 (aminomethyl)-2-methoxy-benzoate (2.0 g, 10.3 mmol) and cyclopropane carboxylic acid (0.82 mL, 10.3 mmol) in DCM (85 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 hours then diluted with DCM (150 mL) and washed with saturated  $\text{NaHCO}_3$  solution (3 x 75 mL), brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was  
20 purified by column chromatography on neutral silica gel using 55% EtOAc/hexane as the eluent to give the title compound (2.2 g, 82%).

13J. N-[4-(2-cyanoacetyl)-3-methoxy-phenyl]methylcyclopropanecarboxamide

A solution of LiHMDS (1.0M in hexane, 29.4 mL, 29.4 mmol) was added dropwise over 20 minutes to a stirred solution of acetonitrile (1.72 g, 42.0 mmol) in dry THF (58 mL)  
25 at  $-78^\circ\text{C}$  under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of methyl 4-[(cyclopropanecarbonylamino)methyl]-2-methoxy-benzoate (2.2 g, 8.4 mmol) in THF (50 mL) was added dropwise over 20 minutes maintaining the temperature at  $-78^\circ\text{C}$ . The mixture was allowed to warm to room temperature and stirring continued for 2 hours. The mixture was poured into cold saturated ammonium  
30 chloride solution (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give the title compound (2.0 g, 88%) as a white solid.

13K. N-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]cyclopropane carboxamide

A stirred mixture of N-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]cyclopropanecarboxamide (0.5 g, 1.8 mmol) and hydrazine hydrate (98% in water, 0.11 g, 2.20 mmol) in EtOH (10 mL) was heated to reflux for 18 hours. The solvents were evaporated under reduced pressure to leave a solid which was recrystallized from EtOH to give the title compound (0.35 g, 67%) as a white solid.

13L. tert-Butyl 3-amino-5-[4-[(cyclopropanecarbonylamino)methyl]-2-methoxy-phenyl]pyrazole-1-carboxylate

A solution of N-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]cyclopropane carboxamide (0.5 g, 1.70 mmol) in a mixture of dry DMF (12 mL) and dry THF (18 mL) was added dropwise to a stirred suspension of sodium hydride (0.07 g, 1.70 mmol) in dry THF (12 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 30 minutes at 0°C then a solution of Boc<sub>2</sub>O (0.37 g, 1.70 mmol) in dry THF (10 mL) was added dropwise maintaining the temperature at 0°C. The reaction mixture was allowed to warm to room temperature and stirring continued for 1.5 hours. The solution was poured into ice-water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 2% MeOH/DCM as the eluent to give the title compound (0.37 g, 55%) as an off-white solid.

13M. N-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]cyclopropanecarboxamide

A solution of tert-butyl 3-amino-5-[4-[(cyclopropanecarbonylamino)methyl]-2-methoxy-phenyl]pyrazole-1-carboxylate (185 mg, 4.80 mmol) in a mixture of dry THF (2 mL) and dry DMF (1 mL) was added dropwise to a stirred suspension of sodium hydride (38 mg, 9.6 mmol) in THF (2 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 10 minutes then a solution of 5-bromopyrazine-2-carbonitrile (88 mg, 4.80 mmol) in dry THF (1 mL) was added dropwise maintaining the temperature at 0°C. The mixture was allowed to slowly warm to room temperature and stirring continued for 2 hours. After pouring into ice-water (20 mL) the mixture was extracted with EtOAc (5 x 25 mL) then the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was dissolved in 4N

HCl in EtOAc (10 mL) and stirred for 30 mins then the solvents were evaporated under reduced pressure to leave a residue which was purified by preparative HPLC to give the title compound (41 mg, 31%) as an off-white solid.

#### Synthetic Route F

5 (Illustrated with reference to Example 14:

#### Example 14

5-[[5-[2-Methoxy-4-[(tetrahydropyran-4-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

#### 14A. Methyl 4-formyl-2-methoxy-benzoate

10 Dess-Martin periodinane (81.2 g, 191 mmol) was added in portions to a stirred solution of methyl 4-(hydroxymethyl)-2-methoxy-benzoate (25.0 g, 128 mmol) in DCM (375 mL) under a nitrogen atmosphere. The solution was stirred for one hour then filtered through a pad of celite washing with DCM (100 mL). The filtrate was evaporated under reduced pressure to leave a residue which was purified by column  
15 chromatography on neutral silica gel using 10%EtOAc/hexane as the eluent to give the title compound (23.5 g, 95%).

#### 14B. Methyl 2-methoxy-4-[(tetrahydropyran-4-ylamino)methyl]benzoate

Sodium methoxide (0.83 g, 15.4 mmol) was added to a stirred solution of tetrahydro-  
2H-pyran-4-amine hydrochloride (2.12 g, 15.4 mmol) in MeOH (35 mL) at room  
20 temperature under a nitrogen atmosphere and the mixture stirred for 30 minutes. The solution was passed through a Millipore filter and the resulting clear solution added to a stirred solution of methyl 4-formyl-2-methoxy-benzoate (3.0 g, 15.4 mmol) in MeOH (35 mL). Glacial acetic acid (1.8 mL, 30.8 mmol) was added and the mixture stirred for one hour then the solution was cooled to 0°C and sodium triacetoxyborohydride (9.79  
25 g, 4.62 mmol) was added in portions over 15 minutes. The mixture was allowed to warm to room temperature and stirring continued for 18 hours before partitioning between saturated NaHCO<sub>3</sub> solution (200 mL) and EtOAc (200 mL). The separated aqueous phase was extracted with EtOAc (2 x 200 mL) then the combined organic extracts were washed with brine (75 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under  
30 reduced pressure. The residue was purified by column chromatography on neutral silica gel using 2% MeOH/DCM as the eluent to give the title compound (3.1 g, 72%).

14C. Methyl 4-[[tert-butoxycarbonyl(tetrahydropyran-4-yl)amino]methyl]-2-methoxy-benzoate

Boc<sub>2</sub>O (1.83 g, 8.40 mmol) was added to a stirred solution of methyl 2-methoxy-4-  
5 [(tetrahydropyran-4-ylamino)methyl]benzoate (2.40 g, 7.60 mmol) and Et<sub>3</sub>N (2.15 g,  
8.40 mmol) in DCM (60 mL) and the resulting mixture stirred at room temperature for  
18 hours. The mixture was diluted DCM (200 mL), washed with 5% citric acid solution,  
water (2 x 50 mL), brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced  
pressure to give the title compound (3.1 g, 95%) which was used without further  
purification.

10 14D. tert-Butyl N-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]-N-tetrahydropyran-4-yl-carbamate

A solution of LiHMDS (1.0M in hexane, 23.1 mL, 23.1 mmol) was added dropwise over  
20 minutes to a stirred solution of acetonitrile (1.35 g, 33.0 mmol) in dry THF (70 mL)  
at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a  
15 solution of methyl 4-[[tert-butoxycarbonyl(tetrahydropyran-4-yl)amino]methyl]-2-  
methoxy-benzoate (2.5 g, 6.6 mmol) in THF (140 mL) was added dropwise over 20  
minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30  
minutes then allowed to warm to room temperature and stirring continued for one hour.  
The mixture was poured into cold saturated ammonium chloride solution (100 mL) and  
20 extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with  
brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title  
compound (2.9 g, 100%) as a white solid.

14E. tert-Butyl N-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]-N-tetrahydropyran-4-yl-carbamate

25 A solution of tert-butyl N-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]-N-  
tetrahydropyran-4-yl-carbamate (2.90 g, 7.5 mmol) and hydrazine hydrate (99% in  
water, 2.9 g, 9.0 mmol) in ethanol (60 mL) was heated to reflux for 18 hours. The  
mixture was allowed to cool to room temperature and the solvents evaporated under  
reduced pressure to leave a residue which was purified by column chromatography on  
30 neutral silica gel using 2-3% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (1.5  
g, 50%).

14F. tert-Butyl N-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]-N-tetrahydropyran-4-yl-carbamate



A stirred solution of tert-butyl N-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]-N-tetrahydropyran-4-yl-carbamate (0.5g, 1.2 mmol), diisopropylethylamine (0.63 mL, 3.6 mmol) and 5-bromopyrazine-2-carbonitrile (0.66 g, 3.6 mmol) in dry 1,4-dioxane (12 mL) was heated to 80°C for 24 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (0.39 g, 64%).

10 14G. 5-[[5-[2-Methoxy-4-[(tetrahydropyran-4-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

4N HCl in dioxane (0.4 mL) was added to a stirred solution of tert-butyl N-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]-N-tetrahydropyran-4-yl-carbamate (0.09 g, 0.18 mmol) in dry dioxane (10 mL) and the resulting mixture stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (52 mg, 72%) as an off-white solid.

Synthetic Route G

(Illustrated with reference to Example 17:

20 Example 17

5-[[5-[4-[1-[2-(Dimethylamino)acetyl]-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

17A. tert-Butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]piperidine-1-carboxylate

A solution of LiHMDS (1.0M in hexane, 90.0 mL, 90.0 mmol) was added dropwise over 20 minutes to a stirred solution of acetonitrile (5.3 g, 129 mmol) in dry THF (250 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of methyl tert-butyl 4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate (Example 11B) (9.0 g, 25.8 mmol) in THF (250 mL) was added dropwise over 20 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into cold saturated ammonium chloride solution (300 mL) and extracted with EtOAc (5 x 200 mL). The combined organic extracts were

washed with brine (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 40% EtOAc/hexane as the eluent to give the title compound (7.0 g, 76%) as a white solid.

5 17B. tert-Butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]piperidine-1-carboxylate

A solution of tert-butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]piperidine-1-carboxylate (7.0 g, 19.5 mmol) and hydrazine hydrate (99% in water, 1.17 g, 23.4 mmol) in ethanol (150 mL) was heated to reflux for 18 hours. The mixture was allowed to cool to room  
10 temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 2% MeOH/ $\text{CHCl}_3$  as the eluent to give the title compound (5.1 g, 70%).

17C. tert-Butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]piperidine-1-carboxylate

15 A stirred solution of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]piperidine-1-carboxylate (0.6 g, 1.6 mmol), diisopropylethylamine (0.84 mL, 4.8 mmol) and 5-bromopyrazine-2-carbonitrile (0.88 g, 4.8 mmol) in dry 1,4-dioxane (12 mL) was heated to 80°C for 24 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 50 mL). The  
20 combined organic extracts were washed with brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 3% MeOH/DCM as the eluent to give the title compound (0.56 g, 73%).

25 17D. 5-[[5-[2-Methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile

4N HCl in dioxane (25 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]piperidine-1-carboxylate (0.56 g, 0.98 mmol) in a mixture of dry dioxane (25 mL) and dry THF (25 mL) and the resulting mixture stirred at room temperature for 2 hours. The solvents were  
30 evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x 10 mL) and dried to give the title compound (0.54 mg, 100%) as an off-white solid.

17E. 5-[[5-[4-[1-[2-(Dimethylamino)acetyl]-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.20g, 1.02 mmol) and hydroxybenzotriazole (12 mg, 0.09 mmol) were added to a stirred solution of 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (0.35 g, 0.93 mmol) and N,N'-dimethylglycine (96 mg, 0.93 mmol) in DMF (4 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 5 hours then diluted with DCM (150 mL) and washed with saturated NaHCO<sub>3</sub> solution (3 x 75 mL), brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 7% MeOH/DCM as the eluent. The resulting solid was dissolved in a mixture of MeOH (4 mL) and MeCN (8 mL) and a solution of 4N HCl in dioxane (0.2 mL) was added and the resulting mixture stirred for 30 minutes. The solvents were evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x 10 mL) and dried to give the title compound (0.24 g, 54%) as an off-white solid.

Synthetic Route H

(Illustrated with reference to Example 60:

Example 60

5-[[5-[4-(1-ethyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

Diisopropylethylamine (0.25 mL, 1.46 mmol) was added to a stirred suspension of 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (prepared using Synthetic Route G) (0.3 g, 0.73 mmol) in a mixture of MeOH (10 mL) and MeCN (20 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Acetaldehyde (0.1 g, 2.19 mmol) was added and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.50 g, 2.34 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further hour then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 9% MeOH/DCM as the eluent. The resulting solid was

dissolved in a mixture of THF (4 mL) and MeCN (4 mL) and a solution of 4N HCl in dioxane (1 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x 10 mL) and dried to give the title compound (71 mg, 29%) as an off-white solid.

### Synthetic Route I

(Illustrated with reference to Example 22:

### Example 22

5-[[5-[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

### 22A. Methyl 4-fluoro-2-methoxy-benzoate

Potassium carbonate (15.5 g, 112 mmol) was added to a stirred solution of 4-fluoro-2-hydroxy-benzoic acid (5.0 g, 32.1 mmol) in acetone (100 mL) and the mixture heated to 40°C under a nitrogen atmosphere for 20 minutes. Methyl iodide (15.8 g, 112 mmol) was added dropwise and then the mixture heated to reflux for 20 hours then allowed to cool to room temperature. The mixture was filtered through celite and the filtrate concentrated under reduced pressure to give the title compound (5.9 g, 100%) which was used without further purification.

### 22B. tert-Butyl 4-(3-methoxy-4-methoxycarbonyl-phenyl)piperazine-1-carboxylate

Potassium carbonate (1.49 g, 10.8 mmol) was added to a stirred solution of methyl 4-fluoro-2-methoxy-benzoate (1.0 g, 5.4 mmol) in DMSO (10 mL) and the mixture stirred at room temperature under a nitrogen atmosphere for 20 minutes. N-Boc piperazine (2.01 g, 10.8 mmol) was added and then the mixture heated to 80°C for 18 hours. The cooled mixture was poured into ice-water (100 mL) and extracted with EtOAc (5 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 45% EtOAc/hexane as the eluent to give the title compound (4.6 g, 41%) as a white solid.

22C. tert-Butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]piperazine-1-carboxylate

A solution of LiHMDS (1.0M in hexane, 46.0 mL, 46.0 mmol) was added dropwise over 40 minutes to a stirred solution of acetonitrile (2.69 g, 65.5 mmol) in dry THF (100 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then  
5 a solution of tert-butyl 4-(3-methoxy-4-methoxycarbonyl-phenyl)piperazine-1-carboxylate (4.6 g, 13.1 mmol) in THF (100 mL) was added dropwise over 20 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into cold saturated ammonium chloride solution (150 mL) and  
10 extracted with EtOAc (5 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (5.3 g, 100%) which was used without further purification.

22D. tert-Butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]piperazine-1-carboxylate

15 A solution of tert-butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]piperazine-1-carboxylate (5.3 g, 14.8 mmol) and hydrazine hydrate (99% in water, 2.96 g, 59.2 mmol) in ethanol (120 mL) was heated to reflux for 18 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 2%  
20 MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (2.0 g, 36%).

22E. tert-Butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]piperazine-1-carboxylate

A stirred solution of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (0.5 g, 1.3 mmol), diisopropylethylamine (0.70 mL, 3.9 mmol) and 5-bromopyrazine-2-carbonitrile (0.71 g, 3.9 mmol) in dry 1,4-dioxane (5 mL)  
25 was heated to 80°C for 4 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column  
30 chromatography on neutral silica gel using 1.5% MeOH/DCM as the eluent to give the title compound (0.32 g, 50%).

22F. 5-[[5-(2-Methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

4N HCl in dioxane (4 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (0.56 g, 0.98 mmol) in a mixture of dry MeCN (10 mL) and dry THF (10 mL) and the resulting mixture stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure to leave a solid that was triturated with n-pentane (3 x 10 mL) and Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (0.24 mg, 100%) as an off-white solid.

10 22G. 5-[[5-[2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.12 mL, 0.68 mmol) was added to a stirred suspension of 5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.14 g, 0.34 mmol) in a mixture of MeOH (2 mL) and MeCN (4 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Formalin (37-41% w/v in water; 31 mg, 0.10 mmol) was added followed by the addition of glacial acetic acid (0.04 mL, 0.68 mmol) and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.22 g, 1.02 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further hour then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (4 x 30 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was triturated with EtOAc (3 x 5 mL) and dried to leave an off-white solid. The solid was dissolved in a mixture of THF (3 mL) and MeCN (3 mL) then a solution of 4N HCl in dioxane (0.5 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with n-pentane (3 x 10 mL) and dried to give the title compound (35 mg, 24%) as an off-white solid.

30 Synthetic Route J

(Illustrated with reference to Example 24:

Example 24

5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile hydrochloride)

24A. tert-Butyl 4-[4-[3-[(6-cyano-3-pyridyl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]piperidine-1-carboxylate

- 5 A stirred suspension of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]piperidine-1-carboxylate (Example 17B) (1.0 g, 2.7 mmol), 5-bromo-2-cyanopyridine (0.59 g, 3.2 mmol), cesium carbonate (1.75 g, 5.4 mmol) and (±)-BINAP (0.125 g, 0.2 mmol) in dry dioxane (10 mL) was degassed with nitrogen for 30 minutes at room temperature. Tris(dibenzylideneacetone)dipalladium(0) (0.183 g, 0.2 mmol)
- 10 was added and the resulting mixture heated to 100°C for 5 hours. After cooling to room temperature the reaction mixture was poured into ice-water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 3%
- 15 MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (0.40 g, 31%).

24B. 5-[[5-[2-Methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile hydrochloride

- 4N HCl in dioxane (10 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(6-cyano-3-pyridyl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]piperidine-1-carboxylate
- 20 (0.40 g, 0.89 mmol) in a mixture of dry MeCN (10 mL) and dry THF (10 mL) and the resulting mixture stirred at room temperature for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (0.38 mg, 100%) as an off-white solid.

24C. 5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile hydrochloride

- Diisopropylethylamine (0.23 mL, 1.30 mmol) was added to a stirred suspension of 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile hydrochloride (0.27 g, 0.65 mmol) in a mixture of MeOH (4 mL) and MeCN (16 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen
- 30 atmosphere. Formalin (37-41% w/v in water; 0.1 mL, 1.3 mmol) was added followed by the addition of glacial acetic acid (0.08 mL, 1.30 mmol) and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.44 g, 2.08 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to

room temperature and stirred for a further hour then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 9% MeOH/CHCl<sub>3</sub> as the eluent to leave an off-white solid. The solid was dissolved in a mixture of THF (10 mL) and MeCN (10 mL) then a solution of 4N HCl in dioxane (0.2 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (140 mg, 51%) as an off-white solid.

#### Synthetic Route K

(Illustrated with reference to Example 28:

#### Example 28

5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)oxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

#### 28A. 4-Hydroxy-2-methoxy-benzoic acid

Sodium dihydrogen phosphate (63.1 g, 526 mmol) and sodium chlorite (41.6 g, 460 mmol) were added to a stirred solution of 4-hydroxy-2-methoxy-benzaldehyde (20.0 g, 132 mmol) in a mixture of DMSO (400 mL) and water (300 mL) at 0°C. The mixture was allowed to warm to room temperature and stirring continued for 6 hours. The mixture was diluted with water (1000 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The solution was washed with EtOAc (1000 mL), the pH adjusted to 4 by the addition of 1N HCl solution and extracted with EtOAc (6 x 500 mL). The combined organic extracts were washed with brine (300 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the title compound (22.0 g, 100%) which was used without further purification.

#### 28B. Methyl 4-hydroxy-2-methoxy-benzoate

Concentrated H<sub>2</sub>SO<sub>4</sub> (52 mL) was added dropwise over 20 minutes to a stirred solution of 4-hydroxy-2-methoxy-benzoic acid (22.0 g, 131 mmol) in MeOH (520 mL) at room temperature. The mixture was heated to reflux for 2 hours then allowed to cool to room temperature and poured into ice-water (300 mL). The mixture was extracted with



EtOAc (2 x 1000 mL) and the combined organic extracts dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 25% EtOAc/hexane as the eluent to give the title compound (12.0 g, 50%).

5 28C. tert-Butyl 4-(3-methoxy-4-methoxycarbonyl-phenoxy)piperidine-1-carboxylate

Diisopropyl azodicarboxylate (5.6 g, 27.5 mmol) was added to a stirred solution of methyl 4-hydroxy-2-methoxy-benzoate (2.0 g, 11.0 mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (6.6 g, 33 mmol) and triphenylphosphine (7.2 g, 27.5 mmol) in THF (100 mL) at 0-10°C under a nitrogen atmosphere. The resulting mixture  
10 was sonicated at 40°C for 2 hours then poured into ice-water (100 mL). The mixture was extracted with EtOAc (2 x 250 mL) and the combined organic extracts washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 10% EtOAc/hexane as the eluent to give the title compound (4.80 g, 100%).

15 28D. tert-Butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenoxy]piperidine-1-carboxylate

A solution of LiHMDS (1.0 M in hexane, 92.0 mL, 92.0 mmol) was added dropwise over 40 minutes to a stirred solution of acetonitrile (5.4 g, 131 mmol) in dry THF (250 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of *tert*-butyl 4-(3-methoxy-4-methoxycarbonyl-phenoxy)piperidine-1-  
20 carboxylate (4.8 g, 13.1 mmol) in THF (250 mL) was added dropwise over 20 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into cold saturated ammonium chloride solution (150 mL) and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with  
25 brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave the title compound (5.0 g, 100%) which was used without further purification.

28E. tert-Butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenoxy]piperidine-1-carboxylate

A solution of *tert*-butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenoxy]piperidine-1-  
30 carboxylate (1.0 g, 2.7 mmol) and hydrazine hydrate (99% in water, 0.54 g, 10.0 mmol) in ethanol (20 mL) was heated to reflux for 16 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a

residue which was purified by column chromatography on neutral silica gel using 90% EtOAc/hexane as the eluent to give the title compound (0.2 g, 19%).

28F. tert-Butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenoxy]piperidine-1-carboxylate

- 5 A stirred solution of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenoxy]piperidine-1-carboxylate (1.0 g, 2.6 mmol), diisopropylethylamine (1.4 mL, 7.8 mmol) and 5-bromopyrazine-2-carbonitrile (1.43 g, 7.8 mmol) in dry 1,4-dioxane (10 mL) was heated to 80°C for 24 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 50 mL). The  
10 combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 45% EtOAc/hexane as the eluent to give the title compound (0.21 g, 17%).

28G. 5-[[5-[2-Methoxy-4-(4-piperidyloxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

- 15 4N HCl in dioxane (6 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenoxy]piperidine-1-carboxylate (0.21 g, 0.50 mmol) in a mixture of dry MeCN (5 mL) and dry THF (5 mL) and the resulting mixture stirred at room temperature for 2 hours. The solvents were  
20 evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x 2 mL) and MeOH (3 x 2 mL) and dried to give the title compound (0.20 g, 100%) as an off-white solid.

28H. 5-[[5-[2-Methoxy-4-[(1-methyl-4-piperidyl)oxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile

- 25 Diisopropylethylamine (0.16 mL, 0.94 mmol) was added to a stirred suspension of 5-[[5-[2-methoxy-4-(4-piperidyloxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.20 g, 0.47 mmol) in a mixture of MeOH (4 mL) and MeCN (8 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Formalin (37-41% w/v in water; 0.08 mL, 0.94 mmol) was added followed by the  
30 addition of glacial acetic acid (0.05 mL, 1.50 mmol) and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.32 g, 1.50 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further hour then poured into ice-water (30 mL) and solid

NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 7% MeOH/CHCl<sub>3</sub> as the eluent to leave an off-white solid. The solid was dissolved in a mixture of THF (5 mL) and MeCN (5 mL) then a solution of 4N HCl in dioxane (0.5 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (68 mg, 69%) as an off-white solid.

10 Synthetic Route L

(Illustrated with reference to Example 64:

Example 64

5-[[5-[4-(4-Fluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

15 64A. 2-(4-Bromo-2-methoxy-phenyl)-1,3-dioxolane

A mixture of 4-bromo-2-methoxy-benzaldehyde (25.0 g, 117 mmol), ethanediol (9.7 mL, 175 mmol) and p-toluenesulfonic acid (67 mg, 0.35 mmol) in toluene (250 mL) was heated to reflux under Dean-Stark conditions for 5 hours. The cooled solution was poured into saturated NaHCO<sub>3</sub> solution (100 mL) and the separated aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel using 5% EtOAc/hexane as the eluent to give the title compound (6.8 g, 23%).

25 64B. tert-Butyl 4-[4-(1,3-dioxolan-2-yl)-3-methoxy-phenyl]-4-hydroxy-piperidine-1-carboxylate

A solution of n-BuLi (1.6 M in hexane, 21.5 mL, 34.3 mmol) was added dropwise to a stirred solution of 2-(4-bromo-2-methoxy-phenyl)-1,3-dioxolane (6.8 g, 26.4 mmol) in dry THF (90 mL) at -78°C under a nitrogen atmosphere. The mixture was stirred for 30 minutes then a solution of tert-butyl 4-oxopiperidine-1-carboxylate (5.26 g, 26.4 mmol) in THF (45 mL) was added dropwise maintaining the temperature at -78°C. The reaction mixture was allowed to slowly warm to room temperature and stirring continued for 12 hours. The mixture was poured into cold saturated ammonium

chloride solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel using 45% EtOAc/hexane as the eluent to give the title compound (2.9 g, 29%).

64C. tert-Butyl 4-fluoro-4-(4-formyl-3-methoxy-phenyl)-piperidine-1-carboxylate

Diethylaminosulfur trifluoride (1.1 mL, 8.4 mmol) was added dropwise to a stirred solution of tert-butyl 4-[4-(1,3-dioxolan-2-yl)-3-methoxy-phenyl]-4-hydroxy-piperidine-1-carboxylate (2.9 g, 7.6 mmol) in DCM (10 mL) at  $-78^\circ\text{C}$  under a nitrogen atmosphere.

10 The reaction mixture was allowed to warm to room temperature and stirring continued for 5 hours. The mixture was poured into saturated sodium carbonate solution (50 mL) and the separated aqueous phase extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1N citric acid solution (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel using 10% EtOAc/hexane as the eluent to give the title compound (1.8 g, 70%).

64D. tert-Butyl 4-[4-(2-cyano-1-hydroxy-ethyl)-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate

A solution of 2-bromoacetonitrile (1.1 g, 9.0 mmol) in dry THF (10 mL) was added to a stirred suspension of tert-butyl 4-fluoro-4-(4-formyl-3-methoxy-phenyl)-piperidine-1-carboxylate (1.8 g, 5.3 mmol) and zinc dust (0.69 g, 10.6 mmol) in dry THF (10 mL). The mixture was stirred for 30 minutes then poured into saturated ammonium chloride solution (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel using 20% EtOAc/hexane as the eluent to give the title compound (1.7 g, 84%).

64E. tert-Butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate

30 Dess-Martin periodinane (2.29 g, 5.4 mmol) was added in portions to a stirred solution of tert-butyl 4-[4-(2-cyano-1-hydroxy-ethyl)-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate (1.7 g, 4.5 mmol) in DCM (50 mL) under a nitrogen atmosphere. The solution was stirred for 30 minutes then filtered through a pad of celite washing with

DCM (50 mL). The filtrate was evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 15%EtOAc/hexane as the eluent to give the title compound (1.6 g, 95%).

5 64F. tert-Butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate

A solution of tert-butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate (1.6 g, 4.3 mmol) and hydrazine hydrate (99% in water, 0.33 g, 6.5 mmol) in ethanol (15 mL) was heated to reflux for 18 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 75% EtOAc/hexane as the eluent to give the title compound (0.73 g, 44%).

64G. tert-Butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate

15 A stirred solution of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate (0.73 g, 1.9 mmol), diisopropylethylamine (1.0 mL, 5.7 mmol) and 5-bromopyrazine-2-carbonitrile (1.04 g, 5.7 mmol) in dry 1,4-dioxane (8 mL) was heated to 80°C for 24 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 4% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (0.52 g, 56%).

64H. 5-[[5-[4-(4-Fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

25 4N HCl in dioxane (4 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-4-fluoro-piperidine-1-carboxylate (0.37 g, 0.75 mmol) in a mixture of dry MeCN (6 mL) and dry THF (10 mL) and the resulting mixture stirred at room temperature for 30 minutes. The solvents were evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x 2 mL) and dried to give the title compound (0.30 g, 92%) as an off-white solid.

64l. 5-[[5-[4-(4-Fluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.08 mL, 0.46 mmol) was added to a stirred suspension of 5-[[5-[4-(4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.10 g, 0.23 mmol) in a mixture of MeOH (2 mL) and MeCN (8 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Formalin (37-41% w/v in water; 0.014 g, 0.46 mmol) was added and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.16 g, 0.74 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further hour then poured into ice-water (30 mL). The mixture was extracted with EtOAc (4 x 25 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 8% MeOH/CHCl<sub>3</sub> as the eluent to leave an off-white solid. The solid was dissolved in a mixture of THF (5 mL) and MeCN (5 mL) and a solution of 4N HCl in dioxane (0.5 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (80 mg, 45%) as an off-white solid.

20 Synthetic Route M

(Illustrated with reference to Example 87:

Example 87

5-[[5-[4-(1-ethyl-3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

25 87A. tert-Butyl 3-hydroxy-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate

Borane.DMS (3.3 mL, 34.5 mmol) was added to a stirred solution of tert-butyl 4-(3-methoxy-4-methoxycarbonyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (Example 11A) (10 g, 28.8 mmol) in dry THF (100 mL) at 0°C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirring continued for 6 hours before adding 3N sodium hydroxide solution (10.6 mL, 3.17 mmol) and hydrogen peroxide solution (30% in water, 11.8 mL, 104 mmol) at 0°C. The mixture was stirred

at 50°C for 15 hours then the cooled mixture poured into ice-water (100 mL). The mixture was extracted with EtOAc (3 x 150 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel  
5 using 20% EtOAc/hexane as the eluent to give the title compound (7.8 g, 74%).

87B. tert-Butyl 3-fluoro-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate

Diethylaminosulfur trifluoride (1.8 mL, 13.6 mmol) was added dropwise over 10 minutes to a stirred solution of tert-butyl 3-hydroxy-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate (2.5 g, 6.8 mmol) in DCM (25 mL) at -78°C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirring continued for 2 hours. The mixture was poured into saturated sodium bicarbonate solution (100 mL) and the separated aqueous phase extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with 1N citric acid solution  
15 (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel using 16% EtOAc/hexane as the eluent to give the title compound (1.8 g, 72%).

87C. tert-Butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]-3-fluoro-piperidine-1-carboxylate

A solution of LiHMDS (1.0 M in hexane, 18.9 mL, 18.9 mmol) was added dropwise over 30 minutes to a stirred solution of acetonitrile (1.1 g, 27.0 mmol) in dry THF (75 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl 3-fluoro-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate (2.0 g, 5.4 mmol) in THF (75 mL) was added dropwise over 20 minutes  
25 maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for two hours. The mixture was poured into cold saturated ammonium chloride solution (100 mL) and extracted with EtOAc (5 x 200 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the  
30 title compound (2.3 g, 100%) which was used without further purification.

87D. tert-Butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]-3-fluoro-piperidine-1-carboxylate

A solution of tert-butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]-3-fluoro-piperidine-1-carboxylate (0.6 g, 1.6 mmol) and hydrazine hydrate (99% in water, 0.12 g, 2.4 mmol) in ethanol (12 mL) was heated to reflux for 18 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 80% EtOAc/hexane as the eluent to give the title compound (0.34 g, 54%).

87E. tert-Butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-3-fluoro-piperidine-1-carboxylate

A stirred solution of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]-3-fluoro-piperidine-1-carboxylate (0.8 g, 2.1 mmol), diisopropylethylamine (1.1 mL, 6.3 mmol) and 5-bromopyrazine-2-carbonitrile (1.2 g, 6.3 mmol) in dry 1,4-dioxane (11 mL) was heated to 80°C for 48 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (4 x 60 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 70% EtOAc/hexane as the eluent to give the title compound (0.70 g, 69%).

87F. 5-[[5-[4-(3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

4N HCl in dioxane (4 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-3-fluoro-piperidine-1-carboxylate (0.70 g, 1.4 mmol) in a mixture of dry MeCN (16 mL) and dry THF (16 mL) and the resulting mixture stirred at room temperature for 3 hours. The solvents were evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x 2 mL) and dried to give the title compound (0.30 g, 92%) as an off-white solid.

87G. 5-[[5-[4-(1-ethyl-3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.16 mL, 0.94 mmol) was added to a stirred suspension of 5-[[5-[4-(3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (0.20 g, 0.47 mmol) in a mixture of MeOH (2 mL) and MeCN (8 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Acetaldehyde (0.05 mL, 0.94 mmol) was added and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.32 g, 1.5 mmol) was



added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further 30 minutes then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 2% MeOH/CHCl<sub>3</sub> as the eluent. The resulting solid was dissolved in a mixture of THF (10 mL) and MeCN (10 mL) and a solution of 4N HCl in dioxane (1 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (75 mg, 35%) as a pale yellow solid.

#### Synthetic Route N

(Illustrated with reference to Example 97:

#### Example 97

15 5-[[5-[4-(3,3-Difluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

#### 97A. tert-Butyl 4-(3-methoxy-4-methoxycarbonyl-phenyl)-3-oxo-piperidine-1-carboxylate

20 Dess-Martin periodinane (29.1 g, 68.5 mmol) was added in portions to a stirred solution of tert-butyl 3-hydroxy-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate (Example 87A) (5.0 g, 13.7 mmol) in DCM (100 mL) under a nitrogen atmosphere. The solution was stirred for 30 minutes then filtered through a pad of celite washing with DCM (50 mL) and then solid NaHCO<sub>3</sub> was added to the filtrate to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (4.9 g, 99%) which was used without further purification.

#### 97B. tert-Butyl 3,3-difluoro-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate

30 Diethylaminosulfur trifluoride (5.4 mL, 40.5 mmol) was added dropwise over 10 minutes to a stirred solution of tert-butyl 4-(3-methoxy-4-methoxycarbonyl-phenyl)-3-oxo-piperidine-1-carboxylate (4.9 g, 13.5 mmol) in DCM (100 mL) at -78°C under a

nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into saturated sodium bicarbonate solution (100 mL) and the separated aqueous phase extracted with EtOAc (4 x 60 mL). The combined organic extracts were washed with 1N citric acid solution (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue that was purified by column chromatography on neutral silica gel using 10% EtOAc/hexane as the eluent to give the title compound (2.6 g, 50%).

97C. tert-Butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]-3,3-difluoro-piperidine-1-carboxylate

10 A solution of LiHMDS (1.0 M in hexane, 22.8 mL, 22.8 mmol) was added dropwise over 30 minutes to a stirred solution of acetonitrile (1.33 g, 3.25 mmol) in dry THF (25 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl 3,3-difluoro-4-(3-methoxy-4-methoxycarbonyl-phenyl)piperidine-1-carboxylate (2.5 g, 6.5 mmol) in THF (25 mL) was added dropwise over 20 minutes  
15 maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into cold saturated ammonium chloride solution (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the  
20 title compound (2.5 g, 98%) which was used without further purification.

97D. tert-Butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]-3,3-difluoro-piperidine-1-carboxylate

A solution of tert-butyl 4-[4-(2-cyanoacetyl)-3-methoxy-phenyl]-3,3-difluoro-piperidine-1-carboxylate (2.5 g, 6.3 mmol) and hydrazine hydrate (99% in water, 1.58 g, 31.5  
25 mmol) in ethanol (50 mL) was heated to reflux for 15 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 50% EtOAc/hexane as the eluent to give the title compound (1.8 g, 70%).

97E. tert-Butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-3,3-difluoro-piperidine-1-carboxylate

30 A stirred solution of tert-butyl 4-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]-3,3-difluoro-piperidine-1-carboxylate (0.5 g, 1.2 mmol), diisopropylethylamine (0.63 mL, 3.6 mmol) and 5-bromopyrazine-2-carbonitrile (0.66 g, 3.6 mmol) in dry 1,4-dioxane

(10 mL) was heated to 80°C for 24 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by  
5 column chromatography on neutral silica gel using 2% MeOH/DCM as the eluent to give the title compound (0.43 g, 69%).

97F. 5-[[5-[4-(3,3-difluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

4N HCl in dioxane (4 mL) was added to a stirred solution of tert-butyl 4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-3,3-difluoro-piperidine-1-carboxylate (0.70 g, 1.4 mmol) in a mixture of dry MeCN (16 mL) and dry THF (16 mL) and the resulting mixture stirred at room temperature for 1 hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (0.30 g, 92%) as an off-white solid.

15 97G. 5-[[5-[4-(3,3-Difluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.12 mL, 0.66 mmol) was added to a stirred suspension of 5-[[5-[4-(3,3-difluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.15 g, 0.33 mmol) in a mixture of MeOH (1.5 mL) and  
20 MeCN (6.5 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Formalin (37-41% w/v in water; 0.05 mL, 1.06 mmol) was added and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.22 g, 1.06 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further 20 minutes then  
25 poured into ice-water (30 mL). The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 2% MeOH/DCM as the eluent to leave an off-white solid. The solid was dissolved in a mixture of THF (3 mL) and MeCN (3 mL)  
30 and a solution of 4N HCl in dioxane (1 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (120 mg, 77%) as an off-white solid.

Synthetic Route O

(Illustrated with reference to Example 107:

Example 107

5 5-[[5-[2-Methoxy-4-[(1-methyl-4-piperidyl)methylamino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

107A. tert-Butyl 4-[(3-methoxy-4-methoxycarbonyl-anilino)methyl]piperidine-1-carboxylate

Nitrogen was bubbled through a stirred suspension of methyl 4-bromo-2-methoxybenzoate (4.0 g, 16.3 mmol), tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (3.5 g, 16.3 mmol), cesium carbonate (10.6 g, 32.6 mmol) and xantphos (3.76 g, 6.5 mmol) in 1,4-dioxane (80 mL) for 20 minutes. Pd<sub>2</sub>(dba)<sub>3</sub> (2.39 g, 2.6 mmol) was added and the resulting mixture heated to 80°C for 6 hours. The cooled reaction mixture was poured into water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 30% EtOAc/hexanes as the eluent to give the title compound (4.5 g, 73%).

107B. tert-Butyl 4-[(N-tert-butoxycarbonyl-3-methoxy-4-methoxycarbonyl-anilino)methyl]piperidine-1-carboxylate

20 A stirred solution of tert-butyl 4-[(3-methoxy-4-methoxycarbonyl-anilino)methyl]piperidine-1-carboxylate (1.15 g, 3.0 mmol), Boc<sub>2</sub>O (9.8 g, 4.5 mmol), diisopropylethylamine (2.6 mL, 1.5 mmol) and 4-dimethylaminopyridine (0.04 g, 0.3 mmol) in THF (5 mL) was heated to 75°C for 18 hours. The cooled reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 20% EtOAc/hexanes as the eluent to give the title compound (2.6 g, 45%).

107C. tert-Butyl 4-[[N-tert-butoxycarbonyl-4-(2-cyanoacetyl)-3-methoxy-anilino]methyl]piperidine-1-carboxylate

A solution of LiHMDS (1.0 M in hexane, 37.8 mL, 37.8 mmol) was added dropwise over 30 minutes to a stirred solution of acetonitrile (2.2 g, 5.40 mmol) in dry THF (100 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl 4-[[N-tert-butoxycarbonyl-3-methoxy-4-methoxycarbonyl-anilino]methyl]piperidine-1-carboxylate (2.6 g, 5.4 mmol) in THF (100 mL) was added dropwise over 30 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for 2 hours. The mixture was poured into cold saturated ammonium chloride solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (2.7 g, 98%) which was used without further purification.

107D. tert-Butyl 4-[[4-(3-amino-1H-pyrazol-5-yl)-N-tert-butoxycarbonyl-3-methoxy-anilino]methyl]piperidine-1-carboxylate

A solution of tert-butyl 4-[[N-tert-butoxycarbonyl-4-(2-cyanoacetyl)-3-methoxy-anilino]methyl]piperidine-1-carboxylate (1.0 g, 2.1 mmol) and hydrazine hydrate (99% in water, 0.42 g, 8.4 mmol) in ethanol (10 mL) was heated to reflux for 18 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1.5% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (0.33 g, 32%).

107E. tert-Butyl 4-[[N-tert-butoxycarbonyl-4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-anilino]methyl]piperidine-1-carboxylate

A stirred solution of tert-butyl 4-[[4-(3-amino-1H-pyrazol-5-yl)-N-tert-butoxycarbonyl-3-methoxy-anilino]methyl]piperidine-1-carboxylate (0.7 g, 1.4 mmol), diisopropylethylamine (0.73 mL, 4.2 mmol) and 5-bromopyrazine-2-carbonitrile (0.77 g, 4.2 mmol) in dry 1,4-dioxane (10 mL) was heated to 80°C for 48 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a

residue which was purified by column chromatography on neutral silica gel using 1% MeOH/DCM as the eluent to give the title compound (0.47 g, 57%).

107F. 5-[[5-[2-Methoxy-4-(4-piperidylmethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

- 5 4N HCl in dioxane (5 mL) was added to a stirred suspension of tert-butyl 4-[[N-tert-butoxycarbonyl-4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-anilino]methyl]piperidine-1-carboxylate (0.50 g, 0.83 mmol) in a mixture of dry MeCN (4 mL) and dry THF (4 mL) and the resulting mixture stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure to leave a solid that
- 10 was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (0.44 g, 98%) as an off-white solid.

107G. 5-[[5-[2-Methoxy-4-[(1-methyl-4-piperidyl)methylamino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

- Diisopropylethylamine (0.12 mL, 0.68 mmol) was added to a stirred suspension of 5-
- 15 [[5-[2-methoxy-4-(4-piperidylmethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.15 g, 0.34 mmol) in a mixture of MeOH (3 mL) and MeCN (6 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Formalin (37-41% w/v in water; 0.06 mL, 6.8 mmol) and glacial acetic acid (0.04 mL, 6.8 mmol) were added and the mixture stirred for a further 20 minutes
- 20 then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.23 g, 1.09 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further 45 minutes then poured into ice-water (30 mL). The mixture was extracted with EtOAc (4 x 25 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure.
- 25 The residue was purified by column chromatography on neutral silica gel using 16% MeOH/DCM as the eluent to leave an off-white solid. The solid was dissolved in a mixture of THF (4 mL) and MeCN (4 mL) and a solution of 4N HCl in dioxane (0.5 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under reduced pressure to leave a solid that was triturated with a 1:1
- 30 mixture of n-pentane/Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (60 mg, 39%) as an off-white solid.

Synthetic Route P

(Illustrated with reference to Example 117:

Example 117

5-[[5-[2-Methoxy-4-[(2R)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

117A. Methyl 2-methoxy-4-vinyl-benzoate

- 5 A stirred solution of methyl 4-bromo-2-methoxybenzoate (25.0 g, 103 mmol), potassium ethenyl(trifluoro)borate (17.8 g, 133 mmol), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) dichloromethane complex (2.5 g, 3.1 mmol) and trimethylamine (14.3 mL, 103 mmol) in n-propanal (250 mL) was heated to reflux for 3 hours. The cooled reaction mixture was poured into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 5% EtOAc/hexanes as the eluent to give the title compound (16.4 g, 83%).

117B. Methyl 4-[(1R)-1,2-dihydroxyethyl]-2-methoxy-benzoate

- 15 Methyl 2-methoxy-4-vinyl-benzoate (3.5 g, 18.2 mmol) was added to a stirred solution of AD-mix-β (22.0 g) in t-butanol (70 mL) and water (70 mL) at 0°C and the resulting mixture allowed to warm to room temperature. The mixture was stirred for 3 hours then sodium sulfite (6.88 g, 54.6 mmol) was added and stirring continued for one hour. The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a solid. The solid was triturated using n-pentane (3 x 40 mL) and dried to give the title compound (3.5 g, 85%) as a white solid.

117C. Methyl 2-methoxy-4-[(2R)-oxiran-2-yl]benzoate

- 25 Chlorotrimethylsilane (15.7 mL, 124 mmol) was added dropwise to a stirred solution of methyl 4-[(1R)-1,2-dihydroxyethyl]-2-methoxy-benzoate (7.0 g, 31 mmol) and trimethylorthoacetate (15.6 mL, 124 mmol) in DCM (70 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 90 minutes then the solvents were evaporated under reduced pressure. The residue was dissolved in MeOH (15 mL) and potassium carbonate (8.56 g, 62 mmol) was added and the resulting mixture stirred at room temperature under a nitrogen atmosphere for 3 hours. The solvents were evaporated under reduced pressure and the residue partitioned between water (100 mL) and EtOAc (100 mL). The separated aqueous phase was extracted with EtOAc (2

x 100 mL) then the combined organic extracts were washed with brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 23% EtOAc/hexanes as the eluent to give the title compound (5.6 g, 87%).

5 117D. Methyl 4-[(1R)-1-hydroxy-2-(2-hydroxyethylamino)ethyl]-2-methoxy-benzoate

A stirred mixture of methyl 2-methoxy-4-[(2R)-oxiran-2-yl]benzoate (1.0 g, 4.8 mmol) and ethanolamine (2.6 mL, 43.2 mmol) in THF (6 mL) was heated to 60°C for 6 hours. The cooled reaction mixture was poured into water (20 mL) and extracted with a mixture of EtOAc and THF (1:1, 3 x 50 mL). The combined organic extracts were  
10 washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave the title compound (0.9 g, 62%) which was used without further purification.

117E. Methyl 4-[(1R)-2-[tert-butoxycarbonyl(2-hydroxyethyl)amino]-1-hydroxy-ethyl]-2-methoxy-benzoate

Boc<sub>2</sub>O (3.64 g, 16.7 mmol) was added to a stirred solution of methyl 4-[(1R)-1-  
15 hydroxy-2-(2-hydroxyethylamino)ethyl]-2-methoxy-benzoate (4.5 g, 16.7 mmol) and Et<sub>3</sub>N (3.5 mL, 25.1 mmol) in DCM (45 mL) and the resulting mixture stirred at room temperature for 3 hours. The reaction mixture was poured into water (50 mL) and the separated aqueous phase was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated  
20 under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 85% EtOAc/hexanes as the eluent to give the title compound (3.45 g, 56%).

117F. tert-Butyl (2R)-2-(3-methoxy-4-methoxycarbonyl-phenyl)morpholine-4-carboxylate

25 Diethylazodicarboxylate (40% solution in toluene, 10.1 mL, 23.3 mmol) was added dropwise to a stirred solution of methyl 4-[(1R)-2-[tert-butoxycarbonyl(2-hydroxyethyl)amino]-1-hydroxy-ethyl]-2-methoxy-benzoate (3.45 g, 9.3 mmol) and triphenylphosphine (3.66 g, 14.0 mmol) in toluene (60 mL) at 0°C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirring  
30 continued for 12 hours then poured into water (100 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to leave a residue which was



purified by column chromatography on neutral silica gel using 32% EtOAc/hexanes as the eluent to give the title compound (1.85 g, 56%).

117G. tert-Butyl (2R)-2-[4-(2-cyanoacetyl)-3-methoxy-phenyl]morpholine-4-carboxylate

5 A solution of LiHMDS (1.0M in hexane, 32.4 mL, 32.4 mmol) was added dropwise over 40 minutes to a stirred solution of acetonitrile (3.13 mL, 6.0 mmol) in dry THF (150 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl (2R)-2-(3-methoxy-4-methoxycarbonyl-phenyl)morpholine-4-carboxylate (2.1 g, 6.0 mmol) in THF (150 mL) was added dropwise over 30 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes  
10 then allowed to warm to room temperature and stirring continued for 30 minutes. The mixture was poured into cold saturated ammonium chloride solution (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (2.1 g, 98%) which was used without further purification.

15 117H. tert-Butyl (2R)-2-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]morpholine-4-carboxylate

A solution of tert-butyl (2R)-2-[4-(2-cyanoacetyl)-3-methoxy-phenyl]morpholine-4-carboxylate (2.1 g, 5.8 mmol) and hydrazine hydrate (99% in water, 0.44 g, 8.7 mmol) in ethanol (20 mL) was heated to reflux for 12 hours. The mixture was allowed to cool  
20 to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1.8% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (0.78 g, 36%).

117I. tert-Butyl (2R)-2-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]morpholine-4-carboxylate

25 A stirred mixture of tert-butyl (2R)-2-[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]morpholine-4-carboxylate (0.78 g, 2.1 mmol), diisopropylethylamine (0.73 mL, 4.2 mmol), potassium iodide (0.18 g, 1.1 mmol) and 5-bromopyrazine-2-carbonitrile (1.04 g, 5.7 mmol) in dry 1,4-dioxane (10 mL) was heated to 80°C for 18 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL)  
30 and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 65% EtOAc/hexanes as the eluent to give the title compound (0.60 g, 61%).

117J. 5-[[5-[2-methoxy-4-[(2R)-morpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

4N HCl in dioxane (5 mL) was added to a stirred suspension of tert-butyl (2R)-2-[4-[3-  
5 [(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]morpholine-4-  
carboxylate (0.6 g, 1.3 mmol) in a mixture of dry MeCN (5 mL) and dry THF (5 mL) and  
the resulting mixture stirred at room temperature for 3 hours. The solvents were  
evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5  
mL) and dried to give the title compound (0.51 g, 98%) as an off-white solid.

117K. 5-[[5-[2-methoxy-4-[(2R)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.17 mL, 0.98 mmol) was added to a stirred suspension of 5-  
[[5-[2-methoxy-4-[(2R)-morpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-  
carbonitrile hydrochloride (0.16 g, 0.39 mmol) in a mixture of MeOH (5 mL) and MeCN  
15 (5 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen  
atmosphere. Formalin (37-41% w/v in water; 0.3 mL, 3.9 mmol) was added and the  
mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and  
NaBH(OAc)<sub>3</sub> (0.26 g, 1.25 mmol) was added in portions over 10 minutes. The mixture  
was allowed to warm to room temperature and stirred for a further 45 minutes then  
20 poured into ice-water (30 mL). The mixture was extracted with EtOAc (4 x 25 mL) and  
the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and  
evaporated under reduced pressure. The residue was triturated with n-pentane (3 x  
10 mL) and dried. The solid was dissolved in a mixture of THF (3 mL) and MeCN (3  
mL) and a solution of 4N HCl in dioxane (3 mL) was added and the resulting mixture  
stirred for 30 minutes. The solvents were evaporated under reduced pressure to leave  
25 a solid that was triturated with a 10% EtOAc/n-pentane/Et<sub>2</sub>O (3 x 5 mL) and dried to  
leave the title compound (0.12 g, 73%) as a beige solid.

Synthetic Route Q

(Illustrated with reference to Example 123:

Example 123

30 5-[[5-[4-[[3-(3R)-3-fluoropyrrolidin-1-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

123A. Methyl 4-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-methoxy-benzoate

A solution of tert-butyldimethylsilyl chloride (9.99 g, 66.3 mmol) in DMF (20 mL) was added dropwise over a period of 15 minutes to a stirred solution of methyl 4-(hydroxymethyl)-2-methoxy-benzoate (5.0 g, 25.5 mmol) and imidazole (4.17 g, 61.2 mmol) in DMF (50 mL) at 0°C. The mixture was allowed to warm to room temperature and stirring continued for one hour then the mixture was poured into water (200 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 4% EtOAc/hexane as the eluent to give the title compound (4.1 g, 52%).

10 123B. 3-[4-[[tert-Butyl(dimethyl)silyl]oxymethyl]-2-methoxy-phenyl]-3-oxo-propanenitrile

A solution of LiHMDS (1.0M in hexane, 90 mL, 90.0 mmol) was added dropwise over 30 minutes to a stirred solution of acetonitrile (5.4 mL, 103 mmol) in dry THF (220 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of methyl 4-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-methoxy-benzoate (4.0 g, 12.9 mmol) in THF (220 mL) was added dropwise over 30 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for one hour. The mixture was poured into cold saturated ammonium chloride solution (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (4.8 g) which was used without further purification.

123C. 5-[4-[[tert-Butyl(dimethyl)silyl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-amine

A solution of 3-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-methoxy-phenyl]-3-oxo-propanenitrile (4.8 g, 13.3 mmol) and hydrazine hydrate (99% in water, 2.7 g, 53.2 mmol) in ethanol (180 mL) was heated to reflux for 16 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1.5% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (2.0 g, 40%).

30 123D. 5-[[5-[4-[[tert-Butyl(dimethyl)silyl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile

A stirred solution of 5-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-amine (0.6 g, 1.8 mmol), diisopropylethylamine (0.95 mL, 5.4 mmol) and 5-bromopyrazine-2-carbonitrile (0.99 g, 5.4 mmol) in dry 1,4-dioxane (7.5 mL) was

heated to 80°C for 20 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1.5% MeOH/DCM as the eluent to give the title compound (0.60 g, 76%).

123E. 5-[[5-[4-(Hydroxymethyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile

A solution of tetrabutylammonium fluoride (1.0M in THF, 4.2 mL, 4.2 mmol) was added to a stirred solution of 5-[[5-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (0.6 g, 1.4 mmol) in THF (12 mL) at 0°C. The resulting solution was allowed to warm to room temperature and stirring continued for one hour then the mixture was poured into water (40 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (0.93 g) which was used without further purification.

123F. 5-[[5-(4-Formyl-2-methoxy-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile

Dess-Martin periodinane (3.69 g, 8.7 mmol) was added in portions to a stirred solution of 5-[[5-[4-(hydroxymethyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (0.92 g, 2.9 mmol) in THF (50 mL) under a nitrogen atmosphere. The solution was stirred for one hour then filtered through a pad of celite washing with THF (50 mL). The filtrate was evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1.8% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (0.3 g, 33%).

123G. 5-[[5-[4-[(3R)-3-fluoropyrrolidin-1-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.16 mL, 0.94 mmol) was added to a stirred suspension of (3R)-3-fluoropyrrolidine hydrochloride (0.12g, 0.94 mmol) in 1,2-dichloroethane (6 mL) and the mixture stirred for 20 minutes resulting in a colourless solution. 5-[[5-(4-Formyl-2-methoxy-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (0.15 g, 0.47 mmol) and glacial acetic acid (0.056 g, 0.94 mmol) were added and the mixture stirred for 30 minutes then cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.32 g, 1.5 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and

stirred for a further 30 minutes then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (2 x 25 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a solid which was triturated with Et<sub>2</sub>O (3 x 5 mL). The resulting solid was dissolved in a mixture of THF (1 mL) and MeCN (1 mL) and a solution of 4N HCl in dioxane (1 mL) was added and the resulting mixture stirred for 30 minutes. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (76 mg, 38%) as an off-white solid.

10 Synthetic Route R

(Illustrated with reference to Example 140:

Example 140

5-[[5-[4-[(3R)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

15 140A. tert-Butyl (3R)-3-[(3-methoxy-4-methoxycarbonyl-phenyl)methoxy]pyrrolidine-1-carboxylate

A solution of tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate (2.9 g, 15.5 mmol) in DMF (8 mL) was added to a stirred slurry of sodium hydride (60% in mineral oil, 1.86 g, 4.65 mmol) in DMF (10 mL) at 0°C under a nitrogen atmosphere and the resulting mixture stirred for 10 minutes. A solution of methyl 4-(bromomethyl)-2-methoxybenzoate (4.0 g, 15.5 mmol) in DMF (7 mL) was added dropwise over 20 minutes maintaining the temperature at 0°C. The resulting mixture was allowed to warm to room temperature and stirring continued for 30 minutes before cooling back to 0°C. Methyl iodide (2.9 mL, 4.65 mmol) was added and the solution was allowed to warm to room temperature and stirring continued for one hour then the mixture was poured into ice cold water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 20%EtOAc/hexane as the eluent to give the title compound (4.3 g, 76%).

140B. tert-Butyl (3R)-3-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methoxy]pyrrolidine-1-carboxylate

A solution of LiHMDS (1.0M in hexane, 42 mL, 42.0 mmol) was added dropwise over 20 minutes to a stirred solution of acetonitrile (3.2 mL, 60 mmol) in dry THF (50 mL) at  
5 -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl (3R)-3-[(3-methoxy-4-methoxycarbonyl-phenyl)methoxy]pyrrolidine-1-carboxylate (4.3 g, 12.0 mmol) in THF (50 mL) was added dropwise over 30 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and  
10 stirring continued for one hour. The mixture was poured into cold saturated ammonium chloride solution (50 mL) and extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (4.4 g) which was used without further purification.

15 140C. tert-Butyl (3R)-3-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methoxy]pyrrolidine-1-carboxylate

A solution of tert-butyl (3R)-3-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methoxy]pyrrolidine-1-carboxylate (4.4 g, 12.0 mmol) and hydrazine hydrate (99% in water, 1.2 g, 24.0 mmol) in ethanol (45 mL) was heated to reflux for 18 hours.  
20 The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 3% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (2.6 g, 57%).

25 140D. tert-Butyl (3R)-3-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methoxy]pyrrolidine-1-carboxylate

A stirred solution of tert-butyl (3R)-3-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methoxy]pyrrolidine-1-carboxylate (1.0 g, 2.6 mmol), diisopropylethylamine (1.4 mL, 7.8 mmol) and 5-bromopyrazine-2-carbonitrile (1.43 g, 7.8 mmol) in dry 1,4-dioxane (20 mL) was heated to 80°C for 48 hours. After cooling to room temperature  
30 the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was

purified by column chromatography on neutral silica gel using 2% MeOH/DCM as the eluent to give the title compound (0.90 g, 71%).

140E. 5-[[5-[2-Methoxy-4-[(3R)-pyrrolidin-3-yl]oxymethyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

- 5 4N HCl in dioxane (3 mL) was added to a stirred solution of tert-butyl (3R)-3-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methoxy]pyrrolidine-1-carboxylate (0.90 g, 1.8 mmol) in a mixture of dry MeCN (10 mL) and dry THF (10 mL) and the resulting mixture stirred at room temperature for 3 hours. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 2  
10 mL) followed by n-pentane (2 x 5 mL) and dried to give the title compound (0.8 g, 100%) as an off-white solid.

140F. 5-[[5-[4-[(3R)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile

- Diisopropylethylamine (0.08 mL, 0.46 mmol) was added to a stirred suspension of 5-  
15 [[5-[2-methoxy-4-[(3R)-pyrrolidin-3-yl]oxymethyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.5 g, 1.2 mmol) in a mixture of MeOH (10 mL) and MeCN (15 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Acetaldehyde (0.35 mL, 6.0 mmol) was added and the mixture stirred for a further 30 minutes then the mixture was cooled to 0°C and  
20 NaBH(OAc)<sub>3</sub> (0.81 g, 3.8 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further 30 minutes then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH to 8. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure.  
25 The residue was purified by column chromatography on neutral silica gel using 10% MeOH/CHCl<sub>3</sub> as the eluent to leave a solid. The solid was dissolved in a mixture of THF (2 mL) and MeCN (2 mL) and a solution of 4N HCl in dioxane (0.5 mL) was added and the resulting mixture stirred for one hour. The solvents were evaporated under  
30 reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 5 mL) and dried to give the title compound (66 mg, 12%) as an off-white solid.

Synthetic Route S

(Illustrated with reference to Example 143:

Example 143

5-[[5-[4-[(1-Ethyl-4-piperidyl)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

143A. Methyl 4-(diethoxyphosphorylmethyl)-2-methoxy-benzoate

- 5 A solution of methyl 4-(bromomethyl)-2-methoxy-benzoate (6.0 g, 23.3 mmol) in triethyl phosphite (12 mL) was heated to 100°C in a sealed tube for 12 hours. The solution was allowed to cool to room temperature and evaporated under reduced pressure to leave the title compound (7.2 g, 98%) as a yellow solid which was used without further purification.

10 143B. tert-Butyl 4-[(3-methoxy-4-methoxycarbonyl-phenyl)methylene]piperidine-1-carboxylate

- A solution of methyl 4-(diethoxyphosphorylmethyl)-2-methoxy-benzoate (7.0 g, 22.1 mmol) in anhydrous THF (25 mL) was added dropwise over 10 minutes to a stirred slurry of sodium hydride (60% dispersion in oil, 2.65 g, 66.3 mmol) in anhydrous THF (50 mL) at 0°C under a nitrogen atmosphere. The resulting mixture was stirred for 30 minutes then a solution of tert-butyl 4-oxopiperidine-1-carboxylate (4.4 g, 22.1 mmol) in THF (25 mL) was added dropwise over 10 minutes. The mixture was allowed to warm to room temperature and stirring continued for one hour then the mixture was poured into ice-water (100 mL) and extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (7.0 g, 91%) which was used without further purification.

20 143C. tert-Butyl 4-[(3-methoxy-4-methoxycarbonyl-phenyl)methyl]piperidine-1-carboxylate

- 25 A suspension of tert-butyl 4-[(3-methoxy-4-methoxycarbonyl-phenyl)methylene]piperidine-1-carboxylate (7.0 g, 19.4 mmol) and 10% Pd on carbon (1.6 g) in MeOH (140 mL) was stirred under a hydrogen atmosphere for 3 hours. The mixture was filtered through a pad of celite and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 30% EtOAc/hexane as the eluent to give the title compound (6.0 g, 85%).
- 30



143D. tert-butyl 4-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]piperidine-1-carboxylate

A solution of LiHMDS (1.0M in hexane, 29 mL, 29.0 mmol) was added dropwise over 20 minutes to a stirred solution of acetonitrile (2.2 mL, 41.5 mmol) in dry THF (30 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl 4-[(3-methoxy-4-methoxycarbonyl-phenyl)methyl]piperidine-1-carboxylate (3.0 g, 8.3 mmol) in THF (30 mL) was added dropwise over 30 minutes maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for 30 minutes. The mixture was poured into cold saturated ammonium chloride solution (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (3.0 g, 98%) which was used without further purification.

143E. tert-Butyl 4-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]piperidine-1-carboxylate

A solution of tert-butyl 4-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]piperidine-1-carboxylate (3.0 g, 8.1 mmol) and hydrazine hydrate (99% in water, 2.1 mL, 40.5 mmol) in ethanol (30 mL) was heated to reflux for 6 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 2% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (1.3 g, 42%).

143F. tert-Butyl 4-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]piperidine-1-carboxylate

A stirred solution of tert-butyl 4-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]piperidine-1-carboxylate (1.0 g, 2.6 mmol), diisopropylethylamine (1.4 mL, 7.8 mmol) and 5-bromopyrazine-2-carbonitrile (1.43 g, 7.8 mmol) in dry 1,4-dioxane (10 mL) was heated to 80°C for 15 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 1.5% MeOH/DCM as the eluent to give the title compound (0.70 g, 55%).

143G. 5-[[5-[2-Methoxy-4-(4-piperidylmethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

4N HCl in dioxane (5 mL) was added to a stirred solution of tert-butyl 4-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]piperidine-1-carboxylate (0.70 g, 1.4 mmol) in a mixture of dry MeCN (10 mL) and dry THF (10 mL) and the resulting mixture stirred at room temperature for 2 hours. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 2 mL) and dried to give the title compound (0.6 g, 99%) as an off-white solid.

143H. 5-[[5-[4-[(1-ethyl-4-piperidyl)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.23 mL, 1.3 mmol) was added to a stirred suspension of 5-[[5-[2-methoxy-4-(4-piperidylmethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.28 g, 0.65 mmol) in a mixture of MeOH (10 mL) and THF (10 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Acetaldehyde (0.18 mL, 3.2 mmol) was added and the mixture stirred for a further 20 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.44 g, 2.08 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further 30 minutes then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 9% MeOH/DCM as the eluent. The resulting solid was dissolved in a mixture of THF (10 mL) and MeCN (10 mL) and a solution of 4N HCl in dioxane (0.5 mL) was added and the resulting mixture stirred for 30 minutes. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (0.18 g, 60%) as a pale yellow solid.

Synthetic Route T

(Illustrated with reference to Example 149:

Example 149

5-[[5-[4-[[[(2R)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride)

149A. tert-Butyl (2R)-2-formylpyrrolidine-1-carboxylate

- 5 Dess-Martin periodinane (15.9 g, 37.4 mmol) was added in portions over 5 minutes to a stirred solution of tert-butyl (2R)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (5.0 g, 24.9 mmol) in DCM (75 mL) under a nitrogen atmosphere. The resulting suspension was stirred for one hour then filtered through a pad of celite washing with DCM (100 mL). The filtrate was evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 12% EtOAc/hexanes as the eluent to give the title compound (4.4 g, 89%).

149B. tert-Butyl (2R)-2-[(E)-(p-tolylsulfonylhydrazono)methyl]pyrrolidine-1-carboxylate

- 10 4-Methylbenzenesulfonylhydrazide (3.7 g, 22.1 mmol) was added to a stirred solution of tert-butyl (2R)-2-formylpyrrolidine-1-carboxylate (4.4 g, 22.1 mmol) in EtOH (45 mL) and the resulting solution was heated to 90°C for 2 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to leave a solid that was recrystallized from EtOH to give the title compound (5.1 g, 63%).

15 149C. tert-Butyl (2R)-2-[(4-acetyl-3-methoxy-phenyl)methyl]pyrrolidine-1-carboxylate

- A mixture of tert-butyl (2R)-2-[(E)-(p-tolylsulfonylhydrazono)methyl]pyrrolidine-1-carboxylate (1.7 g, 4.6 mmol), (3-methoxy-4-methoxycarbonyl-phenyl)boronic acid (1.16 g, 5.5 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.95 g, 6.9 mmol) in 1,4-dioxane (45 mL) was stirred at 110°C for 3 hours. The cooled reaction mixture was evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 13% EtOAc/hexanes as the eluent to give the title compound (1.4 g, 87%).
- 20

149D. tert-Butyl (2R)-2-[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]pyrrolidine-1-carboxylate

- 25 A solution of LiHMDS (1.0M in hexane, 14 mL, 14.0 mmol) was added dropwise over 30 minutes to a stirred solution of acetonitrile (0.8 g, 20.0 mmol) in dry THF (70 mL) at -78°C under a nitrogen atmosphere. Stirring was continued for 30 minutes then a solution of tert-butyl (2R)-2-[(4-acetyl-3-methoxy-phenyl)methyl]pyrrolidine-1-carboxylate (1.4 g, 4.0 mmol) in THF (70 mL) was added dropwise over 30 minutes
- 30 maintaining the temperature at -78°C. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and stirring continued for 30 minutes. The mixture was poured into cold saturated ammonium chloride solution (50 mL) and

extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to leave the title compound (1.9 g, 98%) which was used without further purification.

5 149E. tert-Butyl (2R)-2-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]pyrrolidine-1-carboxylate

A solution of tert-butyl (2R)-2-[[4-(2-cyanoacetyl)-3-methoxy-phenyl]methyl]pyrrolidine-1-carboxylate (1.8 g, 5.2 mmol) and hydrazine hydrate (99% in water, 1.04 g, 20.8 mmol) in ethanol (20 mL) was heated to reflux for 16 hours. The mixture was allowed to cool to room temperature and the solvents evaporated under reduced pressure to  
10 leave a residue which was purified by column chromatography on neutral silica gel using 2% MeOH/CHCl<sub>3</sub> as the eluent to give the title compound (1.0 g, 52%).

149F. tert-Butyl (2R)-2-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]pyrrolidine-1-carboxylate

A stirred solution of tert-butyl (2R)-2-[[4-(3-amino-1H-pyrazol-5-yl)-3-methoxy-phenyl]methyl]pyrrolidine-1-carboxylate (1.0 g, 2.7 mmol), diisopropylethylamine (1.4 mL, 8.1 mmol) and 5-bromopyrazine-2-carbonitrile (1.5 g, 8.1 mmol) in dry 1,4-dioxane (11 mL) was heated to 70°C for 16 hours. After cooling to room temperature the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>)  
15 and evaporated under reduced pressure to leave a residue which was purified by column chromatography on neutral silica gel using 45% EtOAc/hexanes as the eluent to give the title compound (0.70 g, 55%).  
20

149G. 5-[[5-[2-Methoxy-4-[(2R)-pyrrolidin-2-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

25 4N HCl in dioxane (2 mL) was added to a stirred solution of tert-butyl (2R)-2-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]pyrrolidine-1-carboxylate (0.70 g, 1.4 mmol) in a mixture of dry MeCN (10 mL) and dry THF (10 mL) and the resulting mixture stirred at room temperature for 2 hours. The solvents were evaporated under reduced pressure to leave a solid that was triturated with EtOAc (3 x  
30 2 mL) and dried to give the title compound (0.55 g, 91%) as an off-white solid.

149H. 5-[[5-[4-[[[(2R)-1-Ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride

Diisopropylethylamine (0.18 mL, 1.0 mmol) was added to a stirred suspension of 5-[[5-[2-methoxy-4-[[[(2R)-pyrrolidin-2-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride (0.22 g, 0.53 mmol) in a mixture of MeOH (5 mL) and THF (5 mL) and the mixture stirred for 20 minutes at room temperature under a nitrogen atmosphere. Acetaldehyde (0.12 mL, 2.1 mmol) was added and the mixture stirred for a further 30 minutes then the mixture was cooled to 0°C and NaBH(OAc)<sub>3</sub> (0.36 g, 1.7 mmol) was added in portions over 10 minutes. The mixture was allowed to warm to room temperature and stirred for a further one hour then poured into ice-water (30 mL) and solid NaHCO<sub>3</sub> was added to adjust the pH of the solution to 8. The mixture was extracted with EtOAc (5 x 50 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by column chromatography on neutral silica gel using 4% MeOH/DCM as the eluent. The resulting solid was dissolved in a mixture of THF (5 mL) and MeCN (5 mL) and a solution of 4N HCl in dioxane (0.2 mL) was added and the resulting mixture stirred for 30 minutes. The solvents were evaporated under reduced pressure to leave a solid that was triturated with Et<sub>2</sub>O (3 x 10 mL) and dried to give the title compound (84 mg, 36%) as a light brown solid.

20 **BIOLOGICAL ACTIVITY**

**EXAMPLE A**

**Chk-1 Kinase Inhibiting Activity**

The compounds of the invention were tested for activity against Chk-1 kinase using the materials and protocols set out below.

25 **Reaction Buffer:**

Base Reaction buffer: 20 mM Hepes (pH 7.5), 10 mM MgCl<sub>2</sub>, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM DTT, 1% DMSO

\*Required cofactors are added individually to each kinase reaction

**Reaction Procedure:**

30 (i) Prepare indicated substrate in freshly prepared Base Reaction Buffer

- (ii) Deliver any required cofactors to the substrate solution above
- (iii) Deliver indicated kinase into the substrate solution and gently mix
- (iv) Deliver compounds in DMSO into the kinase reaction mixture
- (v) Deliver <sup>33</sup>P-ATP (specific activity 0.01  $\mu$ Ci/ $\mu$ l final) into the reaction mixture to  
5 initiate the reaction.
- (vi) Incubate kinase reaction for 120 minutes at room temperature
- (vii) Reactions are spotted onto P81 ion exchange paper (Whatman # 3698-915)
- (viii) Wash filters extensively in 0.1% phosphoric acid.
- (ix) Dry filters and measure counts in scintillation counter

10 **Kinase information:**

CHK-1 – Genbank Accession # AF016582

Recombinant full length construct, N-terminal GST tagged, purified from insect cells.

No special measures were taken to activate this kinase.

Final concentration in assay = 0.5 nM

15 Substrate: CHKtide

Peptide sequence: [KKKVSRSGLYRSPSPENLNRPR]

Final concentration in assay = 20 $\mu$ M

No additional cofactors are added to the reaction mixture

- From the results obtained by following the above protocol, the IC<sub>50</sub> values against Chk-  
20 1 kinase of each of the compounds of Examples 1-153 were determined and these are shown in Table 3.

Example	IC <sub>50</sub> ( $\mu$ M)	Example	IC <sub>50</sub> ( $\mu$ M)	Example	IC <sub>50</sub> ( $\mu$ M)
1	0.0028	55	0.227	109	0.000087
2	0.0027	56	0.183	110	0.0000069
3	0.00021	57	0.000071	111	0.0000052
4	0.00019	58	0.00054	112	0.0000042
5	0.0020	59	0.000071	113	0.00027
6	0.000097	60	0.00010	114	0.00020
7	0.00010	61	0.00010	115	0.00024
8	0.000058	62	0.000084	116	0.000077
9	0.000077	63	0.000052	117	0.000027
10	0.011	64	0.00015	118	0.000022

Table 3					
Example	IC <sub>50</sub> (μM)	Example	IC <sub>50</sub> (μM)	Example	IC <sub>50</sub> (μM)
11	0.000048	65	0.000022	119	ND
12	0.000034	66	0.00014	120	ND
13	0.00059	67	0.0018	121	0.00015
14	0.000026	68	0.0029	122	0.00014
15	0.00030	69	0.0079	123	0.00016
16	0.000085	70	0.010	124	0.00025
17	0.00029	71	>0.1	125	0.00028
18	0.00017	72	0.00016	126	0.000056
19	0.00029	73	0.00028	127	0.000044
20	0.00029	74	0.00035	128	0.000023
21	0.0024	75	0.00055	129	0.000046
22	0.000026	76	0.00011	130	0.000025
23	0.00012	77	0.00014	131	0.00010
24	0.00024	78	0.00069	132	0.00011
25	0.014	79	0.00040	133	0.00012
26	0.010	80	0.00019	134	0.00011
27	0.0036	81	0.00015	135	0.000054
28	0.00013	82	0.000016	136	0.000053
29	0.000068	83	0.00011	137	0.000048
30	0.017	84	0.00014	138	0.000041
31	0.00037	85	0.00025	139	0.000027
32	0.00026	86	0.00012	140	0.000021
33	0.000074	87	0.000059	141	0.000019
34	0.00014	88	0.000079	142	0.000082
35	0.00014	89	0.000051	143	0.000021
36	0.000095	90	0.000058	144	0.000026
37	0.00011	91	0.00033	145	0.0000084
38	0.00088	92	0.000016	146	0.000012
39	0.00018	93	0.000016	147	0.00016
40	0.00014	94	0.00018	148	0.000031
41	0.00051	95	0.00015	149	ND
42	0.00021	96	0.00040	150	ND
43	0.00073	97	0.0011	151	ND
44	0.00069	98	0.0018	152	ND
45	>0.1	99	0.00015	153	0.0038
46	0.000054	100	0.000053		
47	0.00023	101	0.000055		
48	0.0015	102	0.00016		
49	0.036	103	0.000109		
50	0.020	104	0.00012		
51	0.0063	105	0.000		
52	0.00046	106	0.00017		
53	0.0031	107	0.000081		
54	0.00012	108	0.000043		

ND = Not determined

EXAMPLE BGemcitabine Combination Cell Assay

Exponentially growing MIA PaCa-2 (ATCC CRL-1420) cells are treated with trypsin to remove cells from the plate surface. Approximately 10,000 cells/well are plated in 96 well plates in RPMI containing 10% fetal bovine serum, 1% sodium pyruvate and 1% L-GlutaMax. Cells are allowed to adhere to the plate surface overnight. Serial half-log dilutions of Chk1 inhibitor test compounds and gemcitabine are made with a final highest concentration of 3000nM and 100nM, respectively. Chk1 inhibitors and gemcitabine are combined so that each concentration of Chk1 inhibitor is added to each concentration of gemcitabine. Each drug is also tested as a single agent. Drugs are added to adherent cells (in duplicate) and incubated for 72h. At 72h the cells are treated with Promega Cell Titer Glo reagent for approximately 15 minutes. Luminescence (relative light units, RLU) is recorded using a BMG Polarstar Omega plate reader. The single agent concentration that results in a 50% reduction in total signal (IC<sub>50</sub>) is calculated using PRISM software and a four-parameter non-linear regression curve fit. For combination studies the RLUs are plotted using PRISM on an XY plot with the gemcitabine concentration on the X axis and RLU on the Y axis. The RLU for each concentration of Chk1 inhibitor is plotted as a function of gemcitabine concentration. The IC<sub>50</sub> for gemcitabine alone and at each concentration of Chk1 is determined using a four-parameter non-linear regression curve fit. The approximate concentration of Chk1 inhibitor that results in a two and ten-fold reduction in the IC<sub>50</sub> of gemcitabine alone is calculated as an indication of synergistic potency.

From the results obtained by following the above protocol, the IC<sub>50</sub> values against MIA PaCa-2 cells of the Chk1 inhibitor alone (Chk1 IC<sub>50</sub>), the approximate concentration of Chk1 inhibitor that results in a two-fold (2xLS) and a 10-fold (10xLS) reduction in the IC<sub>50</sub> of gemcitabine alone of each of the compounds of Examples 1-154 are shown in Table 4.

Table 4							
Example	Chk1 IC <sub>50</sub> (nM)	2xLS (nM)	10xLS (nM)	Example	Chk1 IC <sub>50</sub> (nM)	2xLS (nM)	10xLS (nM)
1	5386	100	1000	78	136	10	100
2	1411	100	1000	79	478	3	100
3	275	10	100	80	36	<3	10
4	ND	ND	ND	81	36	<3	<30
5	ND	ND	ND	82	74	<3	<30
6	338	30	300	83	107	<3	<100



Table 4							
Example	Chk1 IC <sub>50</sub> (nM)	2xLS (nM)	10xLS (nM)	Example	Chk1 IC <sub>50</sub> (nM)	2xLS (nM)	10xLS (nM)
7	208	10	~200	84	62	<3	<100
8	259	10	~200	85	138	3	100
9	227	3	100	86	239	<3	<100
10	>3000	1000	>3000	87	540	10	300
11	214	3	<100	88	424	10	300
12	264	<3	~50	89	193	<3	100
13	>3000	~20	300	90	390	10	<300
14	894	<3	~50	91	411	<3	<100
15	2207	~5	~3000	92	132	<3	30
16	1798	<3	100	93	99	<3	<30
17	1819	10	300	94	475	3	100
18	1610	~5	~200	95	183	<3	<100
19	1608	3	~200	96	730	10	<300
20	1111	~5	100	97	1495	10	300
21	3181	100	1000	98	1778	10	<1000
22	88	<3	<30	99	233	<3	30
23	266	<3	<100	100	247	3	<100
24	934	10	300	101	199	3	<100
25	>3000	300	>3000	102	957	10	300
26	5585	1000	>3000	103	184	3	300
27	5753	300	3000	104	214	3	100
28	279	<3	<100	105	2303	30	1000
29	176	3	100	106	441	3	100
30	>3000	1000	>3000	107	160	3	100
31	838	3	100	108	77	<3	30
32	784	30	300	109	82	<3	<30
33	62	<3	<30	110	192	3	100
34	183	3	100	111	184	<3	100
35	217	3	100	112	253	<3	100
36	281	3	100	113	531	3	300
37	182	3	<100	114	469	3	<300
38	2754	100	1000	115	515	3	<300
39	168	<3	30	116	209	3	100
40	188	<3	30	117	1890	10	1000
41	1114	30	300	118	1198	3	300
42	73	<3	<30	119	687	10	<300
43	1329	100	1000	120	397	3	100
44	1264	100	1000	121	177	3	<100
45	ND	ND	ND	122	136	3	<100
46	442	<3	<30	123	440	3	<300
47	235	3	100	124	322	3	<300
48	2021	100	1000	125	550	10	<300
49	3566	1000	<3000	126	210	3	<100
50	>3000	300	3000	127	169	<3	<100
51	>3000	300	3000	128	158	<3	<100

Table 4							
Example	Chk1 IC <sub>50</sub> (nM)	2xLS (nM)	10xLS (nM)	Example	Chk1 IC <sub>50</sub> (nM)	2xLS (nM)	10xLS (nM)
52	953	30	300	129	278	<3	<100
53	2296	100	1000	130	142	3	<100
54	137	<3	30	131	592	3	100
55	>3000	1000	>3000	132	411	3	<300
56	>3000	1000	>3000	133	139	<3	30
57	337	3	100	134	352	3	100
58	676	30	300	135	334	<3	100
59	263	3	100	136	228	3	100
60	329	3	100	137	256	<3	<100
61	251	2	100	138	836	<10	300
62	875	10	300	139	743	10	300
63	600	<3	100	140	618	<10	<300
64	144	3	100	141	970	<10	<300
65	144	3	<100	142	306	3	100
66	111	<3	30	143	820	<10	<300
67	1320	100	1000	144	829	10	<300
68	1384	100	1000	145	267	<3	<100
69	2202	100	1000	146	433	3	100
70	2621	300	3000	147	1205	10	300
71	>3000	>3000	>3000	148	254	<3	<100
72	173	10	100	149	188	<3	30
73	354	10	300	150	259	3	100
74	282	3	100	151	101	<3	<30
75	>3000	>3000	>3000	152	428	3	100
76	482	10	300	153	1197	100	1000
77	164	<3	<100	154	395	3	100

ND = Not determined

### EXAMPLE C

#### PHARMACEUTICAL FORMULATIONS

##### 5 (i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50 mg of the compound with 197 mg of lactose (BP) as diluent, and 3 mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100 mg of a compound of the formula (I) with 100 mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

5 (iii) Injectable Formulation I

A parenteral composition for administration by injection can be prepared by dissolving a compound of the formula (0) or formula (1) (e.g. in a salt form) in water containing 10% propylene glycol to give a concentration of active compound of 1.5 % by weight. The solution is then sterilised by filtration, filled into an ampoule and sealed.

10 (iv) Injectable Formulation II

A parenteral composition for injection is prepared by dissolving in water a compound of the formula (0) or formula (1) (e.g. in salt form) (2 mg/ml) and mannitol (50 mg/ml), sterile filtering the solution and filling into sealable 1 ml vials or ampoules.

v) Injectable formulation III

15 A formulation for i.v. delivery by injection or infusion can be prepared by dissolving the compound of formula (0) or formula (1) (e.g. in a salt form) in water at 20 mg/ml. The vial is then sealed and sterilised by autoclaving.

vi) Injectable formulation IV

20 A formulation for i.v. delivery by injection or infusion can be prepared by dissolving the compound of formula (0) or formula (1) (e.g. in a salt form) in water containing a buffer (e.g. 0.2 M acetate pH 4.6) at 20mg/ml. The vial is then sealed and sterilised by autoclaving.

(vii) Subcutaneous Injection Formulation

25 A composition for sub-cutaneous administration is prepared by mixing a compound of the formula (0) or formula (1) with pharmaceutical grade corn oil to give a concentration of 5 mg/ml. The composition is sterilised and filled into a suitable container.

viii) Lyophilised formulation

Aliquots of formulated compound of formula (0) or formula (1) are put into 50 ml vials and lyophilized. During lyophilisation, the compositions are frozen using a one-step freezing protocol at (−45 °C). The temperature is raised to −10 °C for annealing, then  
5 lowered to freezing at −45 °C, followed by primary drying at +25 °C for approximately 3400 minutes, followed by a secondary drying with increased steps if temperature to 50 °C. The pressure during primary and secondary drying is set at 80 millitor.

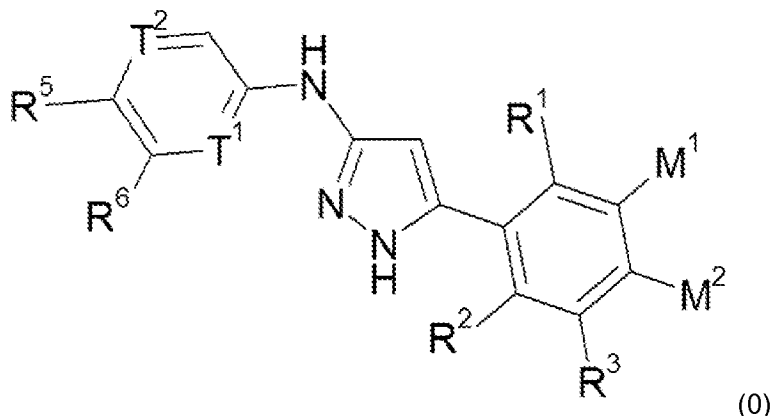
Equivalentents

The foregoing examples are presented for the purpose of illustrating the invention and  
10 should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

15

**CLAIMS**

1. A compound of the formula (0):



or a salt, N-oxide or tautomer thereof, wherein:

T<sup>1</sup> is selected from N and CH;

T<sup>2</sup> is selected from N, CH and CF;

R<sup>1</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy;

R<sup>2</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy;

R<sup>3</sup> is selected from hydrogen, methyl, fluorine, chlorine and bromine;

one of M<sup>1</sup> and M<sup>2</sup> is a group R<sup>4</sup> selected from hydrogen, methyl, fluorine, chlorine and bromine; and the other of M<sup>1</sup> and M<sup>2</sup> is a moiety -A-R<sup>7</sup>;

R<sup>5</sup> is selected from hydrogen, cyano, C<sub>1-3</sub> alkyl, cyclopropyl, chlorine, carboxy, and C<sub>1-3</sub>-alkoxy-carbonyl;

R<sup>6</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> alkyl; and C<sub>1-4</sub> alkoxy optionally substituted with NR<sup>d</sup>R<sup>e</sup> where R<sup>d</sup> and R<sup>e</sup> are the same or different and each is selected from hydrogen and C<sub>1-4</sub> alkyl, or NR<sup>d</sup>R<sup>e</sup> forms a 4 to 7 membered saturated heterocyclic ring optionally containing a second heteroatom ring member selected from N, O and S and oxidized forms of S, the saturated heterocyclic ring being optionally substituted with one or more substituents selected from oxo, methyl, hydroxy and fluorine;

A is selected from:

- (i) a bond;
- (ii) (CR<sup>p</sup>R<sup>q</sup>)<sub>x</sub> where R<sup>p</sup> and R<sup>q</sup> are each independently hydrogen or methyl and x is 1 to 4;
- (iii) an oxygen atom;
- (iv) a group NR<sup>r</sup> wherein R<sup>r</sup> is hydrogen or methyl; and
- (v) a saturated chain of 2 to 10 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member

selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbyl, fluoro-C<sub>1-4</sub> hydrocarbyl, hydroxy-C<sub>1-4</sub> hydrocarbyl, C<sub>1-2</sub>-alkoxy-C<sub>1-4</sub> hydrocarbyl, and fluorine wherein two hydrocarbyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members; R<sup>7</sup> is selected from hydrogen; R<sup>11</sup>SO<sub>2</sub>-; amino; NH-Hyd<sup>1</sup>; N(Hyd<sup>1</sup>)<sub>2</sub>; and a group Cyc<sup>1</sup> wherein Cyc<sup>1</sup> is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 10 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents R<sup>8</sup>; provided that when A is a bond, (CR<sup>p</sup>R<sup>q</sup>)<sub>x</sub>, an oxygen atom or NR<sup>r</sup>, then R<sup>7</sup> is other than hydrogen; and provided also that when R<sup>7</sup> is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members;

R<sup>8</sup> is selected from:

- halogen;
- oxo;
- cyano;
- nitro;
- a carbocyclic or heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; and
- a group R<sup>a</sup>-R<sup>b</sup>;

R<sup>a</sup> is a bond, O, CO, X<sup>1</sup>C(X<sup>2</sup>), C(X<sup>2</sup>)X<sup>1</sup>, X<sup>1</sup>C(X<sup>2</sup>)X<sup>1</sup>, S, SO, SO<sub>2</sub>, NR<sup>c</sup>, SO<sub>2</sub>NR<sup>c</sup> or NR<sup>c</sup>SO<sub>2</sub>;

R<sup>b</sup> is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- an acyclic C<sub>1-12</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C<sub>1-8</sub> non-aromatic hydrocarbylamino; and carbocyclic and

heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ; wherein one or more but not all of the carbon atoms of the acyclic  $C_{1-12}$  hydrocarbyl group may optionally be replaced by O, S, SO,  $SO_2$ ,  $NR^c$ ,  $X^1C(X^2)$ ,  $C(X^2)X^1$  or  $X^1C(X^2)X^1$ ;

$R^c$  is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ;
- an acyclic  $C_{1-12}$  hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di- $C_{1-8}$  non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ; wherein one or more but not all of the carbon atoms of the acyclic  $C_{1-12}$  hydrocarbyl group may optionally be replaced by O, S, SO,  $SO_2$ , NH, N- $C_{1-4}$  alkyl,  $C(O)O$ ,  $OC(O)$ ,  $NH(CO)$ ,  $C(O)NH$ ,  $NH(CO)NH$ ,  $N(C_{1-4} \text{ alkyl})C(O)$ ,  $C(O)N(C_{1-4} \text{ alkyl})$

$X^1$  is O, S or  $NR^c$ ; and

$X^2$  is =O, =S or = $NR^c$ ;

wherein  $R^9$  is selected from  $R^8$  provided that when the substituents  $R^9$  contain a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group is unsubstituted or substituted with one or more substituents  $R^{10}$ ;

$R^{10}$  is selected from halogen, oxo, cyano, and an acyclic  $C_{1-6}$  hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di- $C_{1-2}$  alkylamino; wherein one but not all of the carbon atoms of the acyclic  $C_{1-6}$  hydrocarbyl group may optionally be replaced by O, S, SO,  $SO_2$ , NH or NMe;

$R^{11}$  is selected from amino,  $Hyd^1$ ,  $NH-Hyd^1$ ,  $N(Hyd^1)_2$ ; and  $Cyc^1$ ;

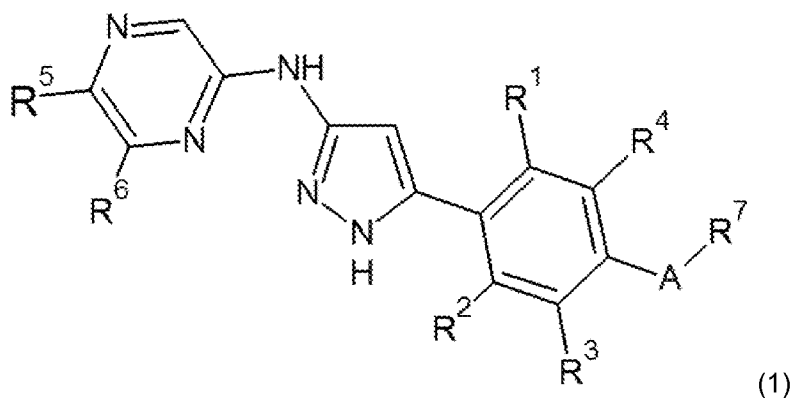
$Hyd^1$  is a non-aromatic  $C_{1-6}$  hydrocarbyl group optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, amino and  $Cyc^1$ , wherein one or two of the carbon atoms of the non-aromatic  $C_{1-6}$  hydrocarbyl group may optionally be

replaced by O, NH, N-Hyd<sup>2</sup>, C(=O), S, SO or SO<sub>2</sub>, provided that at least one carbon atom of the hydrocarbonyl group remains;

Hyd<sup>2</sup> is a C<sub>1-4</sub> hydrocarbonyl group;

and wherein in any group consisting of or containing a hydrocarbonyl moiety, the hydrocarbonyl moiety is a hydrocarbon group optionally containing one or more single, double or triple carbon-carbon bonds or combinations thereof.

2. A compound according to claim 1 having the formula (1):



or a salt, N-oxide or tautomer thereof, wherein:

A is selected from:

- (i) a bond; and
- (ii) a saturated chain of 2 to 10 chain members in length containing at least one carbon atom chain member, at least one heteroatom chain member selected from nitrogen and oxygen, and optionally one or more further carbon atom chain members and/or heteroatom chain members selected from nitrogen, oxygen, sulphur, sulphanyl and sulphonyl; the saturated chain being optionally substituted with one or more substituents selected from =O, C<sub>1-4</sub> hydrocarbonyl and fluorine wherein two hydrocarbonyl substituents on the same carbon atom may optionally link to form a ring of three to five ring members;

R<sup>1</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbonyl and C<sub>1-4</sub> hydrocarbonyloxy;

R<sup>2</sup> is selected from hydrogen, fluorine, C<sub>1-4</sub> hydrocarbonyl and C<sub>1-4</sub> hydrocarbonyloxy;

R<sup>3</sup> is selected from hydrogen, methyl, chlorine and bromine;

R<sup>4</sup> is selected from hydrogen, methyl, chlorine and bromine;

R<sup>5</sup> is selected from hydrogen, cyano and methyl;

R<sup>6</sup> is selected from hydrogen, C<sub>1-4</sub> alkyl; and C<sub>1-4</sub> alkoxy optionally substituted with NR<sup>d</sup>R<sup>e</sup> where R<sup>d</sup> and R<sup>e</sup> are the same or different and each is selected from hydrogen and C<sub>1-4</sub> alkyl, or NR<sup>d</sup>R<sup>e</sup> forms a 4 to 7 membered saturated heterocyclic ring optionally containing a second heteroatom ring member selected from N, O and S and oxidized



forms of S, the saturated heterocyclic ring being optionally substituted with one or more substituents selected from oxo, methyl, hydroxy and fluorine;

$R^7$  is selected from hydrogen;  $R^{11}SO_2^-$ ; amino,  $NH-Hyd^1$ ,  $N(Hyd^1)_2$ ; and a group  $Cyc^1$  wherein  $Cyc^1$  is a carbocyclic or heterocyclic aromatic or non-aromatic group of 3 to 10 ring members of which 0 to 3 are selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic aromatic or non-aromatic group being optionally substituted with one or more substituents  $R^8$ ; provided that when A is a bond, then  $R^7$  is  $Cyc^1$ ; and provided also that when  $R^7$  is hydrogen, then A has a chain length of at least four chain members and contains at least two heteroatom chain members;

$R^8$  is selected from:

- halogen;
- oxo;
- cyano;
- nitro;
- a carbocyclic or heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ; and
- a group  $R^a-R^b$ ;

$R^a$  is a bond, O, CO,  $X^1C(X^2)$ ,  $C(X^2)X^1$ ,  $X^1C(X^2)X^1$ , S, SO,  $SO_2$ ,  $NR^c$ ,  $SO_2NR^c$  or  $NR^cSO_2$ ;

$R^b$  is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ;
- an acyclic  $C_{1-12}$  hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di- $C_{1-8}$  non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents  $R^9$ ; wherein one or more but not all of the carbon atoms of the acyclic  $C_{1-12}$  hydrocarbyl group may optionally be replaced by O, S, SO,  $SO_2$ ,  $NR^c$ ,  $X^1C(X^2)$ ,  $C(X^2)X^1$  or  $X^1C(X^2)X^1$ ;

R<sup>c</sup> is:

- hydrogen;
- a carbocyclic and heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>;
- an acyclic C<sub>1-12</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; nitro; carboxy; amino; mono- or di-C<sub>1-8</sub> non-aromatic hydrocarbylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from O, N and S and oxidised forms thereof, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R<sup>9</sup>; wherein one or more but not all of the carbon atoms of the acyclic C<sub>1-12</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH, N-C<sub>1-4</sub> alkyl, C(O)O, OC(O), NH(CO), C(O)NH, NH(CO)NH, N(C<sub>1-4</sub> alkyl)C(O), C(O)N(C<sub>1-4</sub> alkyl)

X<sup>1</sup> is O, S or NR<sup>c</sup>; and

X<sup>2</sup> is =O, =S or =NR<sup>c</sup>;

wherein R<sup>9</sup> is selected from R<sup>8</sup> provided that when the substituents R<sup>9</sup> contain a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group is unsubstituted or substituted with one or more substituents R<sup>10</sup>;

R<sup>10</sup> is selected from halogen, oxo, cyano, and an acyclic C<sub>1-6</sub> hydrocarbyl group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di-C<sub>1-2</sub> alkylamino; wherein one but not all of the carbon atoms of the acyclic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, S, SO, SO<sub>2</sub>, NH or NMe;

R<sup>11</sup> is selected from amino, Hyd<sup>1</sup>, NH-Hyd<sup>1</sup>, N(Hyd<sup>1</sup>)<sub>2</sub>; and Cyc<sup>1</sup>;

Hyd<sup>1</sup> is a non-aromatic C<sub>1-6</sub> hydrocarbyl group optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, amino and Cyc<sup>1</sup>, wherein one or two of the carbon atoms of the non-aromatic C<sub>1-6</sub> hydrocarbyl group may optionally be replaced by O, NH, N-Hyd<sup>2</sup>, C(=O), S, SO or SO<sub>2</sub>, provided that at least one carbon atom of the hydrocarbyl group remains;

Hyd<sup>2</sup> is a C<sub>1-4</sub> hydrocarbyl group;

and wherein in any group consisting of or containing a hydrocarbyl moiety, the hydrocarbyl moiety is a hydrocarbon group optionally containing one or more single, double or triple carbon-carbon bonds or combinations thereof.

3. A compound according to claim 1 or claim 2 wherein R<sup>1</sup> is selected from hydrogen and methoxy.
4. A compound according to any one of claims 1 to 3 wherein R<sup>2</sup> is selected from hydrogen and methoxy.
5. A compound according to any one of claims 1 to 4 wherein both of R<sup>3</sup> and R<sup>4</sup> are hydrogen.
6. A compound according to any one of claims 1 to 5 wherein R<sup>5</sup> is selected from hydrogen and cyano.
7. A compound according to claim 6 wherein R<sup>5</sup> is cyano.
8. A compound according to any one of claims 1 to 7 wherein R<sup>6</sup> is hydrogen.
9. A compound according to any one of claims 1 to 8 wherein A is selected from a bond; -NH-CH<sub>2</sub>-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; and -(CH<sub>2</sub>)-NH-(CHMe)- and R<sup>7</sup> is a group Cyc<sup>1</sup>.
10. A compound according to claim 9 wherein
  - (i) Cyc<sup>1</sup> is a non-aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> hydrocarbyl, C<sub>1-4</sub>hydrocarbylsulfonyl, oxo, di-C<sub>1-4</sub>hydrocarbylamino-C<sub>1-4</sub>alkanoyl; and C<sub>1-4</sub> hydrocarbylcarbonyl; or
  - (ii) Cyc<sup>1</sup> is an aromatic group and R<sup>8</sup> is absent or is selected from C<sub>1-4</sub> hydrocarbyl; halogen; C<sub>1-4</sub> hydrocarbyloxy; cyano; methylenedioxy; carbamoyl; mono- or di-C<sub>1-4</sub> alkylcarbamoyl; a 5- or 6-membered saturated heterocyclic ring containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic ring being optionally substituted with one or more C<sub>1-4</sub> alkyl group substituents; wherein the hydrocarbyl moieties in each of the C<sub>1-4</sub> hydrocarbyl and C<sub>1-4</sub> hydrocarbyloxy groups are optionally substituted with one or more substituents selected from fluorine, hydroxy, amino, mono-or di-C<sub>1-4</sub> alkylamino, oxo and C<sub>1-2</sub> alkyl.
11. A compound according to claim 9 wherein wherein R<sup>7</sup> is selected from phenyl, fluorophenyl, 4-morpholinyl, 1-methyl-4-piperidinyl and 1-cyclopropylcarbonyl-piperidin-4-yl.
12. A compound according to claim 1 or claim 2 wherein:

R<sup>1</sup> is hydrogen or methoxy;  
R<sup>2</sup> is hydrogen or methoxy;  
R<sup>3</sup> is hydrogen;  
R<sup>4</sup> is hydrogen;

R<sup>5</sup> is hydrogen or cyano;

R<sup>6</sup> is hydrogen;

A is selected from a bond, -NH-CH<sub>2</sub>-

; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-; -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-;

and -(CH<sub>2</sub>)-NH-(CHMe)-; and

R<sup>7</sup> is selected from phenyl, 4-fluorophenyl, 4-morpholinyl, 1-methyl-4-piperidinyl and 1-cyclopropylcarbonyl-piperidin-4-yl.

13. A compound according to claim 1 or claim 2 wherein:

R<sup>1</sup> is methoxy;

R<sup>2</sup> is hydrogen or methoxy;

R<sup>3</sup> is hydrogen;

R<sup>4</sup> is hydrogen;

R<sup>5</sup> is cyano;

R<sup>6</sup> is hydrogen; and

(i) when A is a bond, R<sup>7</sup> is 1-methyl-4-piperidinyl; or

(ii) when A is -(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-, R<sup>7</sup> is selected from phenyl, 4-fluorophenyl and 1-cyclopropylcarbonyl-piperidin-4-yl; or

(iii) when A is (CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-(CH<sub>2</sub>)-, R<sup>7</sup> is 4-morpholinyl; or

(iv) when A is -(CH<sub>2</sub>)-(CH<sub>2</sub>)-NH-(CH<sub>2</sub>)-, R<sup>7</sup> is phenyl; or

(v) when A is -(CH<sub>2</sub>)-NH-(CHMe)-, R<sup>7</sup> is 4-fluorophenyl.

14. A compound according to claim 1 or claim 2 which is selected from:

5-[5-(4-benzylamino-2,6-dimethoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile;

5-[5-(4-benzylamino-2-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile;

5-{5-[4-(benzylamino-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-{5-[4-(2-benzylamino-ethyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-{5-[4-(benzylamino-methyl)-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-[5-(4-[(S)-1-(4-fluoro-phenyl)-ethylamino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-[5-(4-[(R)-1-(4-fluoro-phenyl)-ethylamino]-methyl)-2-methoxy-phenyl]-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-(5-{4-[(4-fluoro-benzylamino)-methyl]-2-methoxy-phenyl}-1H-pyrazol-3-ylamino)-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-(5-{2-methoxy-4-[(2-morpholin-4-yl-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-ylamino)-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

(5-{2-methoxy-4-[(2-morpholin-4-yl-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-pyrazin-2-yl-amine (e.g. the hydrochloride salt);

5-{5-[2-methoxy-4-(1-methyl-piperidin-4-yl)-phenyl]-1H-pyrazol-3-ylamino}-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

5-[5-(4-[[1-(cyclopropane-carbonyl-piperidin-4-ylmethyl)-amino]-methyl]-2-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyrazine-2-carbonitrile (e.g. the hydrochloride salt);

N-[[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]methyl]cyclopropanecarboxamide;

5-[[5-[2-methoxy-4-[(tetrahydropyran-4-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[[methyl(2-morpholinoethyl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(2-morpholinoethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[1-[2-(dimethylamino)acetyl]-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[[[(1R)-1-methyl-2-morpholino-ethyl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[[1,1-dimethyl-2-morpholino-ethyl]amino]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-fluoro-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile;

6-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile;

N-[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]-5-methyl-pyrazin-2-amine;

5-[[5-[4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)oxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

2-fluoro-4-[[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]benzonitrile;

5-[[5-[2-methoxy-4-[(2-pyridylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[5-fluoro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(3S)-pyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(pyrrolidin-2-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(1-methylpyrrolidin-2-yl)methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(4-piperidylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[[1-(1-methyl-4-piperidyl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-isopropoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(3-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(1-methyl-3-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(1-methyl-2-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(3S)-1-methylpyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-chloro-N-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]pyrazin-2-amine;

5-chloro-N-[5-[2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]pyrazin-2-amine;

5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carboxylic acid;

5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(2S,6S)-2,6-dimethyl-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-(2-methoxy-4-tetrahydropyran-4-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

2-fluoro-4-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]benzotrile;

6-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile;

5-[[5-[2-fluoro-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyridine-2-carbonitrile;

5-[[5-[2-isopropoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile; 5-[[5-[4-(1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

N-[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]-5-methyl-pyrazin-2-amine;

5-[[5-[4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(4-piperidyloxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[5-fluoro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(isopropylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-(1-ethyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-(1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

2-[4-[4-[3-[(5-cyanopyrazin-2-yl)amino]-1H-pyrazol-5-yl]-3-methoxy-phenyl]-1-piperidyl]acetamide;

5-[[5-[2-methoxy-4-[[methyl(tetrahydropyran-4-yl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-(4-fluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(1-methylazetidin-3-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-(3-fluoro-1-methyl-azetidin-3-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[5-chloro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[5-chloro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[3-chloro-2-methoxy-4-(1-methyl-4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[3-chloro-2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

methyl 5-[[5-[2-methoxy-4-(4-piperidyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carboxylate;

5-[[5-[2-methoxy-4-[(tetrahydrofuran-3-ylamino)methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[[methyl(tetrahydrofuran-3-yl)amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(tetrahydropyran-4-ylmethylamino)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-(tetrahydropyran-4-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;



- 5-[[5-[4-(4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(3-fluoroazetid-3-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(3R)-1-methylpyrrolidin-3-yl]oxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-(2-methoxy-4-morpholino-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-ethylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;;
- 5-[[5-[4-(4-isopropylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(3R)-3-methylpiperazin-1-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-ethyl-1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-isopropyl-1,4-diazepan-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(1-ethyl-4-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-fluoro-1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(1-ethyl-3-fluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(3-fluoro-1-isopropyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[1-(2-methoxyethyl)-4-piperidyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(ethylaminomethyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(cyclopropylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[(3R)-3,4-dimethylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R)-4-ethyl-3-methyl-piperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3S)-1-isopropylpyrrolidin-3-yl]oxy-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R)-1-isopropylpyrrolidin-3-yl]oxy-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R,S),4(R,S))-3-fluoro-1-methyl-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(3,3-difluoro-1-methyl-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(1-ethyl-3,3-difluoro-4-piperidyl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[1-(2-hydroxyethyl)-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[isopropyl(methyl)amino] methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-(morpholinomethyl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2R)-1-methylpyrrolidin-2-yl]methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride;
- 5-[[5-[2-methoxy-4-[(2S)-1-methylpyrrolidin-2-yl]methoxy]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile hydrochloride;
- 5-[[5-[2-methoxy-4-(oxazol-4-ylmethoxy)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[1-(2-fluoroethyl)-4-piperidyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)methylamino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[(1-ethyl-4-piperidyl)methylamino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)methylamino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)amino]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(1-methyl-4-piperidyl)oxymethyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-(2-fluoro-6-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2R)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2R)-4-ethylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2S)-4-methylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[(2S)-4-ethylmorpholin-2-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-(2,6-dimethoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2,6-dimethoxy-4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R)-3-fluoropyrrolidin-1-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[2-methoxy-4-[[[(3S)-3-methoxypyrrolidin-1-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[[(3R)-3-methoxypyrrolidin-1-yl]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2R)-1-ethylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2R)-1-isopropylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2S)-1-ethylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2S)-1-isopropylpyrrolidin-2-yl]methoxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(cyclopropylmethylamino) methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[[(3R)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[2-methoxy-4-[[[(3S)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(3R)-4-isopropyl-3-methyl-piperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)oxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)oxy]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-ethylpiperazin-1-yl)-2-fluoro-6-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-isopropylpiperazin-1-yl)-2-fluoro-6-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3S)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3S)-1-isopropylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

- 5-[[5-[4-[[[(3R)-1-ethylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3R)-1-isopropylpyrrolidin-3-yl]oxymethyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-(4-isobutylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-ethyl-4-piperidyl)methyl-methyl-amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(isobutylamino)methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(2R)-4-isopropylmorpholin-2-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(1-isopropyl-4-piperidyl)methyl-methyl-amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2R)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[(2S)-4-isopropylmorpholin-2-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2R)-1-isopropylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2S)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-(2-methoxy-4-piperazin-1-yl-phenyl)-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(2S)-1-isopropylpyrrolidin-2-yl]methyl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;
- 5-[[5-[4-[[[(3S)-1-isopropylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[[[(3R)-1-isopropylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[[[(3R)-1-ethylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[[[(3S)-1-ethylpyrrolidin-3-yl]amino]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[2-methoxy-4-[(3S)-3-methylpiperazin-1-yl]phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(3R)-3-ethylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(3S)-3-isopropylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-[(3R)-3-isopropylpiperazin-1-yl]-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

5-[[5-[4-(3,3-dimethylpiperazin-1-yl)-2-methoxy-phenyl]-1H-pyrazol-3-yl]amino]pyrazine-2-carbonitrile;

and salts and tautomers thereof.

15. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 14 and a pharmaceutically acceptable excipient.

16. A combination comprising a compound as defined in any one of claims 1 to 14 and another chemotherapeutic agent, for example an anticancer drug.

17. A compound as defined in any one of claims 1 to 14, optionally in combination with another chemotherapeutic agent or radiotherapy, for use in the treatment of a proliferative disease.

18. An invention as defined in any one of Embodiments 1.0 to 1.107, 2.1 to 2.28, 3.1, 4.1 and 5.1 as defined herein.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/15030

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

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

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: 4-11 and 15-17  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:


**Remark on Protest**

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

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/15030

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61K 31/4965, 31/497; C07D 403/12 (2015.01) CPC - A61K 31/4965, 31/497; C07D 403/12 According to International Patent Classification (IPC) or to both national classification and IPC													
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8): A61K 31/4965, 31/497; C07D 403/12 (2015.01) CPC: A61K 31/4965, 31/497; C07D 403/12 USPC: 514/255.06 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) PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Google Scholar; IP.com; KEYWORDS: chk 1 inhibit*, pyrazin*, cyano pyrazin*, carbonitrile, 4 benzylamino methyl, 2 methoxy phenyl, pyrazol*, hydrocarbyloxy, aminopyrazol*, treat* proliferative, cancer*, treat* cancer*, 1H pyrazol 3 ylamino, pyrazine 2 carbonitrile, acceptable salt, combination therap*, radiation													
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>													
<table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>US 2013/0065900 A1 (BOYLE, RG et al.) 14 March 2013; paragraphs [0008], [0507], Example 22</td> <td>1-2, 3/1-2, 12/1-2, 13/1-2, 14/1-2, 18</td> </tr> <tr> <td>Y</td> <td>WO 2010/077758 A1 (ELI LILLY) 08 July 2010; page 1, lines 3-4; page 28, lines 18-21</td> <td>1-2, 3/1-2, 12/1-2, 13/1-2, 14/1-2, 18</td> </tr> <tr> <td>Y</td> <td>FOLOPPE, N et al., Structure-Based Design of Novel Chk1 Inhibitors: Insights into Hydrogen Bonding and Protein-Ligand Affinity, J. Med. Chem: 48, pages 4332-4345, 2005; [retrieved on 2015-04-13]. Retrieved from the Internet: &lt;URL: <a href="https://ccchub.org/resources/604/download/jm049022c.pdf">https://ccchub.org/resources/604/download/jm049022c.pdf</a> 04/13&gt; &lt;DOI: 10.1021/jm049022c&gt;; abstract; page 4335, column 1, paragraph 3 – column 2, paragraph 3; page 4336, column 1, paragraph 1 – column 2, paragraph 3; page 4337, column 1, paragraph 1; page 4337, column 2, paragraphs 1-3; page 4338, column 1, paragraph 1 – column 2, paragraph 1</td> <td>1-2, 3/1-2, 12/1-2, 13/1-2, 14/1-2, 18</td> </tr> </tbody> </table>	Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	US 2013/0065900 A1 (BOYLE, RG et al.) 14 March 2013; paragraphs [0008], [0507], Example 22	1-2, 3/1-2, 12/1-2, 13/1-2, 14/1-2, 18	Y	WO 2010/077758 A1 (ELI LILLY) 08 July 2010; page 1, lines 3-4; page 28, lines 18-21	1-2, 3/1-2, 12/1-2, 13/1-2, 14/1-2, 18	Y	FOLOPPE, N et al., Structure-Based Design of Novel Chk1 Inhibitors: Insights into Hydrogen Bonding and Protein-Ligand Affinity, J. Med. Chem: 48, pages 4332-4345, 2005; [retrieved on 2015-04-13]. Retrieved from the Internet: <URL: <a href="https://ccchub.org/resources/604/download/jm049022c.pdf">https://ccchub.org/resources/604/download/jm049022c.pdf</a> 04/13> <DOI: 10.1021/jm049022c>; abstract; page 4335, column 1, paragraph 3 – column 2, paragraph 3; page 4336, column 1, paragraph 1 – column 2, paragraph 3; page 4337, column 1, paragraph 1; page 4337, column 2, paragraphs 1-3; page 4338, column 1, paragraph 1 – column 2, paragraph 1	1-2, 3/1-2, 12/1-2, 13/1-2, 14/1-2, 18	
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<input type="checkbox"/> Further documents are listed in the continuation of Box C.		<input type="checkbox"/> 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 14 April 2015 (14.04.2015)	Date of mailing of the international search report <b>29 APR 2015</b>												
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774												