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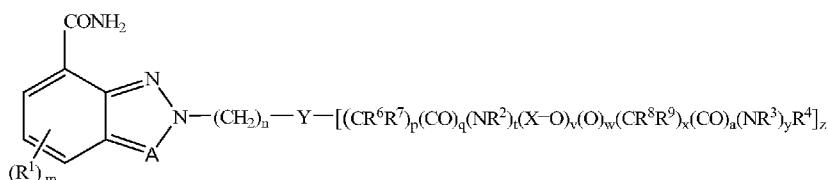
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(54) Title: AMIDE SUBSTITUTED INDAZOLE AND BENZOTRIAZOLE DERIVATIVES AS POLY(ADP-RIBOSE)POLYMERASE (PARP) INHIBITORS



(I)

(57) Abstract: The present invention relates to compounds of formula (I) and pharmaceutically acceptable salts or tautomers thereof which are inhibitors of poly (ADP-ribose) polymerase (PARP) and thus useful for the treatment of cancer, inflammatory diseases, reperfusion injuries, ischemic conditions, stroke, renal failure, cardiovascular diseases, vascular diseases other than cardiovascular diseases, diabetes, neurodegenerative diseases, retroviral infection, retinal damage or skin senescence and UV-induced skin damage, and as chemo- or radiosensitizers for cancer treatment.

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**Amide substituted indazole and benzotriazole derivatives as  
poly(ADP-ribose)polymerase (PARP) inhibitors**

The present invention relates to amide substituted indazoles and benzotriazoles which are  
5 inhibitors of the enzyme poly(ADP-ribose)polymerase (PARP), previously known as poly(ADP-ribose)synthase and poly(ADP-ribosyl)transferase. The compounds of the present invention are useful as mono-therapies in tumors with specific defects in DNA-repair pathways and as enhancers of certain DNA-damaging agents such as anticancer agents and radiotherapy. Further, the compounds of the  
10 present invention are useful for reducing cell necrosis (in stroke and myocardial infarction), down regulating inflammation and tissue injury, treating retroviral infections and protecting against the toxicity of chemotherapy.

Poly(ADP-ribose) polymerase (PARP) constitute a super family of eighteen proteins containing PARP catalytic domains (*Bioessays* (2004) **26**:1148). These proteins include PARP-1, PARP-2, PARP-3, tankyrase-1, tankyrase-2, vaultPARP and TiPARP. PARP-1, the founding member, consists of three  
15 main domains: an amino (N)-terminal DNA-binding domain (DBD) containing two zinc fingers, the automodification domain, and a carboxy (C)-terminal catalytic domain.

PARP are nuclear and cytoplasmic enzymes that cleave NAD<sup>+</sup> to nicotinamide and ADP-ribose to form long and branched ADP-ribose polymers on target proteins, including topoisomerases, histones and PARP itself (*Biochem. Biophys. Res. Commun.* (1998) **245**:1-10).

20 Poly(ADP-ribosyl)ation has been implicated in several biological processes, including DNA repair, gene transcription, cell cycle progression, cell death, chromatin functions and genomic stability.

The catalytic activity of PARP-1 and PARP-2 has been shown to be promptly stimulated by DNA strand breakages (see *Pharmacological Research* (2005) **52**:25-33). In response to DNA damage, PARP-1 binds to single and double DNA nicks. Under normal physiological conditions there is minimal PARP activity, however, upon DNA damage an immediate activation of PARP activity of up to 500-fold occurs.  
25 Both PARP-1 and PARP-2 detect DNA strand interruptions acting as nick sensors, providing rapid signals to halt transcription and recruiting the enzymes required for DNA repair at the site of damage. Since radiotherapy and many chemotherapeutic approaches to cancer therapy act by inducing DNA damage, PARP inhibitors are useful as chemo- and radiosensitizers for cancer treatment. PARP inhibitors  
30 have been reported to be effective in radio sensitizing hypoxic tumor cells (US 5,032,617, US 5,215,738 and US 5,041,653).

35 Most of the biological effects of PARP relate to this poly (ADP-ribosyl)ation process which influences the properties and function of the target proteins; to the PAR oligomers that, when cleaved from poly(ADP-ribosyl)ated proteins, confer distinct cellular effects; the physical association of PARP with nuclear proteins to form functional complexes; and the lowering of the cellular level of its substrate NAD<sup>+</sup> (*Nature Review* (2005) **4**:421-440).

Besides being involved in DNA repair, PARP may also act as a mediator of cell death. Its excessive activation in pathological conditions such as ischemia and reperfusion injury can result in

substantial depletion of the intercellular NAD<sup>+</sup>, which can lead to the impairment of several NAD<sup>+</sup> dependent metabolic pathways and result in cell death (see *Pharmacological Research* (2005) **52**:44-59). As a result of PARP activation, NAD<sup>+</sup> levels significantly decline. Extensive PARP activation leads to severe depletion of NAD<sup>+</sup> in cells suffering from massive DNA damage. The short half-life of 5 poly(ADP-ribose) results in a rapid turnover rate, as once poly(ADP-ribose) is formed, it is quickly degraded by the constitutively active poly(ADP-ribose) glycohydrolase (PARG). PARP and PARG form a cycle that converts a large amount of NAD<sup>+</sup> to ADP-ribose, causing a drop of NAD<sup>+</sup> and ATP to less than 20% of the normal level. Such a scenario is especially detrimental during ischemia when deprivation 10 of oxygen has already drastically compromised cellular energy output. Subsequent free radical production during reperfusion is assumed to be a major cause of tissue damage. Part of the ATP drop, which is typical in many organs during ischemia and reperfusion, could be linked to NAD<sup>+</sup> depletion due to poly(ADP-ribose) turnover. Thus, PARP inhibition is expected to preserve the cellular energy level thereby 15 potentiating the survival of ischemic tissues after insult. Compounds which are inhibitors of PARP are therefore useful for treating conditions which result from PARP mediated cell death, including neurological conditions such as stroke, trauma and Parkinson's disease.

PARP inhibitors have been demonstrated as being useful for the specific killing of BRCA-1 and BRCA-2 deficient tumors (*Nature* (2005) **434**:913-916 and 917-921; and *Cancer Biology & Therapy* (2005) **4**:934-936).

PARP inhibitors have been shown to enhance the efficacy of anticancer drugs (*Pharmacological 20 Research* (2005) **52**:25-33), including platinum compounds such as cisplatin and carboplatin (*Cancer Chemother Pharmacol* (1993) **33**:157-162 and *Mol Cancer Ther* (2003) **2**:371-382). PARP inhibitors have been shown to increase the antitumor activity of topoisomerase I inhibitors such as Irinotecan and 25 Topotecan (*Mol Cancer Ther* (2003) **2**:371-382; and *Clin Cancer Res* (2000) **6**:2860-2867) and this has been demonstrated in *in vivo* models (*J Natl Cancer Inst* (2004) **96**:56-67).

PARP inhibitors have been shown to restore susceptibility to the cytotoxic and antiproliferative 30 effects of temozolomide (TMZ) (see *Curr Med Chem* (2002) **9**:1285-1301 and *Med Chem Rev Online* (2004) **1**:144-150). This has been demonstrated in a number of *in vitro* models (*Br J Cancer* (1995) **72**:849-856; *Br J Cancer* (1996) **74**:1030-1036; *Mol Pharmacol* (1997) **52**:249-258; *Leukemia* (1999) **13**:901-909; *Glia* (2002) **40**:44-54; and *Clin Cancer Res* (2000) **6**:2860-2867 and (2004) **10**:881-889) and *in vivo* models (*Blood* (2002) **99**:2241-2244; *Clin Cancer Res* (2003) **9**:5370-5379 and *J Natl Cancer Inst* (2004) **96**:56-67). PARP inhibitors have also been shown to prevent the appearance of necrosis induced by selective N3-adenine methylating agents such as MeOSO<sub>2</sub>(CH<sub>2</sub>)-lexitropsin (Me-Lex) (*Pharmacological Research* (2005) **52**:25-33).

PARP inhibitors have been shown to act as radiation sensitizers. PARP inhibitors have been 35 reported to be effective in radiosensitizing (hypoxic) tumor cells and effective in preventing tumor cells from recovering from potentially lethal (*Br. J. Cancer* (1984) **49**(Suppl. VI):34-42; and *Int. J. Radiat. Bioi.* (1999) **75**:91-100) and sub-lethal (*Clin. Oncol.* (2004) **16**(1):29-39) damage of DNA after radiation

therapy, presumably by their ability to prevent DNA strand break rejoicing and by affecting several DNA damage signaling pathways.

PARP inhibitors have also been shown to be useful for treating acute and chronic myocardial diseases (see *Pharmacological Research* (2005) **52**:34-43). For instance, it has been demonstrated that 5 single injections of PARP inhibitors have reduced the infarct size caused by ischemia and reperfusion of the heart or skeletal muscle in rabbits. In these studies, a single injection of 3-amino-benzamide (10 mg/kg), either one minute before occlusion or one minute before reperfusion, caused similar reductions in infarct size in the heart (32-42%) while 1,5-dihydroxyisoquinoline (1 mg/kg), another PARP inhibitor, reduced infarct size by a comparable degree (38-48%). These results make it reasonable to assume that 10 PARP inhibitors could salvage previously ischemic heart or reperfusion injury of skeletal muscle tissue (*PNAS* (1997) **94**:679-683). Similar findings have also been reported in pigs (*Eur. J. Pharmacol.* (1998) **359**:143-150 and *Ann. Thorac. Surg.* (2002) **73**:575-581) and in dogs (*Shock.* (2004) **21**:426-32).

PARP inhibitors have been demonstrated as being useful for treating certain vascular diseases, septic shock, ischemic injury and neurotoxicity (*Biochim. Biophys. Acta* (1989) **1014**:1-7; *J. Clin. Invest.* 15 (1997) **100**: 723-735). Oxygen radical DNA damage that leads to strand breaks in DNA, which are subsequently recognized by PARP, is a major contributing factor to such disease states as shown by PARP inhibitor studies (*J. Neurosci. Res.* (1994) **39**:38-46 and *PNAS* (1996) **93**:4688-4692). PARP has also been demonstrated to play a role in the pathogenesis of hemorrhagic shock (*PNAS* (2000) **97**:10203-10208).

20 PARP inhibitors have been demonstrated as being useful for treatment of inflammation diseases (see *Pharmacological Research* (2005) **52**:72-82 and 83-92).

It has also been demonstrated that efficient retroviral infection of mammalian cells is blocked by the inhibition of PARP activity. Such inhibition of recombinant retroviral vector infections has been shown to occur in various different cell types (*J. Virology*, (1996) **70**(6):3992-4000). Inhibitors of PARP 25 have thus been developed for use in anti-viral therapies and in cancer treatment (WO 91/18591).

*In vitro* and *in vivo* experiments have demonstrated that PARP inhibitors can be used for the treatment or prevention of autoimmune diseases such as Type I diabetes and diabetic complications (*Pharmacological Research* (2005) **52**:60-71).

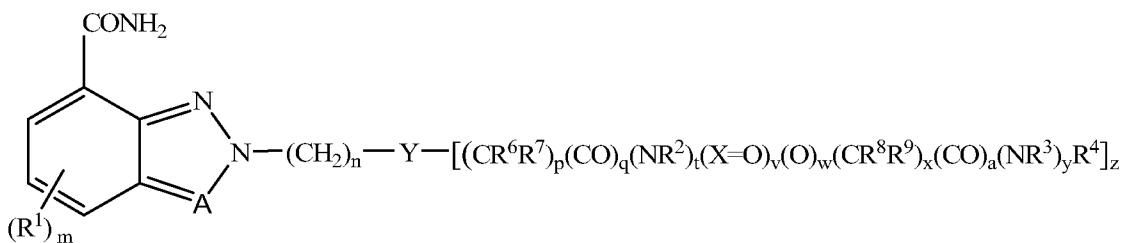
PARP inhibition has been speculated as delaying the onset of aging characteristics in human 30 fibroblasts (*Biochem. Biophys. Res. Comm.* (1994) **201**(2):665-672 and *Pharmacological Research* (2005) **52**:93-99). This may be related to the role that PARP plays in controlling telomere function (*Nature Gen.*, (1999) **23**(1):76-80).

The vast majority of PARP inhibitors to date interact with the nicotinamide binding domain of the enzyme and behave as competitive inhibitors with respect to NAD<sup>+</sup> (*Expert Opin. Ther. Patents* (2004) 35 **14**:1531-1551). Structural analogues of nicotinamide, such as benzamide and derivatives were among the first compounds to be investigated as PARP inhibitors. However, these molecules have a weak inhibitory activity and possess other effects unrelated to PARP inhibition. Thus, there is a need to provide potent inhibitors of the PARP enzyme.

Structurally related PARP inhibitors have previously been described. WO 1999/59973 discloses amide substituted benzene rings fused to 5 membered heteroaromatic rings; WO2001/85687 discloses amide substituted indoles; WO 1997/04771, WO 2000/26192, WO 2000/32579, WO 2000/64878, WO 2000/68206, WO 2001/21615, WO 2002/068407, WO 2003/106430 and WO 2004/096793 disclose amide substituted benzoimidazoles; WO 2000/29384 discloses amide substituted benzoimidazoles and indoles; and EP 0879820 discloses amide substituted benzoxazoles.

It has now surprisingly been discovered that amide substituted indazoles and benzotriazoles of the present invention exhibit high levels of inhibition of the activity of PARP.

The compounds of this invention are useful in the inhibition of poly(ADP-ribose)polymerase (PARP). They are particularly useful as inhibitors of PARP-1 and/or PARP-2. The present invention provides compounds of formula I:



(I)

wherein:

15 a is 0 or 1;  
m is 0, 1, 2 or 3;  
n is 0, 1, 2, 3, 4, 5 or 6;  
each p is independently 0, 1, 2, 3, 4, 5 or 6;  
each q is independently 0 or 1;

20 each t is independently 0 or 1;  
each v is independently 0 or 1;  
each w is independently 0 or 1;  
each x is independently 0, 1, 2, 3, 4, 5 or 6;  
each y is independently 0 or 1;

25 z is 1, 2 or 3;  
A is CH or N;  
each R<sup>1</sup> is independently hydroxy, halogen, cyano, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or haloC<sub>1-6</sub>alkoxy;

Y is a direct bond or a ring which is: a C<sub>3-5</sub>cycloalkyl, a 4 membered saturated heterocycle containing one N atom, a 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms, a 6-13

membered saturated, partially saturated or unsaturated hydrocarbon ring or a 8-13 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S;

each R<sup>2</sup> is independently hydrogen, C<sub>1-6</sub>alkyl or C<sub>3-10</sub>cycloalkyl;

5 each X is independently C or SO;

each R<sup>3</sup> is independently hydrogen or C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently hydrogen, hydroxy, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>2-10</sub>alkenyl, haloC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxycarbonyl, carboxy, nitro or a ring which is: C<sub>6-10</sub>aryl; C<sub>6-10</sub>aryloxy; C<sub>6-10</sub>arylcarbonyl; C<sub>3-10</sub>cycloalkyl; a 4 membered 10 saturated heterocyclic ring containing one N atom; a 5 or 6 membered saturated or partially saturated heterocyclic ring containing one, two or three atoms independently selected from N, O and S; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-15 membered unsaturated, partially saturated or saturated heterocyclic ring 15 containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from (CH<sub>2</sub>)<sub>b</sub>R<sup>5</sup>;

each b is independently 0, 1, 2, 3, 4, 5 or 6;

each R<sup>5</sup> is independently hydroxy, oxo, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>2-10</sub>alkenyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxycarbonyl, carboxy, NR<sup>a</sup>R<sup>b</sup>, 20 CONR<sup>a</sup>R<sup>b</sup>, S(O)<sub>r</sub>R<sup>c</sup> or a ring which is: C<sub>6-10</sub>aryl; C<sub>6-10</sub>arylC<sub>1-6</sub>alkyl; a 4 membered saturated heterocyclic ring containing one N atom; a 5, 6 or 7 membered saturated or partially saturated heterocyclic ring containing one, two or three atoms independently selected from N, O and S; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen 25 atoms; or a 7-10 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>2-10</sub>alkenyl, haloC<sub>1-6</sub>alkyl, amino, C<sub>1-6</sub>alkylamino and di(C<sub>1-6</sub>alkyl)amino;

each of R<sup>a</sup> and R<sup>b</sup> is independently hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, haloC<sub>1-6</sub>alkyl, 30 hydroxyC<sub>1-6</sub>alkyl, S(O)<sub>r</sub>R<sup>c</sup> or S(O)<sub>r</sub>N(R<sup>d</sup>)<sub>2</sub>; or

R<sup>a</sup> and R<sup>b</sup> together with the N atom to which they are attached form a 4 membered saturated heterocycle containing one N atom or a 5, 6 or 7 membered saturated or partially saturated heterocycle containing one, two or three N atoms and zero or one O atom, the ring being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>2-10</sub>alkenyl 35 and haloC<sub>1-6</sub>alkyl;

r is 0, 1 or 2;

R<sup>c</sup> is C<sub>1-6</sub>alkyl, C<sub>6-10</sub>aryl, a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered

heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>2-10</sub>alkenyl and haloC<sub>1-6</sub>alkyl;

5 each R<sup>d</sup> is independently hydrogen or C<sub>1-6</sub>alkyl;  
each of R<sup>6</sup> and R<sup>7</sup> is independently hydrogen or C<sub>1-6</sub>alkyl;  
each of R<sup>8</sup> and R<sup>9</sup> is independently hydrogen, C<sub>1-6</sub>alkyl, hydroxy, haloC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, amino, C<sub>1-6</sub>alkylamino or di(C<sub>1-6</sub>alkyl)amino;  
or a pharmaceutically acceptable salt or tautomer thereof.

10 In an embodiment of the preceding embodiment R<sup>2</sup> is hydrogen or C<sub>1-6</sub>alkyl.  
In an embodiment of the preceding embodiment:  
each R<sup>4</sup> is independently hydrogen, hydroxy, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>2-10</sub>alkenyl, haloC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxycarbonyl, carboxy, nitro or a ring which is: C<sub>6-10</sub>aryl; C<sub>6-10</sub>aryloxy; C<sub>6-10</sub>arylcarbonyl; C<sub>3-10</sub>cycloalkyl; a 4 membered saturated heterocyclic ring containing one N atom; a 5, 6 or 7 membered saturated or partially saturated heterocyclic ring containing one, two or three N atoms and zero or one O atom; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S;

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each R<sup>5</sup> is independently hydroxy, oxo, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>2-10</sub>alkenyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxycarbonyl, carboxy, NR<sup>a</sup>R<sup>b</sup>, CONR<sup>a</sup>R<sup>b</sup> or a ring which is: C<sub>6-10</sub>aryl; C<sub>6-10</sub>arylC<sub>1-6</sub>alkyl; a 4 membered saturated heterocyclic ring containing one N atom; a 5, 6 or 7 membered saturated or partially saturated heterocyclic ring containing one, two or three N atoms and zero or one O atom; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from R<sup>5</sup>;

each R<sup>8</sup> and R<sup>9</sup> is hydrogen;  
or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In an embodiment of the preceding embodiment:

35 a is 0;  
each of R<sup>6</sup> and R<sup>7</sup> is hydrogen; and  
each R<sup>5</sup> is independently hydroxy, oxo, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>2-10</sub>alkenyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkoxy, haloC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxycarbonyl, carboxy, NR<sup>a</sup>R<sup>b</sup>, CONR<sup>a</sup>R<sup>b</sup> or a ring

which is: C<sub>6-10</sub>aryl; a 4 membered saturated heterocyclic ring containing one N atom; a 5, 6 or 7 membered saturated or partially saturated heterocyclic ring containing one, two or three N atoms and zero or one O atom; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered 5 heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>2-10</sub>alkenyl and haloC<sub>1-6</sub>alkyl.

In an embodiment a is 0. In another embodiment a is 1.

10 In an embodiment m is 0, 1 or 2.

In an embodiment m is 0 or 1.

In another embodiment m is 0.

In an embodiment R<sup>1</sup> is C<sub>1-6</sub>alkyl, halogen or haloC<sub>1-6</sub>alkyl.

15 In another embodiment R<sup>1</sup> is halogen, preferably chlorine or fluorine. A further R<sup>1</sup> group is hydroxy.

In an embodiment A is CH. In another embodiment A is N.

In another embodiment n is 0, 1 or 2.

In another embodiment n is 0 or 1. In another embodiment n is 0.

20 In an embodiment Y is a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms, a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring or a 8-13 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S.

In another embodiment Y is a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring.

25 In another embodiment Y is a 4 membered saturated heterocycle containing one N atom or a 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S.

30 Preferably, Y is phenyl. Further preferred Y groups are tetrahydroisoquinolinyl, pyridinyl and pyridazinyl. Further preferred Y groups are pyrrolidinyl, piperidinyl, tetrahydronaphthyridinyl and a direct bond.

Specific Y groups include phenyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl, 1,2,3,4-tetrahydroisoquinolin-5-yl, pyridin-2-yl and pyridazin-3-yl. Further specific Y groups include pyrrolidin-3-yl, piperidin-4-yl, 5,6,7,8-tetrahydro-1,7-naphthyridin-3-yl, piperidin-3-yl and a direct bond.

35 In an embodiment Y is not a direct bond.

In an embodiment p is 0, 1 or 2. In another embodiment p is 0 or 1.

In an embodiment q is 0. In another embodiment q is 1.

In an embodiment t is 0 or 1.

In an embodiment R<sup>2</sup> is hydrogen or C<sub>1-4</sub>alkyl, preferably hydrogen or methyl.

Particular R<sup>2</sup> groups include hydrogen, methyl, ethyl, propyl and cyclobutyl.

In another embodiment R<sup>2</sup> is hydrogen.

In an embodiment X is C. In another embodiment X is SO.

5 In an embodiment v is 0 or 1.

In an embodiment w is 0. In another embodiment w is 1.

In an embodiment x is 0, 1, or 2.

In another embodiment x is 0 or 1.

In an embodiment y is 0 or 1.

10 In an embodiment R<sup>3</sup> is hydrogen or methyl.

In an embodiment z is 1 or 2.

In another embodiment z is 1.

In an embodiment each of p, q, t, v, w, x, a and y is zero.

In an embodiment R<sup>4</sup> is hydrogen, hydroxy, halogen, C<sub>1-4</sub>alkyl, haloC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy or a ring

15 selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl, oxazolyl, pyridinyl, quinoxalinyl, phenyl, azoniaspiro[5.5]undecanyl, quinolinyl, isoquinolinyl, azepanyl, tetrahydroisoquinolinyl, octahydroindolizinyl, morpholinyl, 1'2'-

dihydrospirocyclohexane-1,3'-indolyl, octahydroisoindolyl, azoniabicyclo[3.1.0]hexanyl,

diazoniaspiro[4.4]nonanyl, hexahdropyrrolo[3,4-b]pyrrolyl, oxaazoniabicyclo[2.2.1]heptanyl,

20 diazoniaspiro[5.5]undecanyl, diazoniaspiro[3.3]heptanyl, diazoniaspiro[3.5]nonanyl,

diazoniaspiro[4.5]decanyl, octahdropyrrolo[3,4-c]pyrrolyl, octahdropyrrolo[3,4-b]pyrrolyl,

octahydrocyclopenta[c]pyrrolyl, dihydroindolyl, benzothiazolyl, azoniaspiro[4.5]decanyl,

diazoniabicyclo[2.2.2]octanyl, diazoniaspiro[2.2.1]heptanyl, diazoniaspiro[3.2.1]octanyl,

diazoniabicyclo[2.2.1]heptanyl, azoniabicyclo[3.1.0]hexanyl, tetrahydrothiophenyl,

25 tetrahydronaphthyridinyl, oxaazoniaspiro[4.5]decanyl and oxazepanyl, the ring being optionally substituted by one or more independently selected (CH<sub>2</sub>)<sub>b</sub>R<sup>5</sup> groups. Further R<sup>4</sup> groups are cyano or a ring selected from tetrazolyl, cyclobutyl, dihydroimidazolyl and pyrazolyl, the ring being optionally substituted by one or more independently selected (CH<sub>2</sub>)<sub>b</sub>R<sup>5</sup> groups.

In an embodiment b is 0 or 1. In another embodiment b is 0.

30 In an embodiment R<sup>4</sup> is a 5 or 6 membered saturated or partially saturated heterocyclic ring containing one, two or three atoms independently selected from N, O and S.

In an embodiment R<sup>4</sup> is hydrogen, halogen, C<sub>1-4</sub>alkyl, haloC<sub>1-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl or a ring selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl, oxazolyl, pyridinyl and quinoxalinyl, the ring being optionally substituted by one or more groups independently selected from R<sup>5</sup>.

35 In another embodiment R<sup>4</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, a 4 membered saturated heterocyclic ring containing one N atom; or a 5, 6 or 7 membered saturated or partially saturated heterocyclic ring containing one, two or three N atoms and zero or one O atom; any of which rings being optionally substituted by one or more groups independently selected from R<sup>5</sup>.

In another embodiment R<sup>4</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, or a 5 or 6 membered saturated or partially saturated heterocyclic ring containing one, two or three N atoms and zero or one O atom; any of which rings being optionally substituted by one or more groups independently selected from R<sup>5</sup>.

In an embodiment, when R<sup>4</sup> is a ring it is optionally substituted by one, two or three R<sup>5</sup> groups.

5 More particularly, when R<sup>4</sup> is a ring it is unsubstituted or monosubstituted.

In an embodiment, when R<sup>5</sup> is a ring it is optionally substituted by one, two or three independently selected groups. More particularly, when R<sup>5</sup> is a ring it is unsubstituted or monosubstituted.

10 In an embodiment R<sup>5</sup> is C<sub>1-6</sub>alkyl, NR<sup>a</sup>R<sup>b</sup>, oxo, S(O)<sub>r</sub>R<sup>c</sup>, C<sub>1-6</sub>alkoxycarbonyl, halogen, hydroxy, C<sub>1-6</sub>alkylcarbonyl, hydroxyC<sub>1-6</sub>alkyl, CONR<sup>a</sup>R<sup>b</sup>, haloC<sub>1-6</sub>alkyl or an optionally substituted ring selected from C<sub>6-10</sub>aryl, C<sub>6-10</sub>arylC<sub>1-6</sub>alkyl, pyrrolidinyl, piperazinyl, pyrimidinyl, pyridinyl, piperidinyl, thiomorpholinyl, imidazolyl and benzimidazolyl.

Preferred optional substituents on a R<sup>5</sup> ring are C<sub>1-6</sub>alkyl, halogen, amino, C<sub>1-6</sub>alkylamino and di(C<sub>1-6</sub>alkyl)amino.

15 Particular optional substituents on a R<sup>5</sup> ring are dimethylamino, methyl and chlorine.

In an embodiment R<sup>5</sup> is C<sub>1-6</sub>alkyl, C<sub>6-10</sub>aryl, C<sub>6-10</sub>arylC<sub>1-6</sub>alkyl or pyrrolidinyl.

20 Particular R<sup>5</sup> groups include methyl, phenyl, benzyl, pyrrolidinyl, amino, piperazinyl, pyrimidinyl, oxo, pyridinyl, methylsulfonyl, methoxycarbonyl, piperidinyl, fluorine, (dimethylamino)phenyl, hydroxy, propylcarbonyl, methylpyridinyl, hydroxymethyl, dimethylamino, thiomorpholinyl, (methylsulfonyl)amino, imidazolyl, (hydroxy)(methyl)ethyl, ethyl, chlorobenzyl, (methylamino)carbonyl, methylbenzimidazolyl and fluoromethyl.

25 Specific R<sup>5</sup> groups are methyl, phenyl, benzyl and pyrrolidine-1-yl. Further specific R<sup>5</sup> groups are amino, piperazin-1-yl, pyrimidin-2-yl, oxo, pyridin-2-yl, methylsulfonyl, methoxycarbonyl, piperidin-4-yl, pyridin-4-yl, pyridin-3-yl, fluorine, 4-(dimethylamino)phenyl, hydroxy, isopropylcarbonyl, 3-methylpyridin-2-yl, hydroxymethyl, dimethylamino, thiomorpholin-4-yl, (methylsulfonyl)amino, 1H-imidazol-1-yl, 1-(hydroxy)-1-(methyl)ethyl, ethyl, 4-chlorobenzyl, 3-chlorobenzyl, (methylamino)carbonyl, 5-methyl-1H-benzimidazol-2-yl and fluoromethyl.

In another embodiment R<sup>5</sup> is C<sub>1-6</sub>alkyl, preferably methyl.

30 Thus, particular R<sup>4</sup> groups include hydrogen, chlorine, methyl, methylpiperazine, morpholinyl, pyrrolidinyl and piperidinyl. Further particular R<sup>4</sup> groups are pyridinyl, cyclohexyl, pyrrolidinylpiperidinyl, propyl, fluoroethyl, difluoroethyl, cyclopropyl, diazepanyl, azetidinyl, methylpyrrolidinyl, methylpiperidinyl, benzylpiperidinyl, phenylpiperazinyl, quinoxalinyl, trifluoromethyl, butyl, oxazolyl and fluorine. Further particular R<sup>4</sup> groups include phenyl, methoxy, hydroxy, phenylpyrrolidinyl, aminocyclopentyl, methylazetidinyl, azoniaspiro[5.5]undecanyl, phenylpiperidinyl, (piperazinyl)pyridinyl, quinolinyl, isoquinolinyl, methylazepanyl, methyltetrahydroisoquinolinyl, (pyrimidinyl)piperidinyl, (amino)(oxo)octahydroindolizinyl, (pyridinyl)piperidinyl, methylmorpholinyl, [(methylsulfonyl)-1',2'-dihydrospiro]cyclohexane-1,3'-indolyl, octahydroisoindolyl, benzylmorpholinyl, (methoxycarbonyl)pyrrolidinyl, (piperidinyl)pyrrolidinyl,

(pyridinyl)pyrrolidinyl, difluoropyrrolidinyl, (amino)azoniabicyclo[3.1.0]hexanyl, (methyl)diazoniaspiro[4.4]nonanyl, [(dimethylamino)phenyl]pyrrolidinyl, (methyl)hexahdropyrrolo[3,4-b]pyrrolyl, oxaazoniabicyclo[2.2.1]heptanyl, hydroxypropanyl, difluorocyclobutyl, fluorodiazepanyl, (pyrimidinyl)diazepanyl, benzylpyrrolidinyl, benzylazoniaspiro[4.4]nonanyl, 5 benzylazoniaspiro[5.5]undecanyl, diazoniaspiro[3.3]heptanyl, diazoniaspiro[3.5]nonanyl, diazoniaspiro[5.5]undecanyl, diazoniaspiro[4.5]decanyl, octahdropyrrolo[3,4-c]pyrrolyl, octahdropyrrolo[3,4-b]pyrrolyl, octahydrocyclopenta[c]pyrrolyl, dihydroindolyl, benzothiazolyl, azoniaspiro[4.5]decanyl, fluoropiperidinyl, (benzyl)(methyl)piperidinyl, (isopropylcarbonyl)piperidinyl, (methylpyridinyl)piperidinyl, diazoniabicyclo[2.2.2]octanyl, 10 (methyl)diazoniabicyclo[2.2.1]heptanyl, (pyridinylmethyl)piperazinyl, (benzyl)azaazoniabicyclo[2.2.2]octanyl, (benzyl)azaazoniabicyclo[3.2.1]octanyl, (benzyl)azaazoniabicyclo[2.2.1]heptanyl, azoniabicyclo[3.1.0]hexanyl, dioxohydroxytetrahydrothiophenyl, (hydroxy)(methyl)piperidinyl, (hydroxymethyl)cyclopentyl, tetrahydronaphthyridinyl, [(dimethylamino)methyl]piperidinyl, (thiomorpholinyl)piperidinyl, 15 [(methylsulfonyl)amino]piperidinyl, (imidazolylmethyl)piperidinyl, oxaazoniaspiro[4.5]decanyl, [(hydroxy)(methyl)ethyl]piperidinyl, ethylpiperidinyl, bromine, (chlorobenzyl)azaazoniabicyclo[2.2.1]heptanyl, [(methylamino)carbonyl]piperazinyl, (hydroxymethyl)oxazepanyl, (hydroxymethyl)cyclobutyl, (hydroxymethyl)cyclohexyl, (methylbenzimidazolyl)piperidinyl, (hydroxy)(pyridinyl)piperidinyl, difluoropyrrolidinyl, 20 (fluoromethyl)pyrrolidinyl and oxopyrrolidinyl. Further particular R<sup>4</sup> groups include cyano, tetrazolyl, cyclobutyl, dihydroimidazolyl, pyrazolyl and piperazinyl.

Specific R<sup>4</sup> groups include hydrogen, chlorine, methyl, 4-methylpiperazin-1-yl, morpholin-4-yl, pyrrolidin-1-yl and piperidin-1-yl. Further specific R<sup>4</sup> groups are pyridin-4-yl, cyclohexyl, piperidin-4-yl, 4-pyrrolidin-1-ylpiperidin-1-yl, *iso*-propyl, 2-fluoroethyl, 2,2-difluoroethyl, cyclopropyl, 1,4-diazepan-1-yl, azetidin-3-yl, 1-methylpyrrolidin-2-yl, 1-methylpiperidin-3-yl, 1-methylpiperidin-4-yl, 1-25 benzylpiperidin-4-yl, 4-phenylpiperazin-1-yl, quinoxalin-6-yl, trifluoromethyl, pyridin-2-yl, *tert*-butyl, 1,3-oxazol-2-yl and fluorine. Further specific R<sup>4</sup> groups are pyridin-3-yl, azetidin-2-yl, phenyl, methoxy, hydroxy, (2S)-pyrrolidin-2-yl, pyrrolidin-3-yl, (2R)-pyrrolidin-2-yl, (3R)-1-methylpyrrolidin-3-yl, 1-30 methylpiperidin-2-yl, (3S)-1-methylpyrrolidin-3-yl, (3R)-1-methylpiperidin-3-yl, (3S)-1-methylpiperidin-3-yl, 4-phenylpyrrolidin-2-yl, (1S,3R)-3-aminocyclopentyl, (1R,3R)-3-aminocyclopentyl, (1R,3S)-3-aminocyclopentyl, 2-methylazetidin-2-yl, 3-azoniaspiro[5.5]undecan-9-yl, 4-phenylpiperidin-4-yl, 2-(piperazin-1-yl)pyridin-3-yl, quinolin-4-yl, isoquinolin-4-yl, 1-methylazepan-2-yl, 2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl, 1-(pyrimidin-2-yl)piperidin-4-yl, 2-amino-3-oxooctahydroindolizin-5-yl, 1-(pyridin-2-yl)piperidin-3-yl, 4-methylmorpholin-2-yl, (1R,4R)-4-[1'-(methylsulfonyl)-1',2'-35 dihydrospiro]cyclohexane-1,3'-indol-4-yl, octahydro-1H-isoindol-1-yl, 4-benzylmorpholin-2-yl, (3S,4R)-4-(methoxycarbonyl)pyrrolidin-3-yl, (2S)-1-(piperidin-4-yl)pyrrolidin-2-yl, (1S,3S)-3-aminocyclopentyl, 1-methylpyrrolidin-3-yl, 3-(pyridin-4-yl)pyrrolidin-1-yl, 3-(pyridin-2-yl)pyrrolidin-1-yl, 3-(pyridin-3-yl)pyrrolidin-1-yl, (3S,4S)-3,4-difluoropyrrolidin-1-yl, 6-amino-3-azoniabicyclo[3.1.0]hexan-3-yl, 7-

methyl-2,7-diazoniaspiro[4,4]nonan-2-yl, 3-[4-(dimethylamino)phenyl]pyrrolidin-1-yl, 1-methyl-1,2,4,5,6,6a-hexahydropyrrolo[3,4-b]pyrrol-5-yl, (1R,4S)-2-oxa-5-azoniabicyclo[2.2.1]heptan-5-yl, 2-hydroxypropan-2-yl, 3,3-difluorocyclobutyl, 6-fluoro-1,4-diazepan-1-yl, 4-(pyrimidin-2-yl)-1,4-diazepan-1-yl, 1-benzylpyrrolidin-3-yl, 7-benzyl-2,7-diazoniaspiro[4,4]nonan-2-yl, 8-benzyl-2,8-diazoniaspiro[5,5]undecan-2-yl, 2,6-diazoniaspiro[3,3]heptan-2-yl, 2,7-diazoniaspiro[3,5]nonan-7-yl, 2,6-diazoniaspiro[3,5]nonan-2-yl, 2,8-diazoniaspiro[5,5]undecan-2-yl, 2,8-diazoniaspiro[4,5]decan-2-yl, 2,7-diazoniaspiro[4,5]decan-2-yl, 2,8-diazoniaspiro[4,5]decan-8-yl, 3,9-diazoniaspiro[5,5]undecan-3-yl, octahydropyrrolo[3,4-c]pyrrol-2-yl, octahydropyrrolo[3,4-b]pyrrol-5-yl, octahydrocyclopenta[c]pyrrol-4-yl, 2,3-dihydro-1H-indol-1-yl, 1,3-benzothiazol-5-yl, 8-azoniaspiro[4,5]decan-1-yl, (3R,4R)-3-fluoropiperidin-4-yl, (3R,4R)-3-benzyl-1-methylpiperidin-4-yl, 1-(isopropylcarbonyl)piperidin-4-yl, 1-(3-methylpyridin-2-yl)piperidin-4-yl, 1-benzylpiperidin-3-yl, 5-aza-2-azoniabicyclo[2.2.2]octan-5-yl, (1S,4S)-5-methyl-2,5-diazoniaspiro[2.2.1]heptan-2-yl, 4-(pyridin-2-ylmethyl)piperazin-1-yl, 2-benzyl-5-aza-2-azoniabicyclo[2.2.2]octan-5-yl, 3-benzyl-8-aza-3-azoniabicyclo[3.2.1]octan-8-yl, (1S,4S)-2-benzyl-5-aza-2-azoniabicyclo[2.2.1]heptan-5-yl, 3-azoniabicyclo[3.1.0]hexan-6-yl, (3S,4S)-1,1-dioxo-4-hydroxytetrahydrothiophen-3-yl, 1-methyl-4-hydroxypiperidin-4-yl, 1-(hydroxymethyl)cyclopentyl, 1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl, 3-[(dimethylamino)methyl]piperidin-1-yl, 4-(thiomorpholin-4-yl)piperidin-1-yl, 4-[(methylsulfonyl)amino]piperidin-1-yl, 4-[(1H-imidazol-1-yl)methyl]piperidin-1-yl, 1-oxa-7-azoniaspiro[4,5]decan-7-yl, 4-[1-(hydroxy)-1-(methyl)ethyl]piperidin-1-yl, 1-benzylpiperidin-2-yl, 1-ethylpiperidin-2-yl, 1-ethylpiperidin-3-yl, pyrrolidin-2-yl, bromine, (R)-3-[(dimethylaminol)methyl]piperidin-1-yl, (S)-3-[(dimethylamino)methyl]piperidin-1-yl, (1S,4S)-2-(4-chlorobenzyl)-5-aza-2-azoniabicyclo[2.2.1]heptan-5-yl, (1S,4S)-2-(3-chlorobenzyl)-5-aza-2-azoniabicyclo[2.2.1]heptan-5-yl, 4-[(methylamino)carbonyl]piperazin-1-yl, 6-(hydroxymethyl)-1,4-oxazepan-4-yl, 1-(hydroxymethyl)cyclobutyl, 1-(hydroxymethyl)cyclohexyl, 4-(5-methyl-1H-benzimidazol-2-yl)piperidin-1-yl, 4-hydroxy-4-(pyridin-2-yl)piperidin-1-yl, 3,3-difluoropyrrolidin-1-yl, (2R)-2-(fluoromethyl)pyrrolidin-1-yl, 2-oxopyrrolidin-3-yl, 1-methylazetidin-3-yl and (3R)-1-methylpiperidin-3-yl. Further specific R<sup>4</sup> groups include cyano, 1H-tetrazol-5-yl, cyclobutyl, 4,5-dihydro-1H-imidazol-2-yl, piperidin-2-yl, 1H-pyrazol-1-yl and piperazin-2-yl.

R<sup>4</sup> may be piperidin-3-yl, provided that:

when A is CH; m is 0 or 1; R<sup>1</sup> is fluorine substituted at the 5 position of the indazole ring; and n is 0; then 30 Y-[(CR<sup>6</sup>R<sup>7</sup>)<sub>p</sub>(CO)<sub>q</sub>(NR<sup>2</sup>)<sub>t</sub>(X=O)<sub>v</sub>(O)<sub>w</sub>(CR<sup>8</sup>R<sup>9</sup>)<sub>x</sub>(CO)<sub>a</sub>(NR<sup>3</sup>)<sub>y</sub>R<sup>4</sup>]<sub>z</sub> is not 4-(piperidin-3-yl)phenyl or (fluoro)-4-(piperidin-3-yl)phenyl.

In an embodiment, when y is 1 then R<sup>4</sup> is piperidin-3-yl.

In an embodiment R<sup>4</sup> is piperidinyl.

In an embodiment R<sup>6</sup> is hydrogen or C<sub>1-4</sub>alkyl and R<sup>7</sup> is hydrogen.

35 Particular R<sup>6</sup> groups are hydrogen and methyl.

A particular R<sup>7</sup> group is hydrogen. A further particular R<sup>7</sup> group is methyl.

In an embodiment each of R<sup>6</sup> and R<sup>7</sup> is hydrogen.

In an embodiment  $R^8$  is hydrogen,  $C_{1-4}$ alkyl, hydroxy, halo $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkyl, amino,  $C_{1-6}$ alkylamino or di( $C_{1-6}$ alkyl)amino and  $R^9$  is hydrogen.

Particular  $R^8$  groups are hydrogen, dimethylamino, hydroxymethyl, chloromethyl and hydroxy.

A particular  $R^9$  group is hydrogen.

5 In an embodiment each of  $R^8$  and  $R^9$  is hydrogen.

In an embodiment when  $R^a$  and  $R^b$  together form a ring or  $R^c$  is a ring, the ring is optionally substituted by one, two or three optionally selected groups.

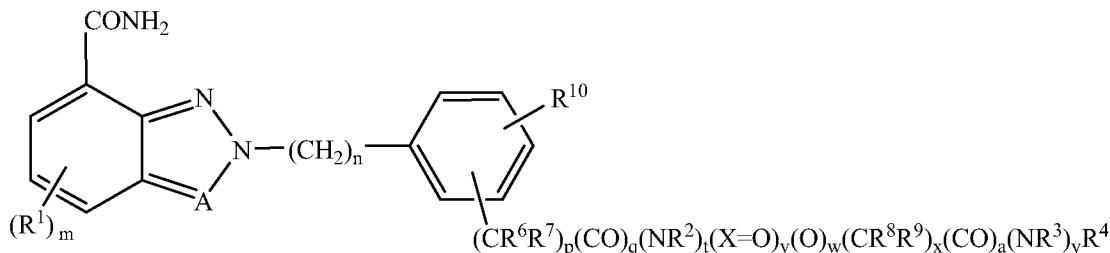
In an embodiment each of  $R^a$  and  $R^b$  is independently selected from hydrogen,  $C_{1-6}$ alkyl and  $SO_2R^c$ .

10 Particular  $R^a$  groups are hydrogen, methyl and methylsulfonyl.

Particular  $R^b$  groups are hydrogen and methyl.

A particular  $R^c$  group is  $C_{1-6}$ alkyl, especially methyl.

The present invention also provides compounds of formula II:



(II)

wherein:

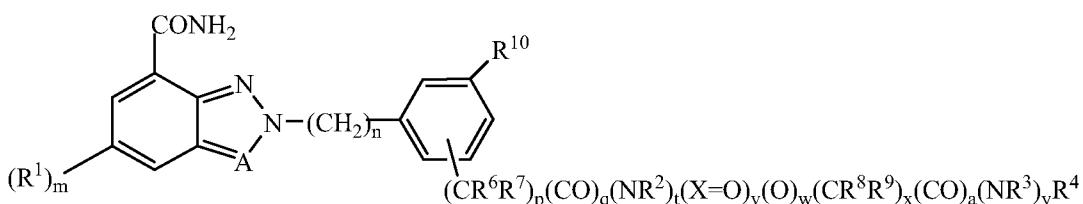
a, m, n, p, q, t, v, w, x, y, A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and X are as defined above;

$R^{10}$  is hydrogen, halogen,  $C_{1-6}$ alkyl or halo $C_{1-6}$ alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

20 In an embodiment of formula II, each of  $R^8$  and  $R^9$  is hydrogen.

The present invention also provides compounds of formula III:



(III)

wherein:

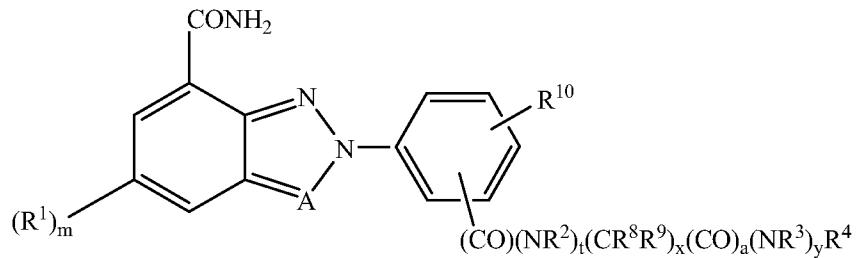
a, m, n, p, q, t, v, w, x, y, A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and X are as defined above;

$R^{10}$  is hydrogen, halogen,  $C_{1-6}$ alkyl or halo $C_{1-6}$ alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In another embodiment of any one of formulae II or III, n is 0.

The present invention also provides compounds of formula IV:



(IV)

5

wherein:

m, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>8</sup> and R<sup>9</sup> are as defined above;

a is 0 or 1;

t is 0 or 1;

x is 0, 1 or 2;

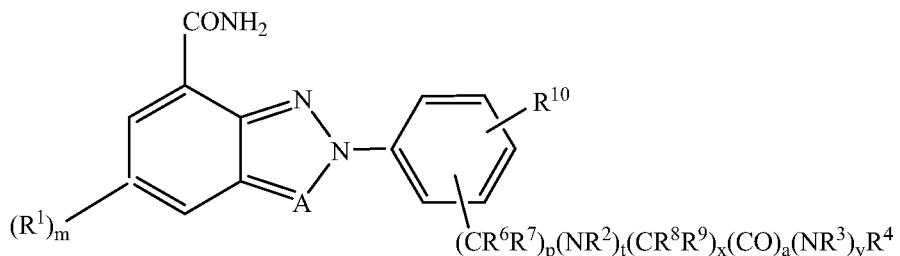
10

y is 0 or 1;

R<sup>10</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl or haloC<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof

The present invention also provides compounds of formula V:



15

(V)

wherein:

a, m, t, y, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are as defined above;

p is 1 or 2;

x is 0, 1 or 2;

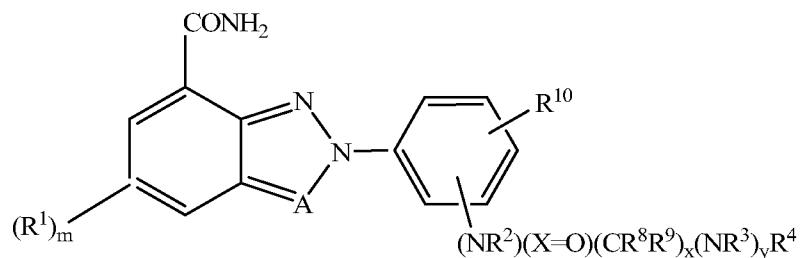
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R<sup>10</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl or haloC<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof

In an embodiment p is 1.

The present invention also provides compounds of formula VI:



(VI)

wherein:

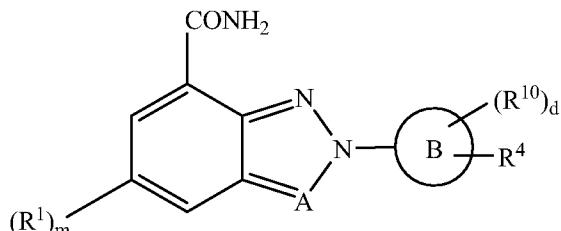
m, y, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>8</sup>, R<sup>9</sup> and X are as defined above;

x is 0, 1 or 2;

5 R<sup>10</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl or haloC<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof

The present invention also provides compounds of formula VII:



(VII)

10

wherein:

m, A, R<sup>1</sup> and R<sup>4</sup> are as defined above;

d is 0, 1 or 2;

15 B is a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms, 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring or a 8-13 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S;

R<sup>10</sup> is halogen or C<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

20 In an embodiment of formula VII, R<sup>1</sup> may be substituted at any substitutable position of the fused benzene ring.The preferred identities with reference to any one of formulae II, III, IV, V, VI and VII are as defined previously for formula I *mutatis mutandis*.

In an embodiment of any one of formulae II, III, IV, V, VI or VII, A is CH.

25 Particular R<sup>10</sup> groups are methyl, chlorine and fluorine, especially chlorine and fluorine.

In an embodiment d is 0 or 1. In another embodiment d is 0.

Particular B groups are phenyl, tetrahydroisoquinoliny, pyridinyl and pyridazinyl. A further particular B group is tetrahydronaphthyridinyl.

More particular B groups are phenyl and tetrahydroisoquinoliny.

Specific B groups are phenyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl, 1,2,3,4-tetrahydroisoquinolin-5-yl, pyridin-2-yl and pyridazin-3-yl. A further specific B group is 5,6,7,8-tetrahydro-1,7-naphthyridin-3-yl.

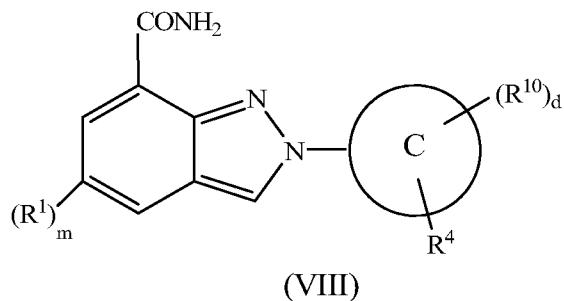
In an embodiment B is phenyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl or 1,2,3,4-tetrahydroisoquinolin-5-yl.

In an embodiment the R<sup>4</sup> ring is unsubstituted, monosubstituted or disubstituted. In another embodiment the ring is unsubstituted.

Particular R<sup>4</sup> rings are azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuran, thiomorpholinyl, diazepanyl, azepanyl and oxazepanyl. A further particular R<sup>4</sup> ring is dihydroimidazolyl.

The present invention also provides compounds of formula VIII:

15



wherein m, R<sup>1</sup> and R<sup>4</sup> are as defined above;

d is 0, 1 or 2;

C is a 4 membered saturated heterocycle containing one N atom or a 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S;

R<sup>10</sup> is halogen or C<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

The preferred identities with reference to formula VIII are as defined previously for formulae I, II, III, IV, V, VI and VII *mutatis mutandis*.

In an embodiment C is a 5 or 6 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S.

Particular C rings are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuran, thiomorpholinyl, diazepanyl, azepanyl and oxazepanyl.

More particularly, C is pyrrolidinyl or piperidinyl.

Specific C rings include pyrrolidin-3-yl, piperidin-4-yl and piperidin-3-yl.

The present invention also includes within its scope N-oxides of the compounds of formula I above. In general, such N-oxides may be formed on any available nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula I with oxone in the presence of wet alumina.

5 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

10 A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible 15 functionality.

The present invention includes within its scope solvates of the compounds of formula I and salts thereof, for example, hydrates.

20 The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual 25 diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

25 The compounds may exist in different isomeric forms, all of which are encompassed by the present invention.

The compounds may exist in a number of different polymorphic forms.

30 When any variable (e.g. R<sup>1</sup> and R<sup>2</sup>, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of 35 the substitutable ring atoms.

35 It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted" should be taken to be equivalent

to the phrase "unsubstituted or substituted with one or more substituents" and in such cases the preferred embodiment will have from zero to three substituents. More particularly, there are zero to two substituents. A substituent on a saturated, partially saturated or unsaturated heterocycle can be attached at any substitutable position.

5 As used herein, "alkyl" is intended to include both branched, straight-chain and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C<sub>1-6</sub>alkyl" is defined to include groups having 1, 2, 3, 4, 5 or 6 carbons in a linear, branched or cyclic arrangement. For example, "C<sub>1-6</sub>alkyl" specifically includes methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and so on. Preferred alkyl groups are 10 methyl and ethyl. The term "cycloalkyl" means a monocyclic, bicyclic or polycyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "C<sub>3-7</sub>cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In an embodiment of the invention the term "cycloalkyl" includes the groups described immediately 15 above and further includes monocyclic unsaturated aliphatic hydrocarbon groups. For example, "cycloalkyl" as defined in this embodiment includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, cyclopentenyl, cyclobutenyl, 7,7-dimethylbicyclo[2.2.1]heptyl and so on. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

20 As used herein, the term "C<sub>2-6</sub>alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 6 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Alkenyl groups include ethenyl, propenyl, butenyl and 2-methylbutenyl. Preferred alkenyl groups include ethenyl and propenyl.

25 As used herein, the term "C<sub>2-6</sub>alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 6 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. Preferred alkynyl groups include ethynyl and propynyl

30 "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl above. Examples of suitable alkoxyl groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. The preferred alkoxyl groups are methoxy and ethoxy. The term 'C<sub>6-10</sub>aryloxy' can be construed analogously, and an example of this group is phenoxy.

35 The terms "haloC<sub>1-6</sub>alkyl" and "haloC<sub>1-6</sub>alkoxy" mean a C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. Preferred are fluoroC<sub>1-6</sub>alkyl and fluoroC<sub>1-6</sub>alkoxy groups, in particular fluoroC<sub>1-3</sub>alkyl and fluoroC<sub>1-3</sub>alkoxy groups, for example, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>CH<sub>2</sub>F, CH<sub>2</sub>CHF<sub>2</sub>, CH<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCHF<sub>2</sub>, OCH<sub>2</sub>F, OCH<sub>2</sub>CH<sub>2</sub>F, OCH<sub>2</sub>CHF<sub>2</sub> or OCH<sub>2</sub>CF<sub>3</sub>, and most especially CF<sub>3</sub>, OCF<sub>3</sub> and OCHF<sub>2</sub>.

As used herein, the term "hydroxyC<sub>1-6</sub>alkyl" means a C<sub>1-6</sub>alkyl group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by hydroxy groups. Preferred are CH<sub>2</sub>OH, CH<sub>2</sub>CHOH and CHOCH<sub>3</sub>.

The term "C<sub>1-6</sub>alkylcarbonyl" or "C<sub>1-6</sub>alkoxycarbonyl" denotes a C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy radical, 5 respectively, attached via a carbonyl (C=O) radical. Suitable examples of C<sub>1-6</sub>alkylcarbonyl groups include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl and *tert*-butylcarbonyl. Examples of C<sub>1-6</sub>alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and *tert*-butoxycarbonyl. The term 'C<sub>6-10</sub>arylcarbonyl' can be construed analogously, and an example of this group is benzoyl.

10 The rings present in the compounds of this invention may be monocyclic or multicyclic, particularly bicyclic. The multicyclic rings may be fused or spiro linked.

As used herein, "C<sub>6-10</sub>aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of 6 to 10 atoms, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and tetrahydrobenzo[7]annulene. The preferred aryl group is 15 phenyl or naphthyl, especially phenyl.

Examples of particular heterocycles of this invention are benzimidazolyl, benzofurandionyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothienyl, benzoxazolyl, benzoxazolonyl, benzothiazolyl, benzothiadiazolyl, benzodioxolyl, benzoxadiazolyl, benzoisoxazolyl, benzoisothiazolyl, chromenyl, chromanyl, isochromanyl, carbazolyl, carbolinyl, cinnolinyl, epoxidyl, 20 furyl, furazanyl, imidazolyl, indolinyl, indolyl, indolizinyl, indolinyl, isoindolinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazolinyl, isoxazolinyl, oxetanyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridinyl, pyrimidinyl, triazinyl, tetrazinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinolizinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, 25 tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidyl, pyridin-2-onyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, 30 dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydroisoquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dihydroisochromenyl, dihydrochromenyl, dihydroimidazolonyl, dihydrotriazolonyl, dihydrobenzodioxinyl, dihydrothiazolopyrimidinyl, dihydroimidazopyrazinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinolinyl, thiazolidinonyl, imidazolonyl, isoindolinonyl, 35 octahydroquinolizinyl, octahydroisoindolyl, imidazopyridinyl, azabicycloheptanyl, chromenonyl, triazolopyrimidinyl, dihydrobenzoxazinyl, thiazolotriazolyl, azoniabicycloheptanyl, azoniabicyclooctanyl, phthalazinyl, naphthyridinyl, quinazolinyl, pteridinyl, dihydroquinazolinyl, dihydrophtalazinyl, benzisoxazolyl, tetrahydronaphthyridinyl, dibenzo[*b,d*]furanyl,

dihydrobenzothiazolyl, imidazothiazolyl, tetrahydroindazolyl, tetrahydrobenzothienyl, hexahydroronaphthyridinyl, tetrahydroimidazopyridinyl, tetrahydroimidazopyrazinyl, pyrrolopyridinyl and N-oxides thereof. Further examples include azoniaspiro[5.5]undecanyl, azepanyl, octahydroindolizinyl, 1'2'-dihydrospirocyclohexane-1,3'-indolyl, azoniabicyclo[3.1.0]hexanyl, diazoniaspiro[4.4]nonanyl, 5 hexahdropyrrolo[3,4-b]pyrrolyl, oxaazoniabicyclo[2.2.1]heptanyl, diazoniaspiro[5.5]undecanyl, diazoniaspiro[3.3]heptanyl, diazoniaspiro[3.5]nonanyl, diazoniaspiro[4.5]decanyl, octahdropyrrolo[3,4-c]pyrrolyl, octahdropyrrolo[3,4-b]pyrrolyl, octahydrocyclopenta[c]pyrrolyl, dihydroindolyl, azoniaspiro[4.5]decanyl, diazoniamicyclo[2.2.2]octanyl, diazoniamicyclo[2.2.1]heptanyl, diazoniamicyclo[3.2.1]octanyl, diazoniamicyclo[2.2.1]heptanyl, azoniabicyclo[3.1.0]hexanyl, 10 tetrahydrothiophenyl, oxaazoniaspiro[4.5]decanyl and oxazepanyl. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

A preferred 4 membered saturated heterocycle is azetidinyl.

Preferred 5 or 6 membered saturated or partially saturated heterocycles are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuran and thiomorpholinyl. A further preferred 15 heterocycle is dihydroimidazolyl.

A preferred 7 membered saturated heterocycle is diazepanyl. Further preferred rings are azepanyl and oxazepanyl.

Preferred 5 membered heteroaromatic rings are thienyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, triazolyl, tetrazolyl, furyl and pyrrolyl.

20 Preferred 6 membered heteraromatic rings are pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl.

Preferred 6-13 membered saturated, partially saturated or unsaturated hydrocarbon rings are cyclohexyl, cyclohexadienyl, cycloheptyl, cyclooctyl, phenyl, naphthyl, tetrahydroronaphthalenyl, dihydroindenyl, fluorenyl, adamantly, tetrahydrobenzo[7]annulenyl, indanyl, tetrahydroindenyl and tetrahydrobenzo[7]annulene.

25 Preferred 7-13 membered partially saturated or unsaturated heterocyclic rings are tetrahydroquinolinyl, quinolinyl, indolyl, imidazopyridinyl, benzothiazolyl, quinoxalinyl, benzothiadiazolyl, benzoxazolyl, dihydrobenzodioxinyl, benzotriazolyl, benzodioxolyl, dihydroisoindolyl, dihydroindolyl, tetrahydroisoquinolinyl, isoquinolinyl, benzoisothiazolyl, dihydroimidazopyrazinyl, benzothienyl, benzoxadiazolyl, thiazolotriazolyl, dihydrothiazolopyrimidinyl, 30 dihydrobenzoxazinyl, dihydrobenzofuranyl, benzimidazolyl, benzofuranyl, dihydrobenzoxazolyl, dihydroquinazolinyl, dihydropthalazinyl, indazolyl, benzisoxazolyl, tetrahydroronaphthyridinyl, triazolopyrimidinyl, dibenzo[b,d]furanyl, naphthyridinyl, dihydroquinolinyl, dihydroisochromenyl, dihydrochromenyl, dihydrobenzothiazolyl, imidazothiazolyl, tetrahydroindazolyl, tetrahydrobenzothienyl, hexahydroronaphthyridinyl, tetrahydroimidazopyridinyl,

35 tetrahydroimidazopyrazinyl and pyrrolopyridinyl. Further preferred rings are quinazolinyl and indolizinyl. Further preferred 7-15 membered saturated, partially saturated or unsaturated heterocycles include azoniaspiro[5.5]undecanyl, azepanyl, octahydroindolizinyl, 1'2'-dihydrospirocyclohexane-1,3'-indolyl, octahydroisoindolyl, azoniabicyclo[3.1.0]hexanyl, diazoniaspiro[4.4]nonanyl,

hexahydropyrrolo[3,4-b]pyrrolyl, oxaazoniabicyclo[2.2.1]heptanyl, diazoniaspiro[5.5]undecanyl, diazoniaspiro[3.3]heptanyl, diazoniaspiro[3.5]nonanyl, diazoniaspiro[4.5]decanyl, octahydropyrrolo[3,4-c]pyrrolyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydrocyclopenta[c]pyrrolyl, dihydroindolyl, azoniaspiro[4.5]decanyl, diazoniacyclo[2.2.2]octanyl, diazoniacyclo[2.2.1]heptanyl, diazoniacyclo[3.2.1]octanyl, diazoniacyclo[2.2.1]heptanyl, azoniabicyclo[3.1.0]hexanyl, tetrahydrothiophenyl, oxaazoniaspiro[4.5]decanyl and oxazepanyl.

As used herein, the term "halogen" refers to fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

Particular compounds within the scope of the present invention are:

- 10 2-phenyl-2*H*-indazole-7-carboxamide;
- 2-(3-chlorophenyl)-2*H*-indazole-7-carboxamide; and
- 2-{4-[(dimethylamino)methyl]phenyl}-2*H*-indazole-7-carboxamide;
- 2-{4-[(N,N-dimethylglycyl)amino]phenyl}-2*H*-indazole-7-carboxamide;
- 2-benzyl-2*H*-indazole-7-carboxamide;
- 15 2-(4-chlorophenyl)-2*H*-indazole-7-carboxamide;
- 2-(2-chlorophenyl)-2*H*-indazole-7-carboxamide;
- 2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-2*H*-indazole-7-carboxamide;
- 2-[4-(morpholin-4-ylmethyl)phenyl]-2*H*-indazole-7-carboxamide;
- 2-{4-[(methylamino)methyl]phenyl}-2*H*-indazole-7-carboxamide;
- 20 2-[4-(pyrrolidin-1-ylmethyl)phenyl]-2*H*-indazole-7-carboxamide;
- 2-[4-(piperidin-1-ylmethyl)phenyl]-2*H*-indazole-7-carboxamide;
- and pharmaceutically acceptable salts or tautomers thereof.

A particular salt of the present invention is:

- 25 {4-[7-(aminocarbonyl)-2*H*-indazol-2-yl]phenyl}-N,N-dimethylmethanaminium chloride;
- or a tautomer thereof.

Further particular compounds within the scope of the present invention are:

- 4-[(4-[7-(aminocarbonyl)-2*H*-indazol-2-yl]benzoyl)amino)methyl]pyridinium trifluoroacetate;
- 2-{4-[1-(methylamino)ethyl]phenyl}-2*H*-indazole-7-carboxamide;
- N*-{4-[7-(aminocarbonyl)-2*H*-indazol-2-yl]benzyl} cyclohexanaminium trifluoroacetate;
- 30 {4-[7-(aminocarbonyl)-4-chloro-2*H*-indazol-2-yl]phenyl}-*N*-methylmethanaminium trifluoroacetate;
- 2-phenyl-2*H*-1,2,3-benzotriazole-4-carboxamide;
- 2-benzyl-2*H*-1,2,3-benzotriazole-4-carboxamide;
- 2-{3-[(methylamino)methyl]phenyl}-2*H*-indazole-7-carboxamide;
- 4-({3-[7-(aminocarbonyl)-2*H*-indazol-2-yl]benzoyl)amino)piperidinium trifluoroacetate;
- 35 {4-[7-(aminocarbonyl)-2*H*-indazol-2-yl]phenyl}-*N*-methylmethanaminium chloride;
- 2-{3-chloro-4-[(dimethylamino)methyl]phenyl}-2*H*-indazole-7-carboxamide;
- 1-[2-({4-[7-(aminocarbonyl)-2*H*-indazol-2-yl]phenyl)amino)-2-oxoethyl]-4-methylpiperazin-1-ium trifluoroacetate;

2-(4-[(4-pyrrolidin-1-yl)piperidin-1-yl]acetyl)amino]phenyl)-2H-indazole-7-carboxamide;  
2-[(4-(pyrrolidin-1-yl)acetyl)amino]phenyl)-2H-indazole-7-carboxamide;  
2-[(4-(piperidin-1-yl)acetyl)amino]phenyl)-2H-indazole-7-carboxamide;  
2-[(4-(morpholin-4-yl)acetyl)amino]phenyl)-2H-indazole-7-carboxamide;  
5 4-[2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]-2-oxoethyl]morpholin-4-ium chloride;  
2-[(4-[(ethylamino)methyl]phenyl)-2H-indazole-7-carboxamide;  
2-[(4-[(isopropylamino)methyl]phenyl)-2H-indazole-7-carboxamide;  
N-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)propan-2-aminium chloride;  
2-(4-[(2-fluoroethyl)amino]methyl)phenyl)-2H-indazole-7-carboxamide;  
10 2-(4-[(2,2-difluoroethyl)amino]methyl)phenyl)-2H-indazole-7-carboxamide;  
2-[(4-[(cyclopropylamino)methyl]phenyl)-2H-indazole-7-carboxamide;  
4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)-1,4-diazepan-1-ium trifluoroacetate;  
2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino]-N,N-dimethylethanaminium trifluoroacetate;  
4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino)methyl]piperidinium trifluoroacetate;  
15 N-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)-N,N',N'-trimethylethane-1,2-diaminium dichloride;  
4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)-1-methylpiperazin-1-ium trifluoroacetate;  
3-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]azetidinium trifluoroacetate;  
(2S)-2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylpyrrolidinium trifluoroacetate;  
20 3-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylpiperidinium trifluoroacetate;  
4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylpiperidinium trifluoroacetate;  
4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino]-1-benzylpiperidinium trifluoroacetate;  
25 2-[(4-[(pyridin-4-yl)amino]carbonyl)phenyl)-2H-indazole-7-carboxamide;  
2-[(4-[(4-phenylpiperazin-1-yl)carbonyl]phenyl)-2H-indazole-7-carboxamide;  
2-[(4-[(methyl(quinoxalin-6-yl)methyl)amino]carbonyl)phenyl)-2H-indazole-7-carboxamide;  
2-(4-formylphenyl)-2H-indazole-7-carboxamide;  
1-[2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino]ethyl]pyrrolidinium trifluoroacetate;  
30 1-[2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino]ethyl]piperidinium trifluoroacetate;  
4-[(2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino]ethyl)morpholin-4-ium trifluoroacetate;  
4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl)amino]-1-methylpiperidinium trifluoroacetate;  
2-[(4-[(4-methylpiperazin-1-yl)methyl]3-(trifluoromethyl)phenyl)-2H-indazole-7-carboxamide;  
2-[(4-[(methylamino)methyl]3-(trifluoromethyl)phenyl)-2H-indazole-7-carboxamide;  
35 1-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl)-N-methylethanaminium chloride;  
2-[(4-(pyrrolidin-1-yl)methyl)3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide;  
2-[(4-(piperidin-1-yl)methyl)3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide;  
2-[(4-[(ethylamino)methyl]3-(trifluoromethyl)phenyl)-2H-indazole-7-carboxamide;

4-{4-[7-(aminocarbonyl)-4-chloro-2H-indazol-2-yl]benzyl}-1-methylpiperazin-1-ium trifluoroacetate; 1-[2-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]ethyl]piperidinium bis(trifluoroacetate); 4-[2-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]ethyl]morpholin-4-ium bis(trifluoroacetate);

5 1-[2-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]ethyl]pyrrolidinium bis(trifluoroacetate); 4-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio)-1-methylpiperidinium bis(trifluoroacetate); 4-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio)-1-benzylpiperidinium bis(trifluoroacetate); 1-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-phenylpiperazinium bis(trifluoroacetate); 10 *N*-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-(dimethylamino)-2-oxoethanaminium trifluoroacetate; 2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]methyl]pyridinium bis(trifluoroacetate); 4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]methyl]pyridinium bis(trifluoroacetate); 15 *N*-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-methylpropan-2-aminium trifluoroacetate; *N*'-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-*N,N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); {4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl}-*N*-(1,3-oxazol-2-ylmethyl)methanaminium trifluoroacetate; and pharmaceutically acceptable salts or tautomers thereof.

Further particular compounds within the scope of the present invention are:

20 7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium chloride; 6-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium chloride; 5-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate; 3-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl)amino]carbonyl]azetidinium trifluoroacetate; 25 2-(4-[(Azetidin-3-ylcarbonyl)(methyl)amino]methyl)phenyl)-2H-indazole-7-carboxamide; 3-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl)amino]carbonyl]azetidinium trifluoroacetate; 2-(4-Bromophenyl)-5-fluoro-2H-indazole-7-carboxamide; 5-Fluoro-2-(4-pyridin-3-ylphenyl)-2H-indazole-7-carboxamide; 2-(4-Pyridin-3-ylphenyl)-2H-indazole-7-carboxamide; 30 4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-1-methylpiperazin-1-ium trifluoroacetate; 4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}piperidinium trifluoroacetate; 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-*N*-methylethanaminium trifluoroacetate; 2-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]azetidinium trifluoroacetate; 2-{5-[(Methylamino)methyl]pyridin-2-yl}-2H-indazole-7-carboxamide; 35 5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide; 5-Fluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate; 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-*N*-methylpropan-2-aminium trifluoroacetate; 2-(6-Phenylpyridazin-3-yl)-2H-indazole-7-carboxamide;

{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-N-{{[1-(hydroxymethyl)cyclohexyl]methyl}methanaminium trifluoroacetate; 5-Chloro-2-(4-formylphenyl)-2H-indazole-7-carboxamide; 2-{3-Methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}-2H-indazole-7-carboxamide; 5 2-{3-Methoxy-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide; 5-Chloro-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-2H-indazole-7-carboxamide; 5-Chloro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide; {4-[7-(Aminocarbonyl)-4-fluoro-2H-indazol-2-yl]phenyl}-N-methylmethanaminium chloride; {4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-N-methylmethanaminium chloride; 10 1-{4-[7-(Aminocarbonyl)-4-fluoro-2H-indazol-2-yl]benzyl}-4-methylpiperazin-1-ium chloride; 1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-4-methylpiperazin-1-ium chloride; 1-{3-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-methylpiperazinediium bis(trifluoroacetate); 2-[4-(1-Hydroxy-1-methylethyl)phenyl]-2H-indazole-7-carboxamide; 2-(4-Acetylphenyl)-2H-indazole-7-carboxamide; 15 3-{{[4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}(methyl)amino]carbonyl}-1-methylpiperidinium trifluoroacetate; 2-{4-[1-(Formylamino)-1-methylethyl]phenyl}-2H-indazole-7-carboxamide; 2-[3-(1,4-Diazepan-1-ylcarbonyl)phenyl]-2H-indazole-7-carboxamide; 3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}amino)carbonyl]-1-methylpiperidinium 20 trifluoroacetate; (2S)-2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium trifluoroacetate; 3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium trifluoroacetate; (2R)-2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium trifluoroacetate; 3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidinium trifluoroacetate; 25 (3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpyrrolidinium trifluoroacetate; 2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium trifluoroacetate; 4-Chloro-2-(4-formylphenyl)-2H-indazole-7-carboxamide; 30 (3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpyrrolidinium trifluoroacetate; (R)-1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylethanaminium chloride; (S)-1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylethanaminium chloride; 2-{3-Fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide; 35 {4-[7-(Aminocarbonyl)-2H-indazol-2-yl]-2-fluorophenyl}-N-methanaminium trifluoroacetate; 2-{4-[1-Methyl-1-(methylamino)ethyl]phenyl}-2H-indazole-7-carboxamide; 1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]-2-hydroxybenzyl}-4-methylpiperazin-1-ium trifluoroacetate;

(3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium chloride;

(3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium chloride;

5 1-(2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}ethyl)-4-methylpiperazinedium bis(trifluoroacetate);  
{4-[7-(Aminocarbonyl)-4-hydroxy-2H-indazol-2-yl]phenyl}-N-methylmethanaminium trifluoroacetate; 2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-phenylpyrrolidinium trifluoroacetate;

10 (1R,3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopantanaminium trifluoroacetate;  
(1R,3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopantanaminium trifluoroacetate;  
(1S,3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopantanaminium trifluoroacetate;

15 2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-2-methylazetidinium trifluoroacetate;  
4-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]-1-methylpiperidinium trifluoroacetate;

20 9-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]-3-azoniaspiro[5.5]undecane trifluoroacetate;  
4-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]-4-phenylpiperidinium trifluoroacetate;  
2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridinium trifluoroacetate;

25 4-{3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridin-2-yl}piperazin-1-ium trifluoroacetate;  
3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridinium trifluoroacetate;  
4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridinium trifluoroacetate;

30 4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]quinolinium trifluoroacetate;  
4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]isoquinolinium trifluoroacetate;  
2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylazepanium trifluoroacetate;  
3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-2-methyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate;

35 2-{4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidin-1-yl}pyrimidin-1-ium trifluoroacetate;  
1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-4-methylpiperazin-1-ium chloride;

5-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-3-oxooctahydroindolizin-2-aminium trifluoroacetate;

2-{3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidin-1-yl}pyridinium trifluoroacetate;

5 2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-methylmorpholin-4-ium trifluoroacetate;

(1R,4R)-N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-1'-(methylsulfonyl)-1',2'-dihydrospiro[cyclohexane-1,3'-indole]-4-carboxamide;

1-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]octahydro-1H-isoindolium 10 trifluoroacetate;

2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-benzylmorpholin-4-ium trifluoroacetate;

(3S,4R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-(methoxycarbonyl)pyrrolidinium trifluoroacetate;

15 4-{(2S)-2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium-1-yl}piperidinium bis(trifluoroacetate);

(1S,3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopentanaminium trifluoroacetate;

3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpyrrolidinium 20 trifluoroacetate;

2-{4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidin-1-yl}pyrimidin-1-ium trifluoroacetate;

2-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}pyrrolidinium-3-yl)pyridinium bis(trifluoroacetate);

3-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}pyrrolidinium-3-yl)pyridinium bis(trifluoroacetate);

25 (3S,4S)-1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,4-difluoropyrrolidinium trifluoroacetate;

3-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-6-ammonio-3-azoniabicyclo[3.1.0]hexane bis(trifluoroacetate);

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-7-methyl-2,7-diazoniaspiro[4.4]nonane 30 bis(trifluoroacetate);

1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3-[4-(dimethylammonio)phenyl]pyrrolidinium bis(trifluoroacetate);

5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-methyl-1,2,4,5,6,6a-hexahydropyrrolo[3,4-b]pyrroledium bis(trifluoroacetate);

3-{[{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}(methyl)ammonio]methyl}-1-methylpiperidinium 35 bis(trifluoroacetate);

(1R,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-oxa-5-azoniabicyclo[2.2.1]heptane trifluoroacetate;

N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-hydroxy-2-methylpropan-1-aminium trifluoroacetate;

N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,3-difluorocyclobutanaminium trifluoroacetate;

4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-6-fluoro-1,4-diazepan-1-ium trifluoroacetate;

5 1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-pyrimidin-1-ium-2-yl-1,4-diazepan-1-ium bis(trifluoroacetate);

3-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-1-benzylpyrrolidinium bis(trifluoroacetate);

3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]-1-methylpyrrolidinium 10 bis(trifluoroacetate);

3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]-1-benzylpyrrolidinium bis(trifluoroacetate);

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-7-benzyl-2,7-diazoniaspiro[4.4]nonane bis(trifluoroacetate);

15 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-8-benzyl-2,8-diazoniaspiro[5.5]undecane bis(trifluoroacetate);

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,6-diazoniaspiro[3.3]heptane bis(trifluoroacetate);

7-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,7-diazoniaspiro[3.5]nonane bis(trifluoroacetate);

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,6-diazoniaspiro[3.5]nonane bis(trifluoroacetate);

20 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,8-diazoniaspiro[5.5]undecane bis(trifluoroacetate);

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,8-diazoniaspiro[4.5]decane bis(trifluoroacetate);

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,7-diazoniaspiro[4.5]decane bis(trifluoroacetate);

8-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,8-diazoniaspiro[4.5]decane bis(trifluoroacetate);

3-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,9-diazoniaspiro[5.5]undecane bis(trifluoroacetate);

25 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}octahydronyrrolo[3,4-c]pyrroledinium bis(trifluoroacetate);

5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}octahydronyrrolo[3,4-b]pyrroledinium bis(trifluoroacetate);

4-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)octahydrocyclopenta[c]pyrrolium 30 bis(trifluoroacetate);

N<sup>2</sup>-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-N<sup>1</sup>,N<sup>1</sup>-dimethyl-1-pyridin-2-ylethane-1,2-diaminium bis(trifluoroacetate);

7-(Aminocarbonyl)-2-[4-({[2-(2,3-dihydro-1H-indol-1-yl)ethyl]ammonio}methyl)phenyl]-2H-indazol-1-ium bis(trifluoroacetate);

35 (3S,4S)-1-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)ethyl]-3,4-difluoropyrrolidinium bis(trifluoroacetate);

5-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}amino)-1,3-benzothiazol-3-ium trifluoroacetate;

1-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-8-azoniaspiro[4.5]decane bis(trifluoroacetate);

4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]-1-methylpiperidinium bis(trifluoroacetate);

5 N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-hydroxyethanaminium trifluoroacetate; 7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate; 3-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]azetidinium trifluoroacetate; 4-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)piperidinium bis(trifluoroacetate); (3R,4R)-4-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-3-fluoropiperidinium 10 bis(trifluoroacetate); (3S,4R)-4-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-3-benzyl-1-methylpiperidinium bis(trifluoroacetate); N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-isobutyrylpiperidin-4-aminium trifluoroacetate; 2-[4-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)piperidin-1-yl]-3-methylpyridinium 15 bis(trifluoroacetate); 3-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)piperidinium bis(trifluoroacetate); 3-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-1-benzylpiperidinium bis(trifluoroacetate); 5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-5-aza-2-azoniabicyclo[2.2.2]octane trifluoroacetate; (1S,4S)-2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-5-methyl-2,5-dazoniabicyclo[2.2.1]heptane 20 bis(trifluoroacetate); 1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(pyridin-2-ylmethyl)piperazinedium bis(trifluoroacetate); 5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-benzyl-5-aza-2-azoniabicyclo[2.2.2]octane trifluoroacetate; 25 8-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3-benzyl-8-aza-3-azoniabicyclo[3.2.1]octane trifluoroacetate; (1S,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-benzyl-5-aza-2-azoniabicyclo[2.2.1]heptane trifluoroacetate; 30 3-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)pyrrolidinium bis(trifluoroacetate); 6-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-3-azoniabicyclo[3.1.0]hexane bis(trifluoroacetate); (3S,4S)-N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-hydroxytetrahydrothiophen-3-aminium 1,1-dioxide trifluoroacetate; 4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]-4-hydroxy-1-methylpiperidinium 35 bis(trifluoroacetate); N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-cyclopropyl-2-hydroxyethanaminium trifluoroacetate; {4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-{{1-(hydroxymethyl)cyclopentyl]}

methyl}methanaminium trifluoroacetate;

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1,2,3,4-tetrahydro-2,7-naphthyridinedium bis(trifluoroacetate);

1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3-[(dimethylammonio)methyl]piperidinium bis(trifluoroacetate);

4-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}piperidinium-4-yl)thiomorpholin-4-ium bis(trifluoroacetate);

1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-[(methylsulfonyl)amino]piperidinium trifluoroacetate;

10 1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(1H-imidazol-3-ium-1-ylmethyl)piperidinium bis(trifluoroacetate);

7-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-oxa-7-azoniaspiro[4.5]decane trifluoroacetate;

1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(1-hydroxy-1-methylethyl)piperidinium trifluoroacetate;

15 2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-benzylpiperidinium trifluoroacetate;

2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-ethylpiperidinium trifluoroacetate;

3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-ethylpiperidinium trifluoroacetate;

20 2-[3-(1,4-Diazepan-1-ylcarbonyl)-4-fluorophenyl]-2H-indazole-7-carboxamide trifluoroacetate;

tert-Butyl {4-[7-(aminocarbonyl)-4-chloro-2H-indazol-2-yl]benzyl} methylcarbamate;

6-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate;

2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}pyrrolidinium trifluoroacetate;

25 6-Fluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide;

5-Fluoro-2-{2-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide;

2-{3-Hydroxy-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate;

2-(4-{{Formyl(methyl)amino}methyl}-3-hydroxyphenyl)-2H-indazole-7-carboxamide;

2-{2-Chloro-4-[(methylamino)methyl]phenyl}-5-fluoro-2H-indazole-7-carboxamide;

30 5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate;

2-{2,5-Difluoro-4-[(methylamino)methyl]phenyl}-5-fluoro-2H-indazole-7-carboxamide trifluoroacetate;

2-(4-Bromophenyl)-2H-indazole-7-carboxamide;

(3R)-3-[({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium chloride;

35 (3R)-3-[({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium trifluoroacetate;

2-(1,2,3,4-Tetrahydroisoquinolin-7-yl)-2H-indazole-7-carboxamide;

(R)-2-[4-({3-[(Dimethylamino)methyl]piperidin-1-yl}methyl)phenyl]-2H-indazole-7-carboxamide;

(S)-2-[4-({3-[(Dimethylamino)methyl]piperidin-1-yl}methyl)phenyl]-2H-indazole-7-carboxamide;  
3-({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)-2-(chloromethyl)-3-oxopropan-1-aminium trifluoroacetate;  
5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide hydrochloride;  
5 2-{4-[(Dimethylamino)methyl]-3-fluorophenyl}-5-fluoro-2H-indazole-7-carboxamide trifluoroacetate;  
2-{4-[(Azetidin-3-ylcarbonyl)amino]phenyl}-5-fluoro-2H-indazole-7-carboxamide;  
2-[4-(2,7-Diazaspiro[4.5]dec-2-ylmethyl)phenyl]-2H-indazole-7-carboxamide;  
(1S,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-(4-chlorobenzyl)-5-aza-2-  
azoniabicyclo[2.2.1]heptane trifluoroacetate;  
10 (1S,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-(3-chlorobenzyl)-5-aza-2-  
azoniabicyclo[2.2.1]heptane trifluoroacetate;  
1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-[(methylamino)carbonyl]piperazin-1-ium  
trifluoroacetate;  
N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-hydroxy-2-pyridin-3-ylethanaminium  
15 trifluoroacetate;  
N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-cyclohexyl-2-hydroxyethanaminium  
trifluoroacetate;  
4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-6-(hydroxymethyl)-1,4-oxazepan-4-ium  
trifluoroacetate;  
20 {4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-{{[1-(hydroxymethyl)cyclobutyl]  
methyl}methanaminium trifluoroacetate;  
{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-{{[1-(hydroxymethyl)cyclohexyl]  
methyl}methanaminium trifluoroacetate;  
1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(5-methyl-1H-benzimidazol-2-yl)piperidinium  
25 trifluoroacetate;  
2-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-hydroxypiperidinium-4-yl)pyridinium  
bis(trifluoroacetate);  
1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,3-difluoropyrrolidinium trifluoroacetate;  
2-(4-[(2R)-2-(Fluoromethyl)pyrrolidin-1-yl]methyl)phenyl)-2H-indazole-7-carboxamide;  
30 N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-oxopyrrolidin-3-aminium trifluoroacetate;  
5-Fluoro-2-(4-formylphenyl)-2H-indazole-7-carboxamide;  
3-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylazetidinium  
trifluoroacetate;  
1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-3-[(dimethylammonio)methyl]piperidinium  
35 bis(trifluoroacetate);  
3-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorophenyl)amino]carbonyl]azetidinium  
trifluoroacetate;

2-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-2,7-diazoniaspiro[4.5]decane bis(trifluoroacetate);  
 4,5-Difluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate;  
 5-Fluoro-2-(3-fluoro-4-[(1-methylazetidin-3-yl)carbonyl]amino)phenyl)-2H-indazole-7-carboxamide trifluoroacetate;  
 5-Fluoro-2-(3-fluoro-4-formylphenyl)-2H-indazole-7-carboxamide;  
 5-Fluoro-2-(5-fluoro-2-formylphenyl)-2H-indazole-7-carboxamide;  
 {4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorophenyl}-N-[(1-hydroxymethyl)cyclopentyl]methyl methanaminium trifluoroacetate;  
 5-Fluoro-2-[3-fluoro-4-[(3R)-1-methylpiperidin-3-yl]carbonyl]amino)phenyl]-2H-indazole-7-carboxamide trifluoroacetate;  
 1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorobenzyl}-4-methylpiperazinium bis(trifluoroacetate);  
 4-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl)ammonio)methyl]-1-methylpiperidinium bis(trifluoroacetate);  
 4-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl)ammonio)methyl]-1-methylpiperidinium bis(trifluoroacetate);  
 and pharmaceutically acceptable salts or tautomers thereof.

Further particular compounds within the scope of the present invention are:

20 7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-methyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate;  
 3-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-1-ethylpiperidinium trifluoroacetate;  
 2-(4-Cyanophenyl)-5-fluoro-2H-indazole-7-carboxamide;  
 5-fluoro-2-[4-(1H-tetrazol-5-yl)phenyl]-2H-indazole-7-carboxamide;  
 2-(4-Aminophenyl)-5-fluoro-2H-indazole-7-carboxamide hydrochloride;  
 25 *tert*-Butyl 3-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]pyrrolidine-1-carboxylate;  
 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]pyrrolidinium trifluoroacetate;  
 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-methylpyrrolidinium trifluoroacetate;  
 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-ethylpyrrolidinium trifluoroacetate;  
 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-propylpyrrolidinium trifluoroacetate;  
 30 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-isopropylpyrrolidinium trifluoroacetate;  
 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-cyclohexylpyrrolidinium trifluoroacetate;  
 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-cyclobutylpyrrolidinium trifluoroacetate;  
*tert*-Butyl 4-[7-(aminocarbonyl)-2H-indazol-2-yl]-4-methylpiperidine-1-carboxylate;  
 4-[7-(Aminocarbonyl)-2H-indazol-2-yl]-4-methylpiperidinium trifluoroacetate;  
 35 2-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}pyrrolidinium trifluoroacetate;  
 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-5-fluoro-2H-indazole-7-carboxamide trifluoroacetate;  
 6-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium chloride;  
 2-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}piperidinium chloride;

5-Fluoro-2-[4-(1H-pyrazol-1-yl)phenyl]-2H-indazole-7-carboxamide;  
5-Fluoro-2-(3-piperidin-3-ylphenyl)-2H-indazole-7-carboxamide;  
2-[4-(Aminosulfonyl)phenyl]-5-fluoro-2H-indazole-7-carboxamide;  
5-Fluoro-2-(5,6,7,8-tetrahydro-1,7-naphthyridin-3-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(4-piperazin-2-ylphenyl)-2H-indazole-7-carboxamide;  
Methyl 4-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzoate;  
5-Fluoro-2-(1-methylpiperidin-3-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-ethylpiperidin-3-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-propylpiperidin-3-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-isopropylpiperidin-3-yl)-2H-indazole-7-carboxamide;  
2-(1-Cyclohexylpiperidin-3-yl)-5-fluoro-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-methylpiperidin-4-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-ethylpiperidin-4-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-propylpiperidin-4-yl)-2H-indazole-7-carboxamide;  
5-Fluoro-2-(1-isopropylpiperidin-4-yl)-2H-indazole-7-carboxamide;  
2-(1-Cyclohexylpiperidin-4-yl)-5-fluoro-2H-indazole-7-carboxamide;  
2-(1-Cyclobutylpiperidin-4-yl)-5-fluoro-2H-indazole-7-carboxamide;  
2-(1-Cyclobutylpiperidin-3-yl)-2H-indazole-7-carboxamide;  
2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-*N,N*-dimethylethanaminium trifluoroacetate;  
2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-*N,N*-diethylethanaminium trifluoroacetate;  
*N*-{2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl}propan-2-aminium trifluoroacetate;  
*N*-{2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl}cyclohexanaminium trifluoroacetate;  
2-[2-(Dicyclobutylamino)ethyl]-5-fluoro-2H-indazole-7-carboxamide;  
tert-Butyl 3-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidine-1-carboxylate;  
tert-Butyl 4-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidine-1-carboxylate;  
3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidinium trifluoroacetate;  
4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidinium trifluoroacetate;  
tert-Butyl 3-[7-(aminocarbonyl)-2H-indazol-2-yl]piperidine-1-carboxylate;  
tert-Butyl {2-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl} carbamate;  
2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethanaminium trifluoroacetate;  
3-[7-(Aminocarbonyl)-2H-indazol-2-yl]piperidinium trifluoroacetate;  
3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-methylpiperidinium trifluoroacetate;  
3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-ethylpiperidinium trifluoroacetate;  
3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-propylpiperidinium trifluoroacetate;  
3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-isopropylpiperidinium trifluoroacetate;  
3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-cyclohexylpiperidinium trifluoroacetate;  
3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-cyclobutylpiperidinium trifluoroacetate;  
*N*-{2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl}-*N*-propylpropan-1-aminium trifluoroacetate;

and pharmaceutically acceptable salts or tautomers thereof.

Included in the instant invention is the free base of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. The compounds of the present invention can be protonated at the N atom(s) of an amine and/or N containing heterocycle moiety to form a salt. The term "free base" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic, organic acid or polymeric acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, sulfamic, phosphoric, phosphorous, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, palmitic, gluconic, ascorbic, phenylacetic, aspartic, cinnamic, pyruvic, ethanesulfonic, ethane, disulfonic, valeric, trifluoroacetic and the like. Examples of suitable polymeric salts include those derived from the polymeric acids such as tannic acid, carboxymethyl cellulose. Preferably, a pharmaceutically acceptable salt of this invention contains 1 equivalent of a compound of formula (I) and 1, 2 or 3 equivalent of an inorganic or organic acid. More particularly, pharmaceutically acceptable salts of this invention are the trifluoroacetate or the chloride salts. In an embodiment the salt is trifluoroacetate. In another embodiment the salt is chloride.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts

derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, lysine, betaine, caffeine, choline, N,N<sup>1</sup>-dibenzylethylenediamine, ethylamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, 5 ethanolamine, diethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine, dicyclohexylamine, butylamine, benzylamine, phenylbenzylamine, tromethamine and the like.

10 The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al* (1977) *J. Pharm. Sci.*, 'Pharmaceutical Salts', **66**:1-19.

15 It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The compounds of the invention can be used in a method of treatment of the human or animal body by therapy.

20 The invention provides compounds for use in the treatment or prevention of conditions which can be ameliorated by the inhibition of poly(ADP-ribose)polymerase (PARP) (see, for example, *Nature Review Drug Discovery* (2005) **4**:421- 440).

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of conditions which can be ameliorated by the inhibition of poly(ADP-ribose)polymerase (PARP).

25 The present invention also provides a method for the treatment or prevention of conditions which can be ameliorated by the inhibition of poly(ADP-ribose)polymerase (PARP), which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

30 The PARP inhibitors of the present invention are useful for the treatment of the diseases specified in WO 2005/082368.

The compounds of the invention are useful for the treatment of inflammatory diseases, including conditions resulting from organ transplant rejection, such as; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney

including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin including scleroderma, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; diabetic complications, including, but not limited to, immune-complex vasculitis, systemic lupus erythematosus (SLE); inflammatory diseases of the heart such as cardiomyopathy, ischemic heart disease, hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma and multiple organ dysfunction syndrome (MODS) (multiple organ failure (MOF)). The inflammatory disease can also be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, e. g., shock associated with pro-inflammatory cytokines. Such shock can be induced, e. g. by a chemotherapeutic agent that is administered as a treatment for cancer.

15 Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating or preventing inflammatory diseases.

The present invention also provides a method for the treatment or prevention of inflammatory diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

20 The compounds of the instant invention may also be useful in the treatment or prevention of reperfusion injuries, resulting from naturally occurring episodes and during a surgical procedure, such as intestinal reperfusion injury; myocardial reperfusion injury; reperfusion injury resulting from cardiopulmonary bypass surgery, aortic aneurysm repair surgery, carotid endarterectomy surgery, or hemorrhagic shock; and reoxygenation injury resulting from transplantation of organs such as heart, lung, 25 liver, kidney, pancreas, intestine, and cornea.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of reperfusion injuries.

30 The present invention also provides a method for the treatment or prevention of reperfusion injuries, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the instant invention may also be useful in the treatment or prevention of ischemic conditions, including those resulting from organ transplantation, such as stable angina, unstable angina, myocardial ischemia, hepatic ischemia, mesenteric artery ischemia, intestinal ischemia, critical limb ischemia, chronic critical limb ischemia, cerebral ischemia, acute cardiac ischemia, ischemia kidney 35 disease, ischemic liver disease, ischemic retinal disorder, septic shock, and an ischemic disease of the central nervous system, such as stroke or cerebral ischemia.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of ischemic conditions.

The present invention also provides a method for the treatment or prevention of ischemic conditions, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

5 The present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of stroke.

The present invention also provides a method for the treatment or prevention of stroke, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

10 The compounds of the instant invention may also be useful for the treatment or prevention of chronic or acute renal failure.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of renal failure.

15 The present invention also provides a method for the treatment or prevention of renal failure, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the instant invention may also be useful for the treatment or prevention of vascular diseases other than cardiovascular diseases, such as peripheral arterial occlusion, thromboangiitis obliterans, Reynaud's disease and phenomenon, acrocyanosis, erythromelalgia, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema and lipedema.

20 Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of vascular diseases other than cardiovascular diseases.

The present invention also provides a method for the treatment or prevention of vascular diseases other than cardiovascular diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

25 The compounds of the instant invention may also be useful for the treatment or prevention of cardiovascular diseases such as chronic heart failure, atherosclerosis, congestive heart failure, circulatory shock, cardiomyopathy, cardiac transplant, myocardial infarction, and a cardiac arrhythmia, such as atrial fibrillation, supraventricular tachycardia, atrial flutter, and paroxysmal atrial tachycardia.

Thus, the present invention provides a compound of formula I for use in the manufacture of a 30 medicament for the treatment or prevention of cardiovascular diseases.

The present invention also provides a method for the treatment or prevention of cardiovascular diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

35 The compounds of this invention may also be useful for the treatment and prevention of diabetes mellitus, including Type I diabetes (Insulin Dependent Diabetes Mellitus), Type II diabetes (Non-Insulin Dependent Diabetes Mellitus), gestational diabetes, autoimmune diabetes, insulinopathies, diabetes due to pancreatic disease, diabetes associated with other endocrine diseases (such as Cushing's Syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism or somatostatinoma), Type A

insulin resistance syndrome, Type B insulin resistance syndrome, lipatrophic diabetes, and diabetes induced by(3-cell toxins. The compounds of this invention may also be useful for the treatment or prevention of diabetic complications, such as diabetic cataract, glaucoma, retinopathy, nephropathy, (such as microalbuminuria and progressive diabetic nephropathy), polyneuropathy, gangrene of the feet,

5 atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, mononeuropathies, autonomic neuropathy, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabetorumobesity), hyperlipidemia, hypertension, syndrome of insulin resistance, coronary artery disease, retinopathy, diabetic neuropathy, polyneuropathy, mononeuropathies, autonomic

10 neuropathy, a foot ulcer, a joint problem, a fungal infection, a bacterial infection, and cardiomyopathy.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of diabetes.

The present invention also provides a method for the treatment or prevention of diabetes, which method comprises administration to a patient in need thereof of an effective amount of a compound of

15 formula I or a composition comprising a compound of formula I.

The compounds of this invention may also be useful for the treatment or prevention of cancer including solid tumors such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma,

lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma,

20 rhabdomyosarcoma, colon cancer, colorectal cancer, kidney cancer, pancreatic cancer, bone cancer, breast cancer, ovarian cancer, prostate cancer, esophageal cancer, stomach cancer, oral cancer, nasal cancer, throat cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas,

cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, 25 bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms'tumor, cervical cancer, uterine cancer, testicular cancer, small cell lung carcinoma, bladder carcinoma, lung cancer, epithelial carcinoma, skin cancer, melanoma, neuroblastoma and retinoblastoma; blood-borne cancers such as acute lymphoblastic leukemia("ALL"), acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia ("AML"), acute promyelocytic leukemia("APL"), acute

30 monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute nonlymphocytic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia("CML"), chronic lymphocytic leukemia("CLL"), hairy cell leukemia and multiple myeloma; acute and chronic leukemias such as lymphoblastic, myelogenous, lymphocytic, myelocytic leukemias; Lymphomas such as Hodgkin's disease, non-Hodgkin's Lymphoma, Multiple myeloma,

35 Waldenstrom's macroglobulinemia, Heavy chain disease and Polycythemia vera; CNS and brain cancers such as glioma, pilocytic astrocytoma, astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma,

oligodendrogloma, meningioma, vestibular schwannoma, adenoma, metastatic brain tumor, meningioma, spinal tumor and medulloblastoma.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of cancer.

5 The present invention also provides a method for the treatment or prevention of cancer, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the present invention may also be used for the treatment of cancer which is deficient in Homologous Recombination (HR) dependent DNA DSB repair activity (see WO  
10 2006/021801).

The HR dependent DNA DSB repair pathway repairs double-strand breaks (DSBs) in DNA via homologous mechanisms to reform a continuous DNA helix (*Nat. Genet.* (2001) **27**(3):247-254). The components of the HR dependent DNA DSB repair pathway include, but are not limited to, ATM (NM-000051), RAD51 (NM-002875), RAD51 L1 (NM-002877), RAD51 C (NM-002876), RAD51L3 (NM-15 002878), DMC1 (NM-007068), XRCC2 (NM7005431), XRCC3 (NM-005432), RAD52 (NM-002879), RAD54L (NM-003579), RAD54B (NM-012415), BRCA-1 (NM-007295), BRCA-2 (NM-000059), RAD50 (NM-005732), MRE1 1A (NM-005590), NBS1 (NM-002485), ADPRT (PARP-1), ADPRTL2, (PARP02) CTPS, RPA, RPA1, RPA2, RPA3, XPD, ERCC1, XPF, MMS19, RAD51, RAD51p, RAD51C, RAD51D, DMC1, XRCCR, XRCC3, BRCA1, BRCA2, RAD52, RAD54,  
20 RAD50, MRE11, NB51, WRN, BLMKU70, RU80, ATM, ATRCHK1, CHK2, FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, RAD1 and RAD9. Other proteins involved in the HR dependent DNA DSB repair pathway include regulatory factors such as EMSY (*Cell* (2003) **115**:523-535).

A cancer which is deficient in HR dependent DNA DSB repair may comprise or consist of one or  
25 more cancer cells which have a reduced or abrogated ability to repair DNA DSBs through that pathway, relative to normal cells i.e. the activity of the HR dependent DNA DSB repair pathway may be reduced or abolished in the one or more cancer cells.

The activity of one or more components of the HR dependent DNA DSB repair pathway may be abolished in the one or more cancer cells of an individual having a cancer which is deficient in HR  
30 dependent DNA DSB repair. Components of the HR dependent DNA DSB repair pathway are well characterized in the art (see for example, *Science* (2001) **291**:1284-1289) and include the components listed above.

The present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of a cancer which is deficient in HR dependent DNA DSB  
35 repair activity.

The present invention also provides a method for the treatment or prevention of a cancer which is deficient in HR dependent DNA DSB repair activity, which method comprises administration to a patient

in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I

In an embodiment the cancer cells are deficient in the HR dependent DNA DSB repair activity of one or more phenotypes selected from ATM (NM-000051), RAD51 (NM-002875), RAD51 L1 (NM-002877), RAD51 C (NM-002876), RAD51L3 (NM-002878), DMC1 (NM-007068), XRCC2 (NM7005431), XRCC3 (NM-005432), RAD52 (NM-002879), RAD54L (NM-003579), RAD54B (NM-012415), BRCA-1 (NM-007295), BRCA-2 (NM-000059), RAD50 (NM-005732), MREI 1A (NM-005590), NBS1 (NM-002485), ADPRT (PARP-1), ADPRTL2, (PARP02) CTPS, RPA, RPA1, RPA2, RPA3, XPD, ERCC1, XPF, MMS19, RAD51, RAD51p, RAD51C, RAD51D, DMC1, XRCCR, XRCC3, BRCA1, BRCA2, RAD52, RAD54, RAD50, MRE11, NB51, WRN, BLMKU70, RU80, ATM, ATRCHK1, CHK2, FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, RAD1 and RAD9.

In another embodiment, the cancer cells have a BRCA1 and/or a BRCA2 deficient phenotype.

Cancer cells with this phenotype may be deficient in BRCA1 and/or BRCA2, i. e. expression and/or activity of BRCA1 and/or BRCA2 may be reduced or abolished in the cancer cells, for example by means of mutation or polymorphism in the encoding nucleic acid, or by means of amplification, mutation or polymorphism in a gene encoding a regulatory factor, for example the EMSY gene which encodes a BRCA2 regulatory factor (*Cell* (2003) **115**:523-535).

BRCA-1 and BRCA-2 are known tumor suppressors whose wild-type alleles are frequently lost in tumors of heterozygous carriers (*Oncogene*, (2002) **21**(58):8981-93; *Trends Mol Med.*, (2002) **8**(12):571-6). The association of BRCA-1 and/or BRCA-2 mutations with breast cancer has been well-characterized (*Exp Clin Cancer Res.*, (2002) **21** (3 Suppl):9-12). Amplification of the EMSY gene, which encodes a BRCA-2 binding factor, is also known to be associated with breast and ovarian cancer. Carriers of mutations in BRCA-1 and/or BRCA-2 are also at elevated risk of cancer of the ovary, prostate and pancreas. The detection of variation in BRCA-1 and BRCA-2 is well-known in the art and is described, for example in EP 699 754, EP 705 903, *Genet. Test* (1992) **1**:75-83; *Cancer Treat Res* (2002) **107**:29-59; *Neoplasm* (2003) **50**(4):246-50; *Ceska Gynekol* (2003) **68**(1):11-16). Determination of amplification of the BRCA-2 binding factor EMSY is described in *Cell* **115**:523-535. PARP inhibitors have been demonstrated as being useful for the specific killing of BRCA-1 and BRCA-2 deficient tumors (*Nature* (2005) **434**:913-916 and 917-920).

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of BRCA-1 or BRCA-2 deficient tumors.

The present invention also provides a method for the treatment or prevention of BRCA-1 or BRCA-2 deficient tumors, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

In an embodiment, the PARP inhibitors of the present can be used in prophylactic therapy for elimination of BRCA2-deficient cells (see, *Cancer Res.* (2005) **65**:10145).

The compounds of this invention may be useful for the treatment or prevention of

5 neurodegenerative diseases, including, polyglutamine-expansion-related neurodegeneration, Huntington's disease, Kennedy's disease, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy (DRPLA), protein-aggregation-related neurodegeneration, Machado-Joseph's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spongiform encephalopathy, a prion-related disease and multiple sclerosis (MS).

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating or preventing neurodegenerative diseases.

10 The present invention also provides a method for treating or preventing neurodegenerative diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the present invention may also be useful for the treatment or prevention of retroviral infection (US 5652260), retinal damage (*Curr. Eye Res.* (2004), **29**:403), skin senescence and UV-induced skin damage (US5589483 and *Biochem. Pharmacol* (2002) **63**:921).

15 The compounds of the invention are useful for the treatment or prevention of premature aging and postponing the onset of age-related cellular dysfunction (*Pharmacological Research* (2005) **52**:93-99).

20 The compounds of this invention may be administered to mammals, preferably humans, either alone or in combination with pharmaceutically acceptable carriers, excipients, diluents, adjuvants, fillers, buffers, stabilisers, preservatives, lubricants, in a pharmaceutical composition, according to standard pharmaceutical practice.

25 The compounds of this invention may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, (e.g. by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal); and by implant of a depot (e.g. subcutaneously or intramuscularly).

30 The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orangutang, gibbon), or a human.

35 The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more

agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as 5 calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and 10 absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

15 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

20 Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with 25 partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or 30 aspartame.

35 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent,

suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters 10 with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

15 The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

20 The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and 25 glycerol mixture and processed to form a microemulsion.

25 The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

30 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile 35 injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

35 Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated

gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include 5 mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than 10 intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a compound according to this invention is administered into a subject, the selected dosage 15 level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the severity of the individuals symptoms, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately 20 be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g. in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most 25 effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 100 µg to about 250 30 mg per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

The instant compounds are also useful in combination with anti-cancer agents or 35 chemotherapeutic agents.

The compounds of this invention may be useful as chemo- and radiosensitizers for cancer treatment. They are useful for the treatment of mammals who have previously undergone or are presently undergoing treatment for cancer. Such previous treatments include prior chemotherapy, radiation therapy, surgery or immunotherapy, such as cancer vaccines.

Thus, the present invention provides a combination of a compound of formula I and an anti-cancer agent for simultaneous, separate or sequential administration.

The present invention also provides a compound of formula I for use in the manufacture of a medicament for use as an adjunct in cancer therapy or for potentiating tumor cells for treatment with 5 ionizing radiation or chemotherapeutic agents.

The present invention also provides a method of chemotherapy or radiotherapy, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I in combination with ionizing radiation or chemotherapeutic agents.

10 In combination therapy, the compounds of this invention can be administered prior to (e. g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48, hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concurrently with, or subsequent to (e. g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of the other anticancer agent to a 15 subject in need thereof. In various embodiments the instant compounds and another anticancer agent are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 20 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart, or no more than 48 hours apart.

25 The compounds of this invention and the other anticancer agent can act additively or synergistically. A synergistic combination of the present compounds and another anticancer agent might allow the use of lower dosages of one or both of these agents and/or less frequent dosages of one or both of the instant compounds and other anticancer agents and/or to administer the agents less frequently can reduce any toxicity associated with the administration of the agents to a subject without reducing the efficacy of the agents in the treatment of cancer. In addition, a synergistic effect might result in the improved efficacy of these agents in the treatment of cancer and/or the reduction of any adverse or unwanted side effects associated with the use of either agent alone.

30 Examples of cancer agents or chemotherapeutic agents for use in combination with the compounds of the present invention can be found in *Cancer Principles and Practice of Oncology* by V.T. DeVita and S. Hellman (editors), 6<sup>th</sup> edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-35 cancer agents include, but are not limited to, the following: HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors and other angiogenesis inhibitors, inhibitors of cell

proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

Examples of “HDAC inhibitors” include suberoylanilide hydroxamic acid (SAHA), LAQ824, LBH589, PXD101, MS275, FK228, valproic acid, butyric acid and CI-994.

5 “Estrogen receptor modulators” refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

10 “Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 $\alpha$ -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

15 “Retinoid receptor modulators” refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid,  $\alpha$ -difluoromethylornithine, ILX23-7553, trans-*N*-(4'-hydroxyphenyl) retinamide, and *N*-4-carboxyphenyl retinamide.

20 “Cytotoxic/cytostatic agents” refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell’s functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites, biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

25 Examples of cytotoxic agents include, but are not limited to, cyclophosphamide, chlorambucil carmustine (BCNU), lomustine (CCNU), busulfan, treosulfan, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, aroplatin, oxaliplatin, temozolomide, methyl methanesulfonate, procarbazine, dacarbazine, heptaplatin, estramustine, imrosulfan tosilate, trofosfamide, nimustine, dibrospidium 30 chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexamifosfamide, cis-aminodichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, 35 amrubicin, doxorubicin, epirubicin, pirarubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755 and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

In an embodiment the compounds of this invention can be used in combination with alkylating agents.

Examples of alkylating agents include but are not limited to, nitrogen mustards: cyclophosphamide, ifosfamide, trofosfamide and chlorambucil; nitrosoureas: carmustine (BCNU) and 5 lomustine (CCNU); alkylsulphonates: busulfan and treosulfan; triazenes: dacarbazine, procarbazine and temozolamide; platinum containing complexes: cisplatin, carboplatin, aroplatin and oxaliplatin.

In an embodiment, the alkylating agent is dacarbazine. Dacarbazine can be administered to a subject at dosages ranging from about 150 mg/m<sup>2</sup> (of a subject's body surface area) to about 250 mg/m<sup>2</sup>. In another embodiment, dacarbazine is administered intravenously to a subject once per day for five 10 consecutive days at a dose ranging from about 150 mg/m<sup>2</sup> to about 250 mg/m<sup>2</sup>.

In an embodiment, the alkylating agent is procarbazine. Procarbazine can be administered to a subject at dosages ranging from about 50 mg/m<sup>2</sup> (of a subject's body surface area) to about 100 mg/m<sup>2</sup>. In another embodiment, procarbazine is administered intravenously to a subject once per day for five consecutive days at a dose ranging from about 50 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup>.

15 In an embodiment, the alkylating agent is temozoloamide. Temozolamide can be administered to a subject at dosages ranging from about 150 mg/m<sup>2</sup> (of a subject's body surface area) to about 200 mg/m<sup>2</sup>. In another embodiment, temozolamide is administered orally to an animal once per day for five consecutive days at a dose ranging from about 150 mg/m<sup>2</sup> to about 200 mg/m<sup>2</sup>.

20 Examples of anti-mitotic agents include: allocolchicine, halichondrin B, colchicine, colchicine derivative, dolastatin 10, maytansine, rhizoxin, thiocolchicine and trityl cysteine.

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin, bortezomib, epoxomicin and peptide aldehydes such as MG 132, MG 115 and PSI.

25 Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, vincristine, vinblastine, vinorelbine, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

30 Some examples of topoisomerase inhibitors are topotecan, hydrazine, irinotecan, rubitecan, exatecan, gemtuzumab, diflomotecan, silyl-camptothecins, 9-aminocamptothecin, camptothecin, crisnatol, mitomycin C, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chlorotetrahydro-9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-k]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 35 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa, 9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-

dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguineoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, *N*-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthene-4-ylmethyl]formamide, *N*-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna; non-camptothecin topoisomerase-1 inhibitors such as indolocarbazoles; and dual topoisomerase-I and II inhibitors such as benzophenazines, XR 20 11576IMLN 576 and benzopyridoindoles.

10 In an embodiment, the topoisomerase inhibitor is irinotecan. Irinotecan can be administered to a subject at dosages ranging from about about 50 mg/m<sup>2</sup> (of a subject's body surface area) to about 150 mg/m<sup>2</sup>. In another embodiment, irinotecan is administered intravenously to a subject once per day for five consecutive days at a dose ranging from about 50mg/m<sup>2</sup> to about 150mg/m<sup>2</sup> on days 1-5, then again intravenously once per day for five consecutive days on days 28-32 at a dose ranging from about 15 50mg/m<sup>2</sup> to about 150mg/m<sup>2</sup>, then again intravenously once per day for five consecutive days on days 55-59 at a dose ranging from about 50mg/m<sup>2</sup> to about 150mg/m<sup>2</sup>.

20 Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768, WO 01/98278, WO 02/056880, WO 03/050,064, WO 03/050,122, WO 03/049,527, WO 03/049,679, WO 03/049,678, WO 03/039460, WO 03/079973, WO 03/099211, WO 2004/039774, WO 03/105855, WO 03/106417, WO 2004/087050, WO 2004/058700, WO 2004/058148 and WO 2004/037171 and US applications US 2004/132830 and US 2004/132719. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

25 "Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

30 "Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidene-cytidine, 2'-fluoromethylene-2'-deoxycytidine, *N*-[5-(2,3-dihydro-benzofuryl)sulfonyl]-*N'*-(3,4-dichlorophenyl)urea, *N*6-[4-deoxy-4-[*N*2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacicabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester,

swainsonine, lometrexol, dextrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific 5 monoclonal antibody. Examples include Bexxar.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see 10 U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and 15 atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, “Cholesterol Lowering Drugs”, *Chemistry & Industry*, 15 pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

“Prenyl-protein transferase inhibitor” refers to a compound which inhibits any one or any 20 combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and 25 patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, 30 WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, 35 WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359.

For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer* (1999), **35(9):1394-1401**.

“Angiogenesis inhibitors” refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- $\alpha$ , interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (*PNAS* (1992) 89:7384; *JNCI* (1982) 69:475; *Arch. Ophthalmol.* (1990) 108:573; *Anat. Rec.* (1994) 238:68; *FEBS Letters* (1995) 372:83; *Clin. Orthop.* (1995) 313:76; *J. Mol. Endocrinol.* (1996) 16:107; *Jpn. J. Pharmacol.* (1997) 75:105; *Cancer Res.* (1997) 57:1625 (1997); *Cell* (1998) 93:705; *Intl. J. Mol. Med.* (1998) 2:715; *J. Biol. Chem.* (1999) 274:9116), steroid anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillo, thalidomide, angiostatin, tropomin-1, angiotensin II antagonists (see *J. Lab. Clin. Med.* (1985) 105:141-145), and antibodies to VEGF (see *Nature Biotechnology* (1999) 17:963-968; Kim *et al* (1993) *Nature* 362:841-844; WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* (2000) 38:679-692). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* (1998) 80:10-23), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* (2001) 101:329-354). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed January 18, 2002).

“Agents that interfere with cell cycle checkpoints” refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, staurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

“Inhibitors of cell proliferation and survival signaling pathway” refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR (for example those disclosed in WO 03/059951), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in (WO 03/086404, WO 03/086403, WO 03/086394, WO 03/086279, WO 02/083675, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of

MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

“Apoptosis inducing agents” include activators of TNF receptor family members (including the TRAIL receptors).

5 The invention also encompasses combinations with NSAID’s which are selective COX-2 inhibitors. For purposes of this specification NSAID’s which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC<sub>50</sub> for COX-2 over IC<sub>50</sub> for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat.

10 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265, U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598, all of which are hereby incorporated by reference.

15 Inhibitors of COX-2 that are particularly useful in the instant method of treatment are 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

20 Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyl dinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-*N*-methyl-4,2-pyrrolocarbonylimino[*N*-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

25 As used above, “integrin blockers” refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the  $\alpha_v\beta_3$  integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the  $\alpha_v\beta_5$  integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the  $\alpha_v\beta_3$  integrin and the  $\alpha_v\beta_5$  integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the  $\alpha_v\beta_6$ ,  $\alpha_v\beta_8$ ,  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_5\beta_1$ ,  $\alpha_6\beta_1$  and  $\alpha_6\beta_4$  integrins. The term also refers to antagonists of any combination of  $\alpha_v\beta_3$ ,  $\alpha_v\beta_5$ ,  $\alpha_v\beta_6$ ,  $\alpha_v\beta_8$ ,  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\beta_5\alpha_1$ ,  $\alpha_6\beta_1$  and  $\alpha_6\beta_4$  integrins.

30 Some specific examples of tyrosine kinase inhibitors include *N*-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1*H*-

diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7*H*-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, *N*-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

5 In an embodiment, the compounds of the present invention are useful for the treatment or prevention of the appearance of necrosis induced by selective *N*3-adenine methylating agents such as MeOSO<sub>2</sub>(CH<sub>2</sub>)-lexitropsin (Me-Lex).

Combinations with compounds other than anti-cancer compounds are also encompassed in the 10 instant methods. For example, combinations of the instantly claimed compounds with PPAR- $\gamma$  (i.e., PPAR-gamma) agonists and PPAR- $\delta$  (i.e., PPAR-delta) agonists are useful in the treatment of certain maligtnancies. PPAR- $\gamma$  and PPAR- $\delta$  are the nuclear peroxisome proliferator-activated receptors  $\gamma$  and  $\delta$ . The expression of PPAR- $\gamma$  on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* (1998) **31**:909-913; *J. Biol. Chem.* (1999) **274**:9116-9121; 15 *Invest. Ophthalmol Vis. Sci.* (2000) **41**:2309-2317). More recently, PPAR- $\gamma$  agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthalmol.* (2001) **119**:709-717). Examples of PPAR- $\gamma$  agonists and PPAR- $\gamma/\alpha$  agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, 20 GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(*R*)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

25 Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with anti-viral agents (such as nucleoside analogs including ganciclovir for the treatment of cancer. See WO 98/04290.

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to 30 treating cancer see Hall et al (*Am J Hum Genet* (1997) **61**:785-789) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-35 Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August (1998) **5**(8):1105-13), and interferon gamma (*J Immunol* (2000) **164**:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of

expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853, verapamil and PSC833 (valsopdar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result 5 from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABA<sub>B</sub> receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or 10 others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis 15 that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 20 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT 25 International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 30 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 35 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1*H*,4*H*-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with ionizing radiation and/or in combination with a second compound selected from: HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an angiogenesis inhibitor, a PPAR- $\gamma$  agonist, a PPAR- $\delta$  agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

5 The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

10 The term "treatment" refers to the treatment of a mammal afflicted with a pathological condition and refers to an effect that alleviates the condition by killing the cancerous cells, but also to an effect that results in the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

15 The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

20 The term "adjunct" refers to the use of compounds in conjunction with known therapeutic means. Such means include cytotoxic regimes of drugs and/or ionising radiation as used in the treatment of 20 different cancer types. In particular, the active compounds are known to potentiate the actions of a number of cancer chemotherapy treatments, which include the topoisomerase class of poisons (e. g. topotecan, irinotecan, rubitecan), most of the known alkylating agents (e. g. DTIC, temozolamide) and platinum based drugs (e. g. carboplatin, cisplatin) used in treating cancer.

25 Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from: HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an angiogenesis inhibitor, a PPAR- $\gamma$  agonist, a PPAR- $\delta$  agonist, an anti-viral agent, an inhibitor of 30 inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

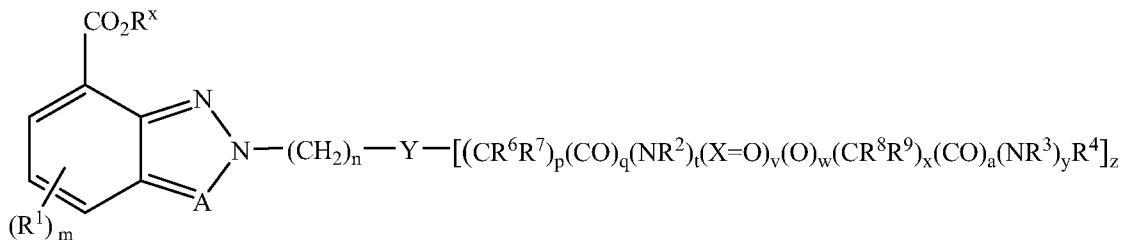
35 These and other aspects of the invention will be apparent from the teachings contained herein.

**Abbreviations used in the description of the chemistry and in the Examples that follow are:**

AcCl (acetyl chloride); (BzO)<sub>2</sub> (benzoyl peroxide); Cbz-Cl (benzylchloroformate); DCM (dichloromethane); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); eq. (equivalent); ES (electrospray); EtOAc (ethyl acetate); EtOH (ethanol); mol. sieves (molecular sieves); HATU [*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluoro-phosphate]; IBX (1-hydroxy-1*λ*<sup>3</sup>,2-benziodoxol-3(1*H*)-one 1-oxide); MeCN (acetonitrile); MeOH (methanol); MS (mass spectrometry); MW (microwave); NBS (*N*-bromosuccinimide); NMMO (*N*-methylmorpholine-*N*-oxide); NMR (nuclear magnetic resonance); Pcol (column pressure); iPrOH (isopropanol); RT (room temperature); sat. aq. (saturated aqueous); SiO<sub>2</sub> (silica gel); and THF (tetrahydrofuran). Ac<sub>2</sub>O (acetic acid); *t*-BuOH (tert-butanol); DIPEA (di-iso-propylethylamine); KOAc (potassium acetate); MW microwave; IST ISOLUTE<sup>®</sup> SPE column SCX (International Sorbent Technology ISOLUTE<sup>®</sup> Solid Phase Extraction column cationic exchange resin); SFC (supercritical fluid chromatography); TBTU *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and Tcol (column temperature).

Compounds of formula I can be prepared by reacting a compound of formula IA with a primary amine:

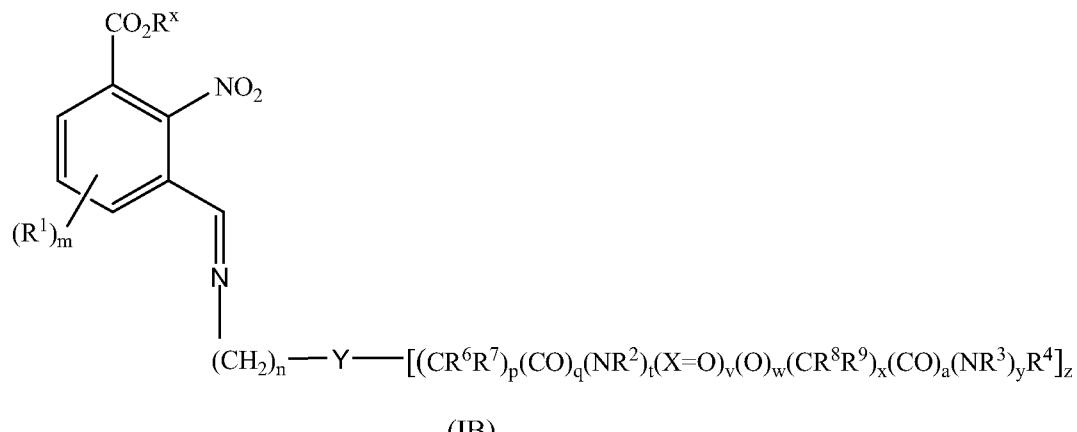
15



(IA)

wherein a, m, n, p, q, t, v, w, x, y, z, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X and Y are as defined above and R<sup>x</sup> is C<sub>1-6</sub>alkyl, such as methyl. The reaction is generally carried out using an aqueous solution of NH<sub>3</sub> in a solvent such as THF at about 70°C, in a sealed reaction vessel (with caution). Alternatively, a base such as NaOH may be added to hydrolyse the ester to the corresponding carboxylic acid (R<sup>x</sup> is hydrogen), followed by the addition of NH<sub>3</sub> in the presence of coupling agents such as HATU and DIPEA in a solvent such as DMF, the reaction being carried out at about room temperature. Alternatively, ammonia in a solvent such as MeOH can be used at about 120°C, for example in a MW.

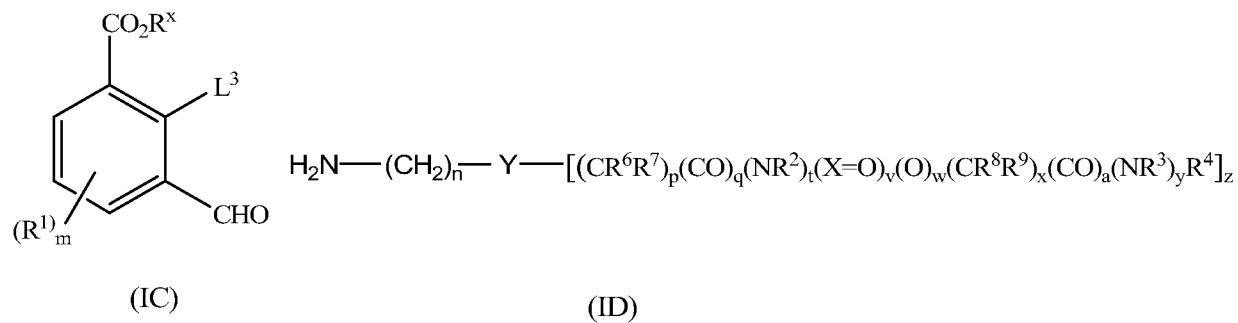
25 Compounds of formula IA wherein A is CH can be prepared by reacting a compound of formula IB with an azide:



wherein a, m, n, p, q, t, v, w, x, y, z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X, Y and R<sup>x</sup> are as defined above. An azide such as NaN<sub>3</sub> can be used, generally in a solvent such as DMF at about 90°C to 140°C.

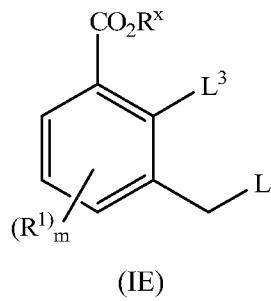
5 The reaction may be carried out under a nitrogen atmosphere.

Compounds of formula IB can be prepared by the condensation of a compound of formula IC with a compound of formula ID:



wherein a, m, n, p, q, t, v, w, x, y, z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X, Y and R<sup>x</sup> are as defined above and L<sup>3</sup> is a leaving group such as nitro or halogen, for example fluorine. In an embodiment L<sup>3</sup> is nitro. Methods include condensation in the presence of a dehydrating agent such as MgSO<sub>4</sub> or molecular sieves or heating in an alcohol solvent such as ethanol at reflux. The reaction may be carried out under a nitrogen atmosphere.

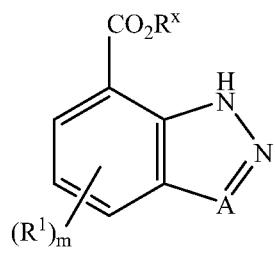
Compounds of formula IC can be prepared by oxidizing a compound of formula IE with an oxidizing agent such as NMNO:



wherein m, R<sup>1</sup>, R<sup>x</sup> and L<sup>3</sup> are as defined above and L is a leaving group such as halogen, for example bromine, generally in a solvent such as MeCN at about room temperature. The reaction may be carried out under a nitrogen atmosphere.

Compounds of formula IA wherein Y is an aromatic ring and

5 (CR<sup>6</sup>R<sup>7</sup>)<sub>p</sub>(CO)<sub>q</sub>(NR<sup>2</sup>)<sub>t</sub>(X=O)<sub>v</sub>(O)<sub>w</sub>(CR<sup>8</sup>R<sup>9</sup>)<sub>x</sub>(CO)<sub>a</sub>(NR<sup>3</sup>)<sub>y</sub>R<sup>4</sup> is an electron withdrawing group can alternatively be prepared by the condensation of a compound of formula IF with a compound of formula IG:



10

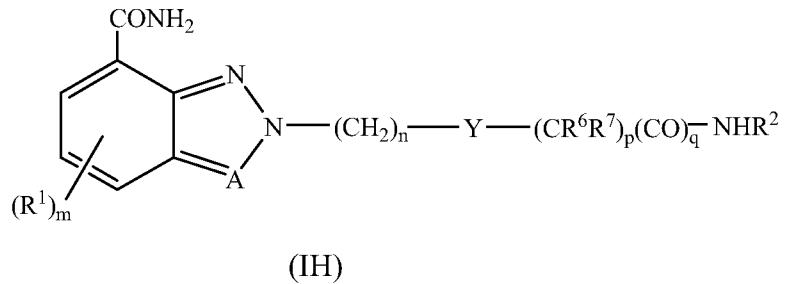


(IG)

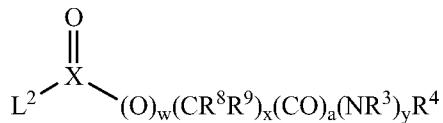
wherein a, m, n, p, q, t, v, w, y, z, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X and R<sup>x</sup> are as defined above  
15 and L<sup>1</sup> is a leaving group such as halogen, for example fluorine. The reaction is generally carried out in the presence of a base such as K<sub>2</sub>CO<sub>3</sub>, a solvent such as DMF at about 200°C. The reaction may be accelerated by using microwave heating. A base such as Cs<sub>2</sub>CO<sub>3</sub> may also be used.

Compounds of formula IF can be prepared using the method described in WO 2004/029050.

Compounds of formula I wherein t is 1, v is 1 and z is 1 can be prepared by the condensation of a  
20 compound of formula IH with a compound of formula IJ:



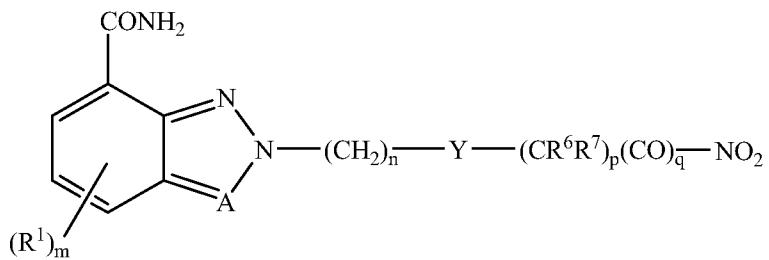
(IH)



(IJ)

wherein a, m, n, p, q, w, x, y, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X and Y are as defined above and L<sup>2</sup> is a leaving group such as hydroxy. The reaction is generally carried out in the presence of a coupling agent such as HATU and a base such as Et<sub>3</sub>N in solvents such as DMF and DCM at about room temperature. The coupling agents TBTU or TEA may also be used. Other amide or sulfonamide moieties in compounds of formula I can be prepared by an analogous method using appropriate variations of the compounds of formula IH and IJ.

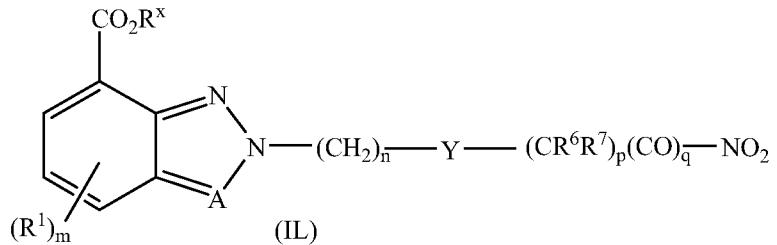
Compounds of formula IH wherein R<sup>2</sup> is hydrogen can be prepared by hydrogenation of a compound of formula IK:



(IK)

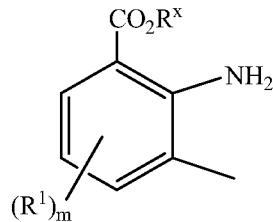
wherein m, n, p, q, A, R<sup>1</sup>, R<sup>6</sup>, R<sup>7</sup> and Y are as defined above. Standard hydrogenation conditions can be used, such as treating with a catalyst such as Pd/C, in a solvent such as methanol in a hydrogen atmosphere at about room temperature.

Compounds of formula IK can be prepared by reacting a compound of formula IL with ammonia:



wherein m, n, p, q, A, R<sup>1</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>x</sup> and Y are as defined above. The reaction is generally carried out using NH<sub>3</sub> in a solvent such as MeOH at about 50°C, in a sealed vessel (with caution).

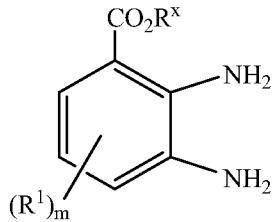
5 Compounds of formula IF wherein A is CH can be prepared by cyclisation of a compound of formula IM:



(IM)

10 wherein m, R<sup>1</sup> and R<sup>x</sup> are as defined above, in the presence of a nitrite such as isoamyl nitrite, with acetic anhydride and potassium acetate. The reaction is carried out in a solvent like chloroform. Alternatively, the compound of formula IM can initially be acylated, generally using acetyl chloride in a solvent such as 1,2-dichloroethane at about 55°C, and then cyclised using an inorganic nitrite such as sodium nitrite in the presence of a mineral acid such as HCl at about 0°C.

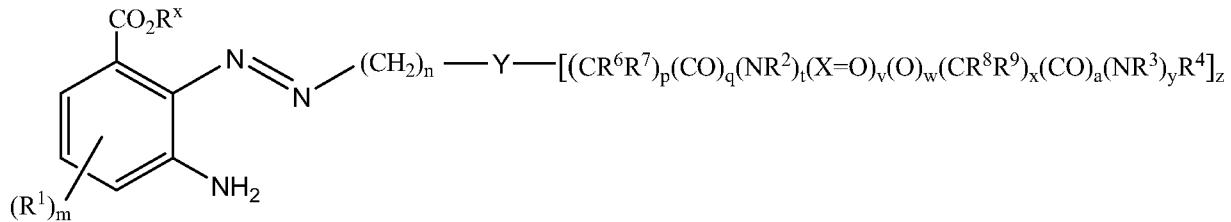
15 Compounds of formula IF wherein A is N can be prepared by cyclisation of a compound of formula IN:



(IN)

20 wherein m, R<sup>1</sup> and R<sup>x</sup> are as defined above, in the presence of a nitrite such as sodium nitrite and a weak acid such as acetic acid.

Compounds of formula IA wherein A is N can be prepared by cyclisation of a compound of formula IO:

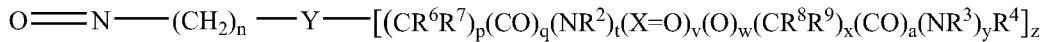


(IO)

5

wherein a, m, n, p, q, t, v, w, x, y, z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X, Y and R<sup>x</sup> are as defined above. The reaction is generally carried out in the presence of a cyclising agent such as Cu(OAc)<sub>2</sub> in a solvent such as DMF under an oxygen atmosphere at about 80°C.

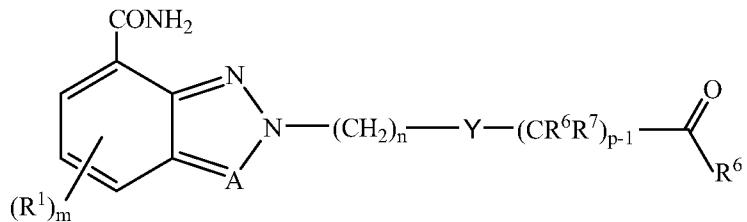
Compounds of formula IO can be prepared by reacting a compound of formula IN with a compound of formula IP:



(IP)

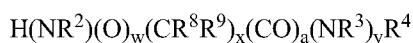
wherein a, n, p, q, t, v, w, x, y, z, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X and Y are as defined above, generally in an acidic solvent such as AcOH at about room temperature.

Compounds of formula I wherein p is 1 to 6, q is 0, t is 1 and z is 1 can be prepared by reductive amination of a compound of formula IQ with an amine of formula IR:



(IQ)

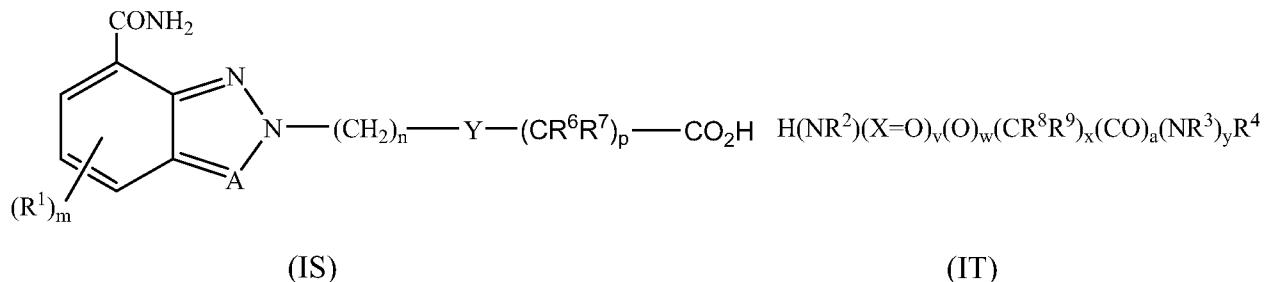
20



(IR)

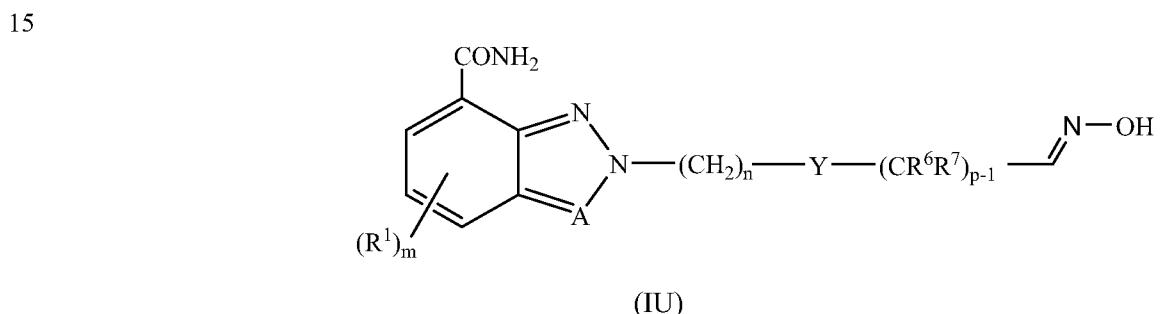
wherein a, m, n, w, x, y, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and Y are as defined above. The reaction is generally carried out in the presence of a reducing agent such as NaBH<sub>3</sub>(CN) or MP-triaceetoxyborohydride, in a solvent such as MeOH or DMF at about room temperature to 80°C. A catalyst such as ZnCl<sub>2</sub> may also be used.

5 Alternatively, compounds of formula I wherein q is 1, t is 1 and z is 1 can be prepared by a coupling reaction of a compound of formula IS with an amine of formula IT:



10 wherein a, m, n, p, v, w, x, y, A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ , X and Y are as defined above. The reaction is generally carried out in the presence of coupling agents such as HATU and a base such as  $Et_3N$  in a solvent such as DMF at about room temperature.

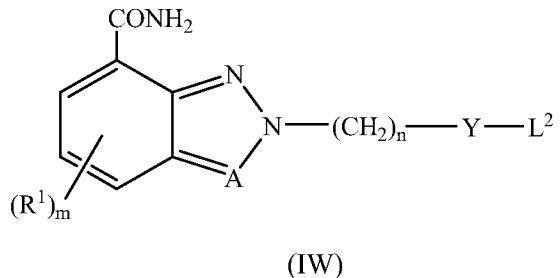
Compounds of formula IH wherein p is 1 to 6 and q is 0 can be prepared by hydrogenation of a compound of formula IU:



wherein m, n, R<sup>1</sup>, R<sup>6</sup>, R<sup>7</sup>, A and Y are as defined above. Standard hydrogenation conditions such as those described above can be used.

20 Compounds of formula IU can be prepared by condensation with a compound of formula IQ in which R<sup>y</sup> is hydrogen with a hydroxyamine such as NH<sub>2</sub>OH.HCl, in the presence of a base such as Et<sub>3</sub>N and a solvent such as MeCN at reflux.

Compounds of formula I wherein a, p, q, t, v, w, x and y are each 0, z is 1 and Y is a ring can be prepared by cross-coupling a compound of formula IW with a compound of formula IX:

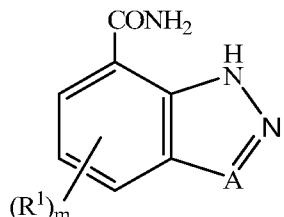


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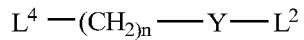


wherein m, n, A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and X are as defined above and L<sup>2</sup> is a leaving group such as halogen, for example bromine. The reaction is generally carried out under Suzuki coupling conditions such as using catalysts such as Pd<sub>2</sub>(dba)<sub>3</sub> and tri(tert-butyl)phosphine together with a base such as sodium carbonate and solvents such as DMF and water at about 90°C.

Compounds of formula IW can be prepared by condensation of a compound of formula IY with a compound of formula IZ:



15

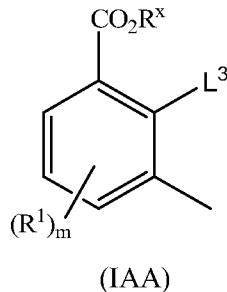


wherein m, n, R<sup>1</sup>, A, Y and L<sup>2</sup> are as defined above and L<sup>4</sup> is a leaving group such as halogen, for example fluorine, generally in a solvent such as DMF at about 180°C.

Compounds of formula IY can be prepared by reacting a compound of formula IF with a base such as KOH or NaOH at about room temperature to hydrolyse the ester to the corresponding carboxylic acid (R<sup>x</sup> is hydrogen), followed by the addition of NH<sub>3</sub> in the presence of coupling agents such as HATU, DIPEA and TBTU in a solvent such as DMF, the reaction being carried out at about room temperature.

Compounds of formula IE can be prepared by oxidizing a compound of formula IAA with a brominating agent such as NBS in the presence of a radical initiator such as benzoyl peroxide:

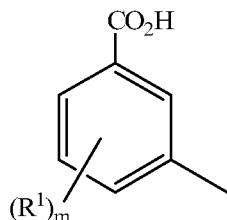
25



wherein m, L<sup>3</sup>, R<sup>1</sup> and R<sup>x</sup> are as defined above, generally in a solvent such as CCl<sub>4</sub> at reflux.

Compounds of the formula IAA wherein L<sup>3</sup> is fluorine can be prepared by diazonitisation of a 5 compound of formula IM followed by decomposition of the intermediate diazonium salt. For example, the diazonitisation can be carried out using nitrosium tetrafluoroborate in a solvent such as DCM at about 0°C. The corresponding diazonium tetrafluoroborate salt can then be isolated and subsequently decomposed at elevated temperatures to the corresponding fluorobenzene derivative (Caution), such as by heating to 160°C in a solvent such as dichlorobenzene.

10 Compounds of formula IAA wherein L<sup>3</sup> is nitro can be prepared by nitration of a compound of formula IBB followed by esterification:



(IBB)

wherein m and R<sup>1</sup> are as defined above. The nitration reaction can be carried out in the presence 15 of a nitrate such as potassium nitrate and an acid such as sulfuric acid at about room temperature. The esterification step can be carried out under standard conditions, such as by reacting with an alkyl halide of formula R<sup>x</sup>-X wherein X is a halogen such as iodine, in the presence of a base such as cesium carbonate and in a solvent such as DMF at about room temperature. An alcohol of formula R<sup>x</sup>-OH can also be used together with an acid catalyst, such as HCl generated in situ from AcCL/MeOH, at reflux.

20 Where the synthesis of intermediates and starting materials is not described, these compounds are commercially available or can be made from commercially available compounds by standard methods or by extension of the synthesis above, schemes and Examples herein.

Compounds of formula I may be converted to other compounds of formula I by known methods 25 or by methods described in the synthesis above, schemes and Examples herein. For example, pyridine derivatives can be reduced to the corresponding piperidine derivatives by a Fowler reaction using an acyl chloride such as Cbz-Cl, a reducing agent such as NaBH<sub>4</sub> and in a solvent such as methanol at about -65°C to RT, followed by hydrogenation. Alternatively, alkylation with reactive alkyl halides, such as ethyl iodide in a solvent such as acetonitrile gives rise to a pyridinium salt that can be reduced with

sodium borohydride in an alcohol solvent such as MeOH. This can then be hydrogenated to the corresponding 1-alkyl piperidine using hydrogen and palladium on carbon.

During any of the synthetic sequences described herein it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means 5 of conventional protecting groups, such as those described in *Protecting Groups in Organic Synthesis*, 3rd Edition, Greene, T. W. and Wuts, P. G. M.; Wiley Interscience, 1999 and Kocienski, P. J. *Protecting Groups*, Thieme, 1994. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. For example, when the Boc (*tert*-butoxycarbonyl) or benzylcarbonyl 10 protecting group is present, it may be removed by the addition of solvents such as TFA, DCM and/or MeCN at about room temperature. The compound may also be hydrogenated using standard methods, such as treating with a catalyst such as Pd/C, in a solvent such as methanol under a hydrogen atmosphere. EtOAc in the presence of HCl and 1,4-dioxane may also be added to remove the Boc or benzylcarbonyl 15 protecting group, at about room temperature.

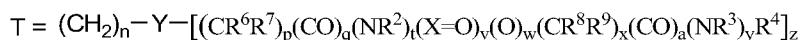
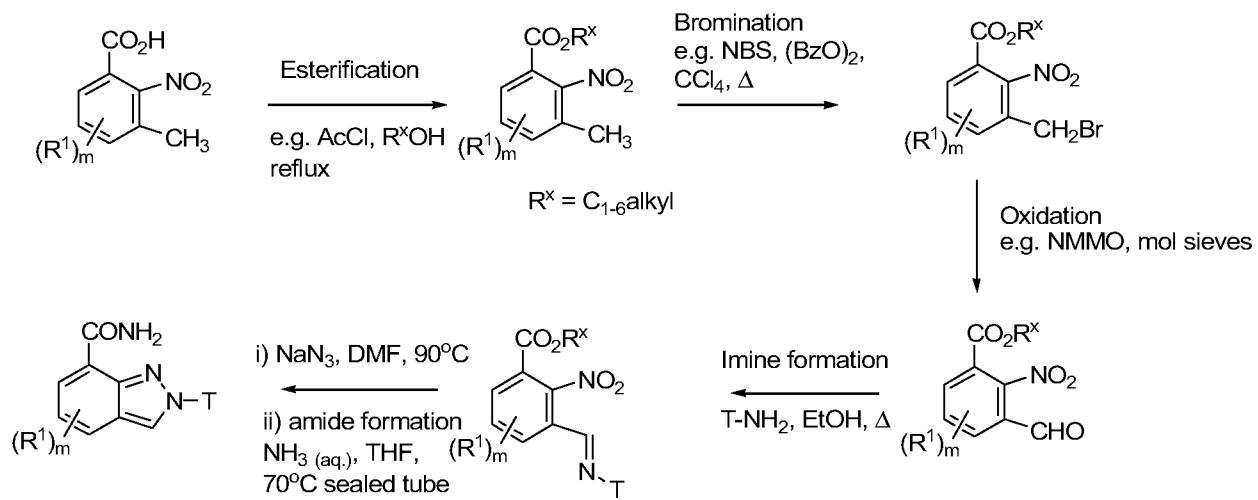
The compounds of this invention were prepared according to the following schemes. All

15 variables within the formulae are as defined above.

When the compounds of the present invention have chiral centres, the enantiomers may be separated from the racemic mixtures by standard separating methods such as using SFC.

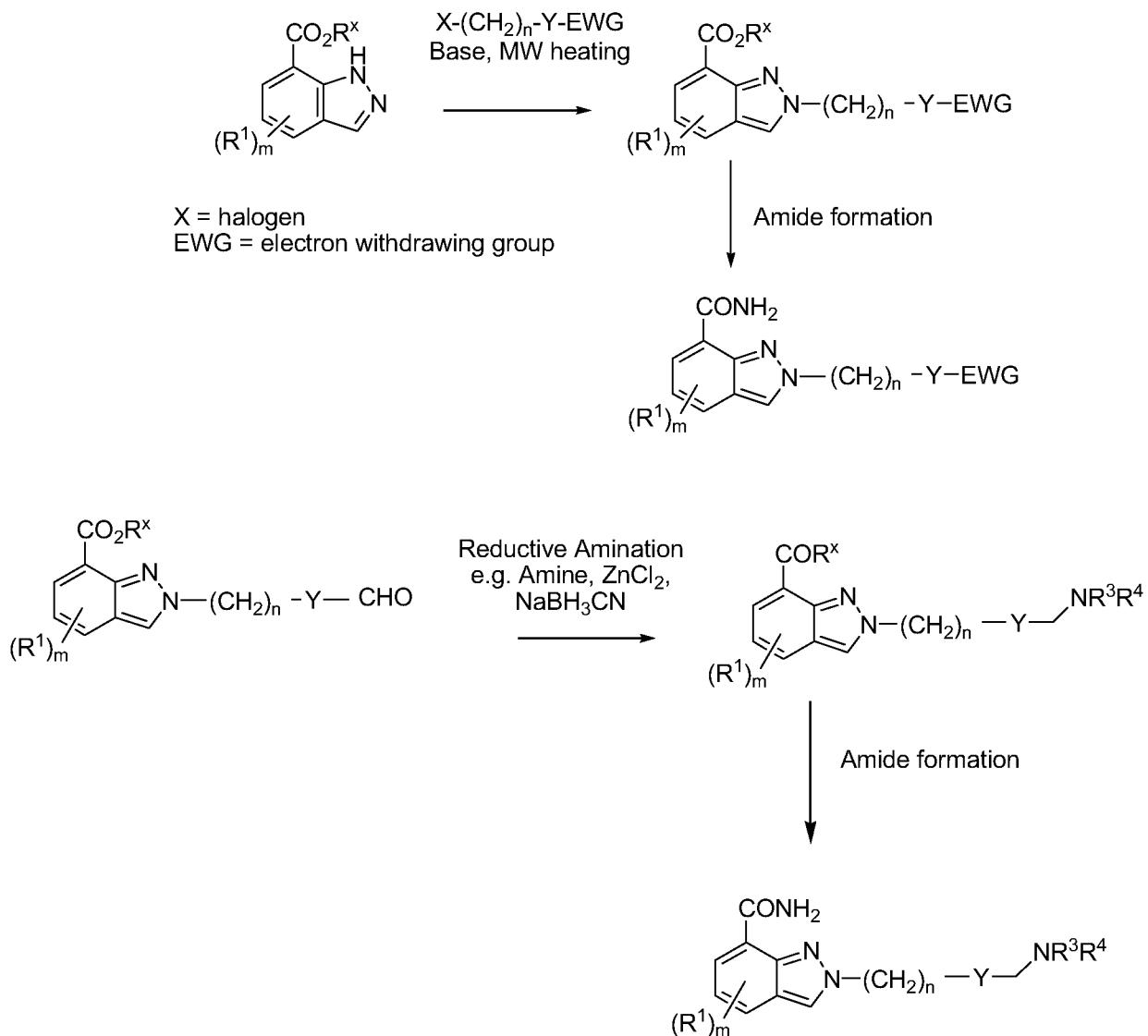
**Scheme 1**

A procedure to synthesize derivatives of those compounds of this invention wherein A = CH is shown in **scheme 1**, whereby the substituted 2*H*-indazoles are prepared using a synthetic route similar to that described in WO 2005/066136. Following initial conversion of the 2-nitro-3-methyl-benzoic acid derivative into the corresponding ester, radical bromination of the methyl group using reagents like N-bromosuccinimide and benzoyl peroxide yields the key benzyl bromide derivative. Oxidation of this benzylic bromide to the corresponding benzaldehyde can be accomplished for instance using *N*-methylmorpholine-*N*-oxide and molecular sieves. Following the condensation of the aldehyde with an amine, ring closure can be accomplished by treating the key intermediate with sodium azide at elevated temperature to introduce the final nitrogen atom and the resultant extrusion of nitrogen to furnish the indazole ring. Final conversion of the ester to the primary amide yields the desired derivatives.



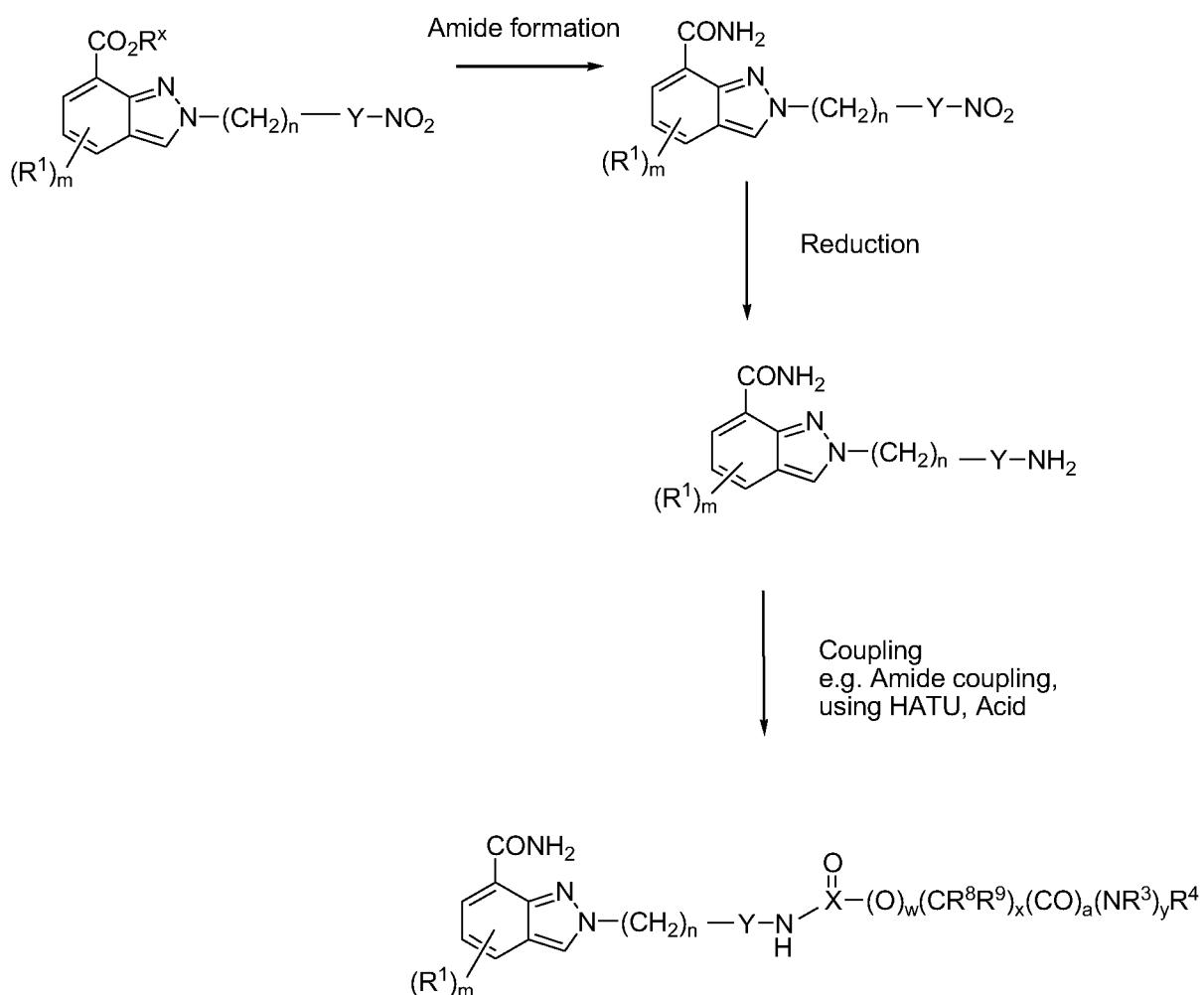
**Scheme 2**

Alternatively, compounds of the present invention can be prepared by a microwave assisted  $S_NAr$  5 on the methyl-2H-indazole-7-carboxylate (for the preparation see WO2004/029050) using the appropriate substituted activated haloaromatic or haloheteroaromatic derivative in a polar solvent, like DMF, in presence of a base, such as  $K_2CO_3$ . The functional groups on the (hetero)aromatic groups can then be further manipulated for instance performing reductive amination of an aldehyde functionality such as using  $ZnCl_2$  and  $NaBH_3(CN)$  together with the appropriate amines. Conversion to the desired 10 carboxamide can be achieved by treatment an aqueous solution of  $NH_3$  in THF at reflux (**Scheme 2**).

**Scheme 2**

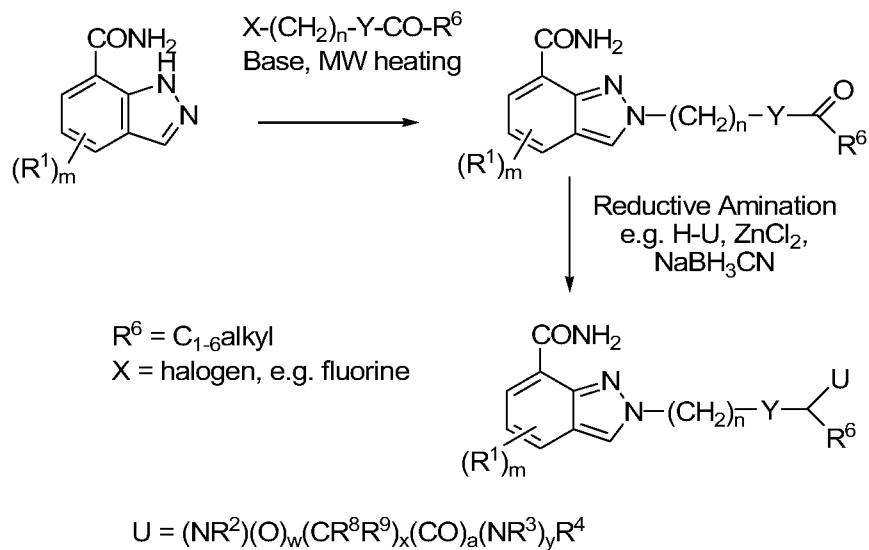
**Scheme 3**

A modification of the procedure in **scheme 2** is where the displacement is carried out with a fluoronitrobenzene, to yield the corresponding *N*-nitrophenyl indazole analogs, which after conversion to the corresponding amide, the nitro group can be reduced, for instance by hydrogenation using palladium on carbon as catalyst. The resulting anilines can be coupled by standard methods to yield the desired inhibitors.



**Scheme 4**

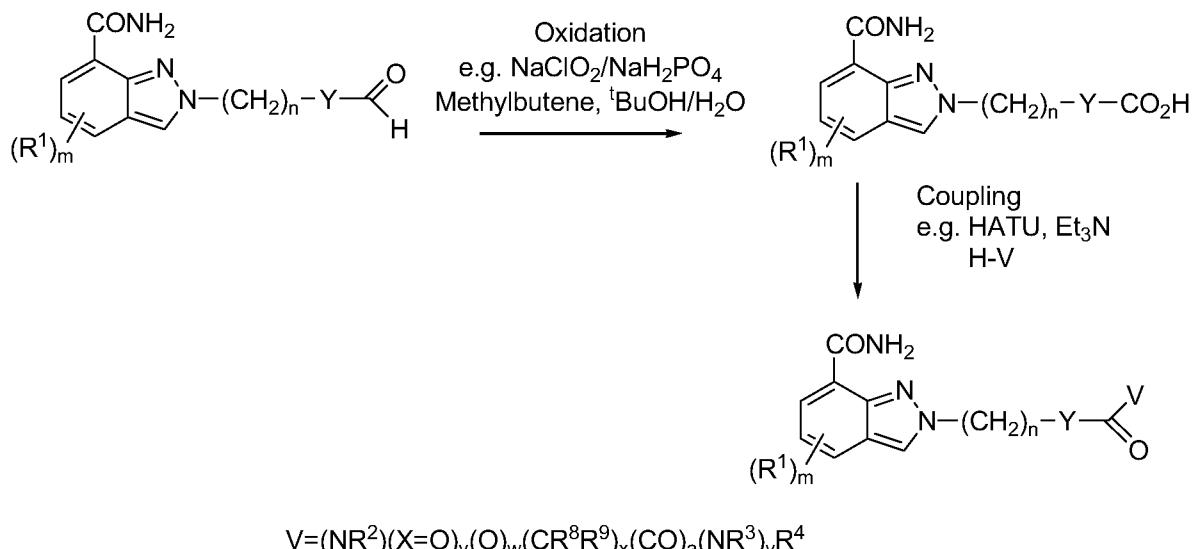
A modification of the procedure in **scheme 2** is shown below in **scheme 4** whereby the displacement is carried out with a fluoroacetophenone or related ketone derivative, in this case subsequent reductive amination yields the corresponding amine derivative with a branch at the *alpha*-position. The two enantiomers can be subsequently resolved by chiral separation.

**Scheme 4**

**Scheme 5**

Further derivatives can be prepared by late stage modification of these compounds, for instance if an aldehyde has been carried through the earlier procedures it can be oxidized to the corresponding carboxylic acid using reagents such as  $\text{NaClO}_2/\text{NaH}_2\text{PO}_4$  in the presence of a scavenger such as methylbutene. The resulting acid can be coupled with a variety of amines using coupling reagents such as HATU in the presence of a base such as  $\text{Et}_3\text{N}$ .

10

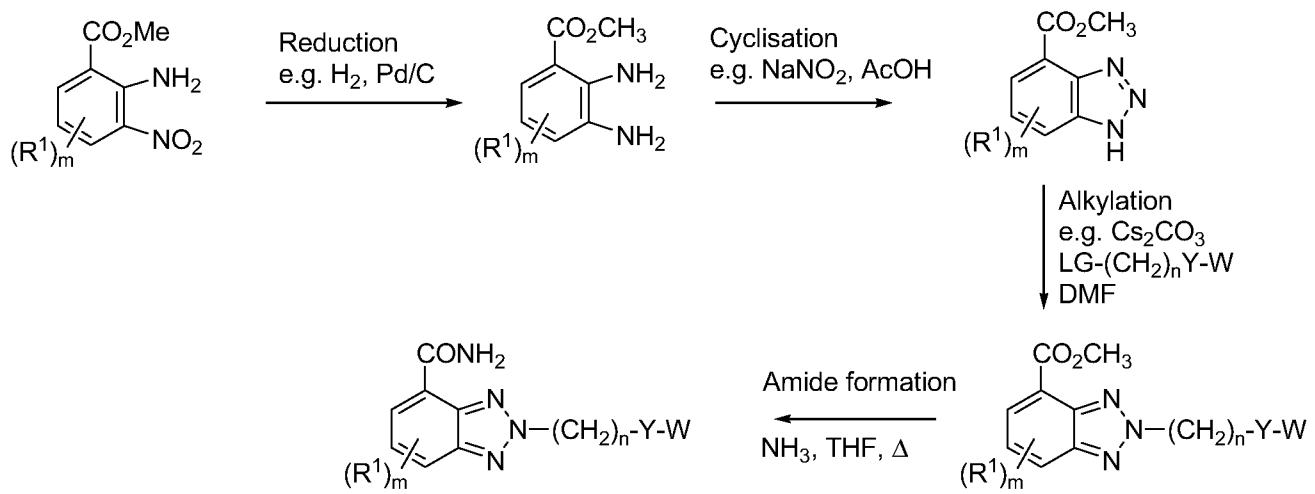
**Scheme 5**

**Scheme 6**

Alternatively benzotriazoles can be prepared as described in **scheme 6**. A functionalised *ortho*-nitroaniline can be reduced to the corresponding 1,2-diaminobenzene using conditions such as

5 hydrogenation over palladium on carbon. In turn, this 1,2-diaminobenzene can be treated with sodium nitrite in acetic acid to give rise to the corresponding benzotriazole as described in *Heterocycles* (1985) **23(9)**:2225-2228 and *J. Med. Chem.*; (1989) **32(7)**:1566-1571. The resulting heterocycle can then be alkylated under basic conditions to give an isomeric mixture of benzotriazoles from which can be isolated the desired 2-substituted isomer. Conversion of the ester to the corresponding primary amide

10 gives the desired inhibitors.



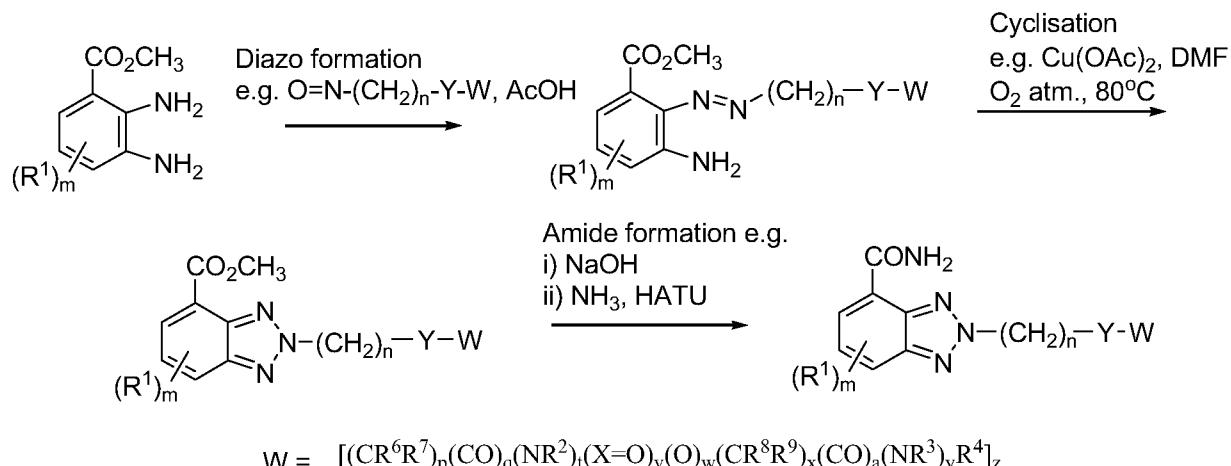
LG = Leaving group, e.g. Br, OTs

W =  $[(CR^6R^7)_p(CO)_q(NR^2)_t(X=O)_v(O)_w(CR^8R^9)_x(CO)_y(NR^3)_yR^4]_z$

**Scheme 6**

**Scheme 7**

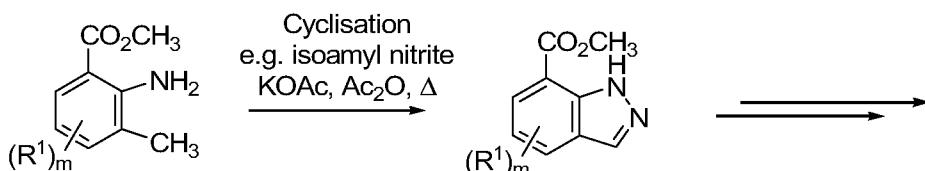
In a related manner, the 1,2-diaminobenzene can be reacted with a nitroso derivatives at RT in a solvent like AcOH to form a diazo compound. This diazo compound can then be cyclised to the corresponding benzotriazole by treatment with copper acetate in DMF at 80°C under an oxygen atmosphere. Manipulation of the ester to the amide as previously, or by hydrolysis to the carboxylic acid and coupling to ammonia, yields the desired compounds.

**Scheme 7**

10

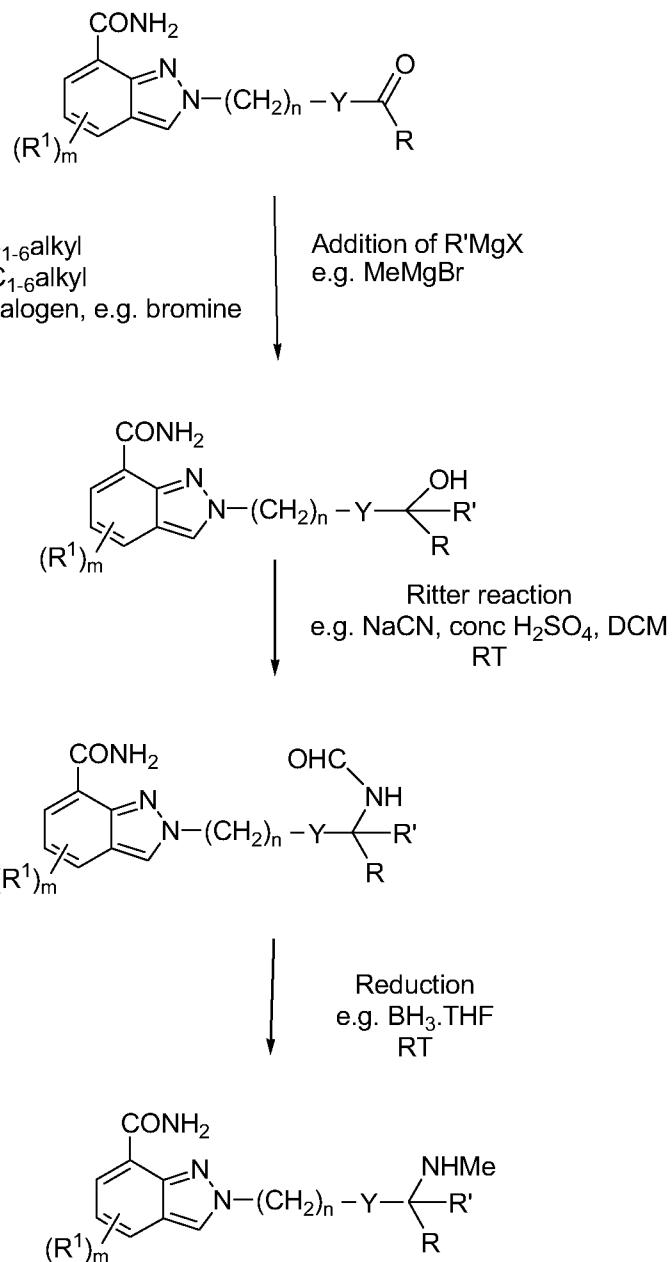
**Scheme 8**

An alternative preparation of the indazole scaffold is shown in **scheme 8** whereby a substituted alkyl 2-amino-3-methylbenzoate can be treated with isoamyl nitrite and potassium acetate in the presence of acetic anhydride as reported in *Bioorganic & Medicinal Chemistry*, 2004, 12(9), 2115-2137 and the desired functionalised indazole can be isolated. In turn this indazole can be derivatised as previously described.

**Scheme 8**

**Scheme 9**

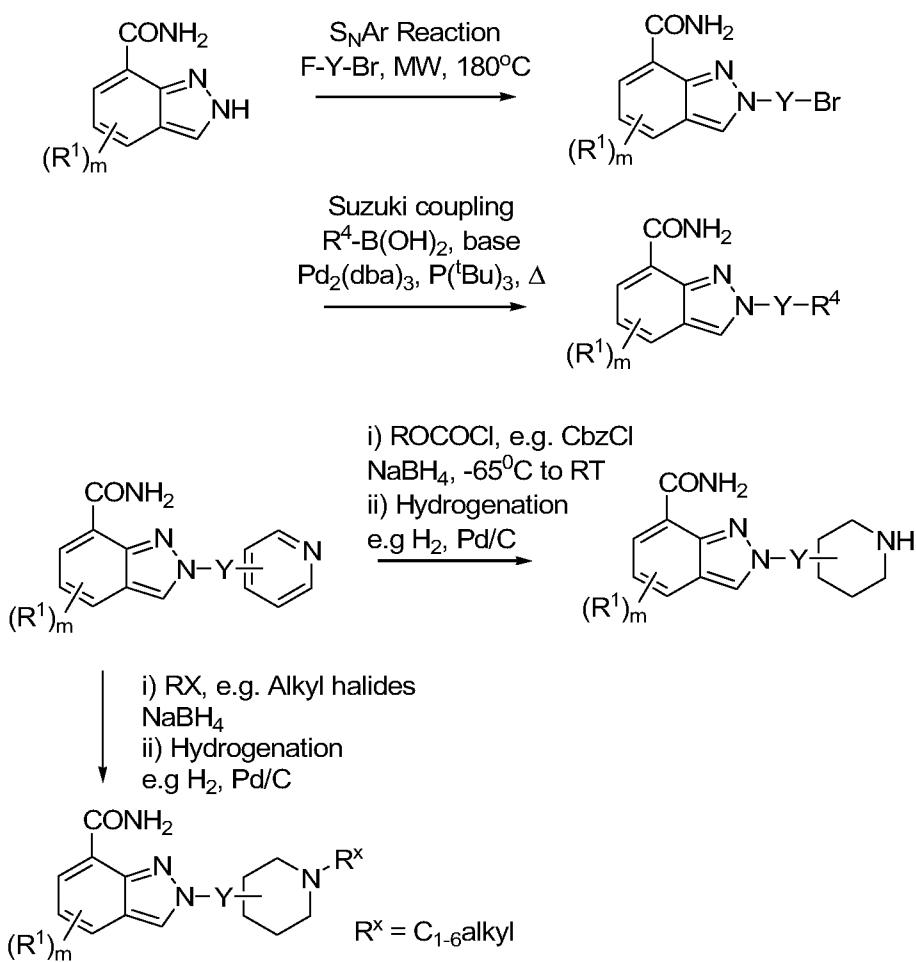
Further derivativedation to allow the preparation of compounds with a *gem*-dialkyl substituent can be achieved as described in **scheme 9**. Here a ketone derivative can be treated with an appropriate Grignard reagent to yield the corresponding tertiary alcohol. This alcohol can, in turn, be treated with an inorganic cyanide in concentrated acid to yield the corresponding formamide by Ritter rearrangement reaction (Ritter, J. J.; Kalish J.; *Org. Synth. Col. Vol. V*, 1973, 471). This formamide can be reduced to give (hetero)benzylic amines.

**Scheme 9**

**Scheme 10**

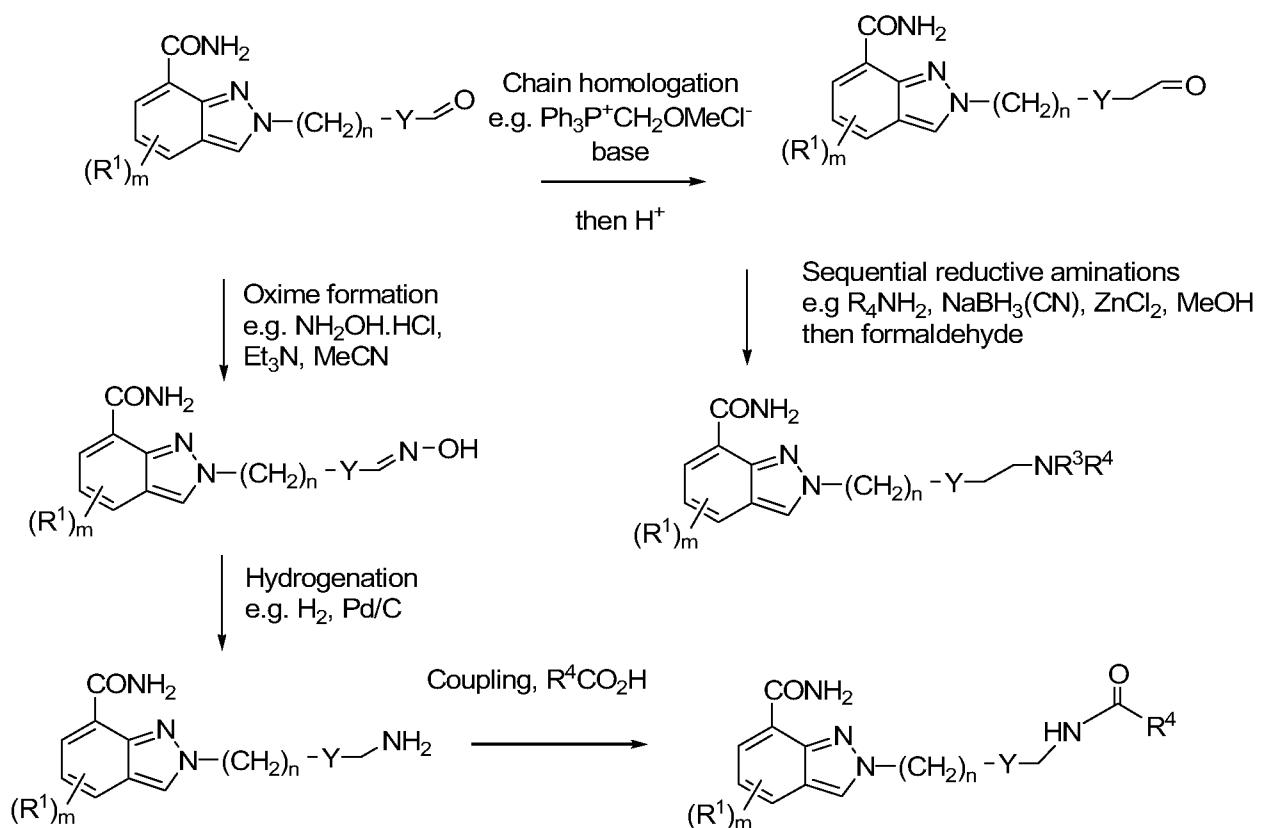
Late stage modifications of these derivatives also allow the preparation of other derivatives and further examples are shown in **scheme 10**. Here nucleophilic aromatic substitution of the appropriate

5 fluoro(hetero)aromatic bromide allows the preparation of a bromide derivative that can be cross coupled under Suzuki coupling conditions, for instance using tri(tert-butyl)phosphine and  $\text{Pd}_2(\text{dba})_3$  as catalysts in the presence of a base, such as sodium carbonate. If a pyridine derivative has been prepared it can then be reduced in a Fowler reaction using an acyl chloride and a reducing agent such as  $\text{NaBH}_4$ . Final 10 hydrogenation reaction can yield the corresponding piperidine derivatives. Alternatively quaternisation of the corresponding pyridine derivative followed by reduction and hydrogenation gives alkylated piperidine derivatives.

**Scheme 10**

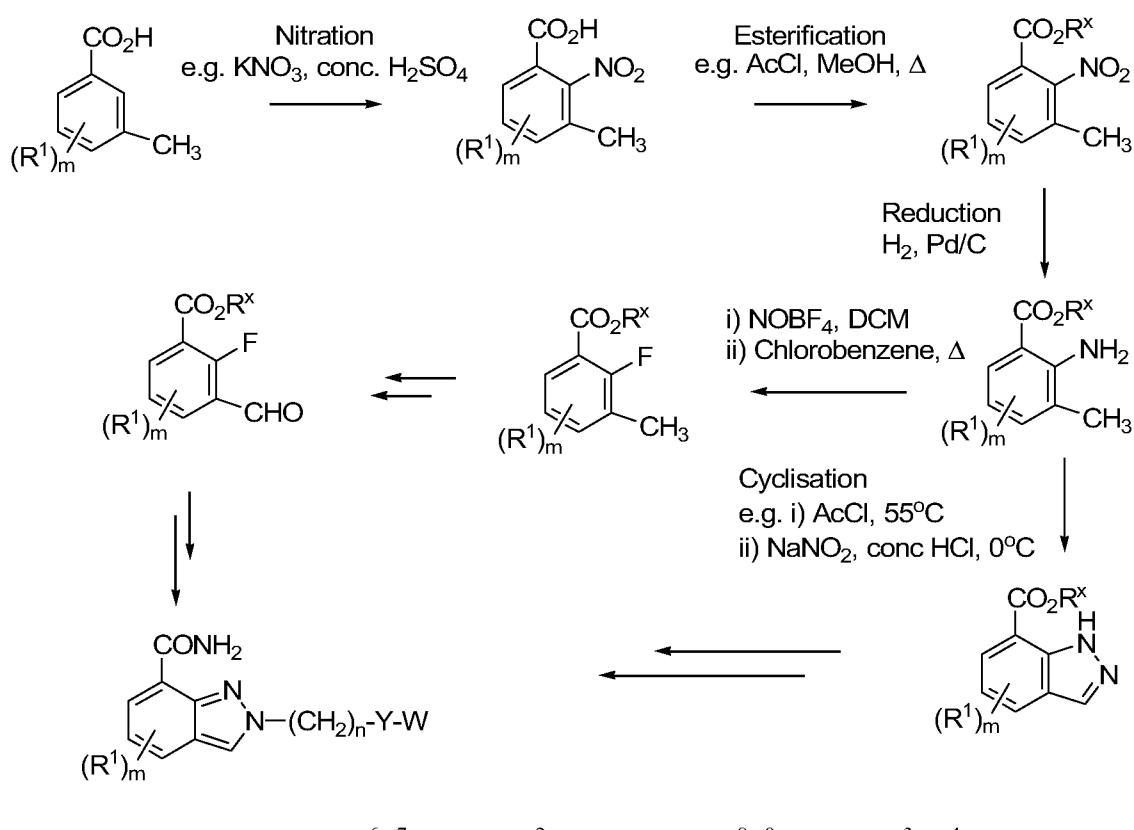
**Scheme 11**

Homologation reactions of advanced intermediates are also possible as shown in **scheme 11**, for instance treating an aldehyde with methoxymethyltriphenylphosphonium chloride and a base such as potassium *tert*-butoxide followed by mild acid treatment to allow a one-carbon homologation reaction. The aldehyde can then be elaborated as described above to introduce amino functionalities. Furthermore, the aldehyde can also be condensed with hydroxylamine and hydrogenated to yield the corresponding primary amines that can in turn be manipulated further into the desired derivatives.

**Scheme 11**

**Scheme 12**

A variation of **schemes 1 and 8** is shown below in **scheme 12** and allows the introduction of substituents onto the indazole cores. When the required nitrobenzoic acid derivatives are not commercial available they can be prepared through nitration of the corresponding benzoic acid derivatives, for instance using 5 potassium nitrate in concentrated sulphuric acid. Synthetic manipulations as described above allow the formation of the corresponding aniline which can either be cyclised to the indazole by firstly acetylation of the indazole and cyclisation with sodium nitrite in concentrated HCl acid at 0°C. Alternatively, the aniline can be diazonised with nitrosium tetrafluoroborate and the corresponding diazonium 10 tetrafluoroborate salt decomposed at elevated temperatures to the corresponding difluorobenzene derivative by a Schiemann reaction (Caution). Following the synthetic sequence as described in **scheme 1** allows oxidation of the benzylic methyl group to the corresponding aldehyde and elaboration of the desired indazole derivatives by coupling with a (hetero)anilide and cyclisation with sodium azide.

**Scheme 12**

The exemplified compounds described herein were tested by the assays described below and were found to have an IC<sub>50</sub> value of less than 5μM.

5 **PARP-1 SPA assay**

**Working Reagents**

**Assay buffer:** 100 mM Tris pH 8, 4 mM MgCl<sub>2</sub>, 4 mM Spermine, 200 mM KCl, 0.04% Nonidet P-40.

**Enzyme Mix:** Assay buffer (12.5 ul), 100 mM DTT (0.5 ul), PARP-1 (5 nM, Trevigen 4668-500-01), H<sub>2</sub>O (to 35 ul).

10 **Nicotinamide-adenine dinucleotide (NAD)/ DNA Mix:** [<sup>3</sup>H-NAD] (250 uCi/ml, 0.4 ul, Perkin-Elmer NET-443H), NAD (1.5 mM, 0.05 ul, SIGMA N-1511), Biotinylated-NAD (250 uM, 0.03 ul, Trevigen 4670-500-01), Activated calf thymus (1mg/ml, 0.05ul, Amersham Biosciences 27-4575), H<sub>2</sub>O (to 10ul).

**Developing Mix:** Streptavidin SPA beads (5mg/ml, Amersham Biosciences RPNQ 0007) dissolved in 500 mM EDTA.

15 **Experimental Design**

The reaction is performed in 96-well microplate with a final volume of 50 uL/well. Add 5ul 5%DMSO/compound solution, add enzyme mix (35ul), start the reaction by adding NAD/DNA mix (10 uL) and incubate for 2 hrs at RT. Stop the reaction by adding developing mix (25 ul) and incubate 15 min at RT. Measure using a Packard TOP COUNT instrument.

20

**Proliferation Assay in BRCA-1 silenced HeLa cells.**

**Abbreviations:**

IMDM (Iscove's Modified Dulbecco's Media); RPMI (Roswell Park Memorial Institute Media); MOI (multiplicity of infection); GFP (green fluorescent protein); PBS (Phosphate Buffered Saline); FCS (fetal calf serum); and DMEM (Dulbecco's Modified Eagle's Medium).

30 Compounds were also tested in an anti-proliferative assay in matched pair BRCA1wt and BRCA1-(shRNA) HeLa cells. The assay shows that PARP inhibitors are able to show selectivity with growth inhibition of the BRCA deficient cells. Certain compounds showed CC<sub>50</sub>'s less than 10 μM in BRCA1 deficient cells and a greater than 10 fold selectivity over the BRCA proficient cells.

The assay is based on the ability of living cells to convert a redox dye (resazurin) into a fluorescent end product (resofuran). The amount of resofuran produced is directly proportional to the cell number.

35 **Cell lines:**

**HeLa shBRCA1-GFP** - These are HeLa cells transduced at an MOI of 100 with a Lentivirus containing a shRNA against BRCA-1 and an expression cassette for GFP. BRCA-1 silencing is more than 80 % as assessed by Taqman analysis and the cells stably express GFP.

**HeLa THM-GFP** - These are HeLa cells transduced at an MOI of 100 with a control vector not expressing any shRNA.

5 **Protocol**

- Seed 300 cell/well in 96 wells viewplate black in 90µl culture Medium\*:
- Incubate 4 hours at 37°C, 5 % CO<sub>2</sub>
- Add 10ul/well of 10X compound (5 % DMSO in H<sub>2</sub>O)
- Incubate for 168 hours at 37°C, 5 % CO<sub>2</sub>
- 10 - Add 10µl of Celltiter Blue solution (Promega, G8081) pre-diluted 1:1 in PBS1x
- Incubate the mixture for 45' at 37°C, 5 % CO<sub>2</sub>
- Incubate 15' at RT in the dark
- Read plate at fluorimeter ex: 550 nm; em: 590 nm

15 \*Culture Medium: DMEM (GIBCO, 41966-029), 10% FCS (GIBCO, 10106-169), 0.1mg/ml Penicillin-Streptomycin (GIBCO, 15140-114), 2mM L-Glutamine (GIBCO, 3042190)

**Proliferation Assay in naturally BRCA deficient cells lines.**

20 Certain compounds of the present invention were also demonstrated to inhibit the proliferation of naturally BRCA-1 (MDA-MB-436) and BRCA-2 (CAPAN-1) deficient cell lines with CC<sub>50</sub>'s less than 5 micromolar.

**Proliferation Assay**

25 Cells are seeded in a 96-well plate at 700 cells/well in 100ul of the appropriate medium/well.\* The following day, serial dilutions of the compound are added in a final volume of 200 µl/well. Each dilution is assayed in triplicates. Six days later, cell viability is estimated using CellTiter-Blue Cell Viability Assay according to the manufacturer instructions (Promega). Plates are read at the Fusion Alpha microplate reader (Packard 30 Bioscience).

For low-proliferating cell lines (i.e. CAPAN-1), proliferation is assayed 14 days after adding the compounds and changing the medium once at day 7 (170 µl of medium per well are aspirated and replaced with 170 µl fresh medium containing the compounds).

35

\* Culture Medium:

MDA-MB-436: RPMI (GIBCO), 10 % FBS (5% CO<sub>2</sub>)

CAPAN-1: IMDM (GIBCO), 20 % FBS (5% CO<sub>2</sub>)

**EXAMPLE 1****2-Phenyl-2H-indazole-7-carboxamide (A6)**

5

**Step 1: Methyl 3-methyl-2-nitrobenzoate (A1)**

To a suspension of 3-methyl-2-nitro-benzoic acid (1.0 eq.) in MeOH (0.4 M) at 0°C was added dropwise AcCl (3.0 eq.). The reaction mixture was stirred for 20 hr at reflux. The solvent was reduced in vacuo and the residue was dissolved in EtOAc and washed several times with sat. aq. NaHCO<sub>3</sub> solution, brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave (**A1**) as a white solid which was used in the next step without further purification. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>, 300K) δ 7.86 (1H, d, J = 7.5 Hz), 7.53-7.42 (2H, m), 3.89 (3H, s), 2.36 (3H, s). MS (ES) C<sub>9</sub>H<sub>9</sub>NO<sub>4</sub> requires: 195, found: 218 (M+Na)<sup>+</sup>.

**Step 2: Methyl 3-(bromomethyl)-2-nitrobenzoate (A2)**

A mixture of (**A1**) (1.0 eq.), (BzO)<sub>2</sub> (0.06 eq.) and NBS (1.18 eq.) in CCl<sub>4</sub> (0.2 M) was heated at reflux under N<sub>2</sub> atmosphere for 12 hr. The mixture was cooled to RT, diluted with DCM, concentrated under reduced pressure whilst dry loading onto SiO<sub>2</sub>. The residue was purified by flash column chromatography on SiO<sub>2</sub> using 10:90 EtOAc/Petroleum ether to yield the desired (**A2**) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>, 300K) δ 7.93 (1H, d, J = 7.7 Hz), 7.72 (1H, d, J = 7.7 Hz), 7.57 (1H, t, J = 7.7 Hz), 4.43 (2H, s), 3.88 (3H, s). MS (ES) C<sub>9</sub>H<sub>8</sub>BrNO<sub>4</sub> requires: 273:275, found: 242:244 (M-MeO)<sup>+</sup>, 227:229 (M-NO<sub>2</sub>)<sup>+</sup>.

**Step 3: Methyl 3-formyl-2-nitrobenzoate (A3)**

To a mixture of (**A2**) and 4Å mol. sieves (15 g) in MeCN (0.2M) at RT was added NMMO (2.0 eq.) and the reaction mixture was stirred for 1.5 hr under N<sub>2</sub> atmosphere. Then, the mixture was diluted with EtOAc, filtered and the filtrate was washed with H<sub>2</sub>O, 1N HCl, brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave (**A3**) as a white solid which was used in the next step without further purification. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>, 300K) δ 9.96 (1H, s), 8.26 (1H, d, J= 7.9 Hz), 8.18 (1H, d, J = 7.9 Hz), 7.77 (1H, t, J = 7.9 Hz), 3.93 (3H, s). MS (ES) C<sub>9</sub>H<sub>7</sub>NO<sub>5</sub> requires: 209, found: 208 (M-H)<sup>-</sup>.

**Step 4: Methyl 2-nitro-3-[(phenylimino)methyl]benzoate (A4)**

A mixture of (**A3**) (1.0 eq.) and aniline (1.05 eq.) in EtOH (0.2 M) was stirred at reflux under N<sub>2</sub> atmosphere for 2 hr until TLC revealed completion of the reaction (Hexane/EtOAc = 75:25). Evaporation of the solvent gave (**A4**) as a white solid which was used in the next step without further purification. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>, 300K) δ 8.51 (1H, d, J = 7.3 Hz), 8.41 (1H, s), 8.11 (1H, d, J = 7.8 Hz), 7.67 (1H, t, J = 7.8 Hz), 7.43 (2H, t, J = 7.8 Hz), 7.31 (1H, t, J = 7.3 Hz), 7.16 (2H, d, J = 7.8 Hz), 3.94 (3H, s).

**Step 5: Methyl 2-phenyl-2H-indazole-7-carboxylate (A5)**

A mixture of (**A4**) (1.0 eq.) and NaN<sub>3</sub> (1.05 eq.) in dry DMF (0.3 M) was stirred at 90 °C overnight under N<sub>2</sub> atmosphere. The crude was reduced in vacuo and the residue purified by flash column chromatography on silica using a gradient of EtOAc/Petroleum ether from 10:90 to 40:60 to yield the

desired (**A5**) as a brown oil.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ , 300K)  $\delta$  8.50 (1H, s), 8.12 (1H, d,  $J$  = 7.0 Hz), 7.96-7.90 (3H, m), 7.49 (2H, t,  $J$  = 7.6 Hz), 7.38 (1H, t,  $J$  = 7.4 Hz), 7.15 (1H, t,  $J$  = 7.4 Hz), 4.03 (3H, s). MS (ES)  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$  requires: 252, found: 253 ( $\text{M}+\text{H}$ ) $^+$ .

**Step 6: 2-Phenyl-2*H*-indazole-7-carboxamide (**A6**)**

5 The ester (**A5**) was heated in a mixture of THF and 32% aq.  $\text{NH}_3$  solution at 70 °C overnight in a sealed tube. The solvents were reduced in vacuo and the residue purified by flash column chromatography on silica using a gradient of EtOAc/Petroleum ether from 30:70 to 50:50 to yield the desired (**A6**) as white solid.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}$ , 300K)  $\delta$  9.33 (1H, s), 8.56 (1H, bs), 8.16 (2H, d,  $J$  = 7.9 Hz), 8.08-8.00 (2H, m), 7.88 (1H, bs), 7.63 (2H, t,  $J$  = 7.7 Hz), 7.50 (1H, t, 7.4 Hz), 7.27 (1H, t,  $J$  = 7.9 Hz). MS (ES)  $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$  requires: 237, found: 238 ( $\text{M}+\text{H}$ ) $^+$ .

10

**EXAMPLE 2**

**2-(3-Chlorophenyl)-2*H*-indazole-7-carboxamide (**B2**)**

15 **Step 1: Methyl 2-(3-chlorophenyl)-2*H*-indazole-7-carboxylate (**B1**)**

(**B1**) was prepared following the general procedure reported in Example 1 step 4 using methyl 3-formyl-2-nitrobenzoate and 3-chloroaniline and was used in the next step without further purification.  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ , 300K)  $\delta$  8.49 (1H, s), 8.13 (1H, d,  $J$  = 8.2 Hz), 8.01 (1H, s), 7.92 (1H, d,  $J$  = 8.2 Hz), 7.83 (1H, d,  $J$  = 7.5 Hz), 7.37 (1H, t,  $J$  = 7.5 Hz), 7.18 (1H, d,  $J$  = 7.5 Hz), 7.03 (1H, t,  $J$  = 8.2 Hz), 20 4.03 (3H, s). MS (ES)  $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}_2$  requires: 286:288, found: 287:289 ( $\text{M}+\text{H}$ ) $^+$ .

**Step 2: 2-(3-Chlorophenyl)-2*H*-indazole-7-carboxamide (**B2**)**

(**B2**) was prepared from (**B1**) following the general procedure reported for Example 1 step 5 and the crude was purified by reverse phase HPLC and the desired fractions were freeze dried to yield the 25 desired product (**B2**) as a white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ , 300K)  $\delta$  9.02 (1H, bs), 8.54 (1H, s), 8.32 (1H, d,  $J$  = 7.8 Hz), 7.95 (1H, s), 7.92 (1H, d,  $J$  = 8.0 Hz), 7.79 (1H, d,  $J$  = 7.8 Hz), 7.50 (1H, t, 8.0 Hz), 7.44 (1H, d,  $J$  = 8.0 Hz), 7.26 (1H, t,  $J$  = 7.8 Hz), 6.34 (1H, bs). MS (ES)  $\text{C}_{15}\text{H}_{10}\text{ClN}_3\text{O}$  requires: 271:273, found: 272:274 ( $\text{M}+\text{H}$ ) $^+$ .

30

**EXAMPLE 3**

**2-{4-[(Dimethylamino)methyl]phenyl}-2*H*-indazole-7-carboxamide (**C3**)**

**Step 1: Methyl 2-(4-formylphenyl)-2*H*-indazole-7-carboxylate (**C1**)**

To a solution of methyl 2*H*-indazole-7-carboxylate (1.0 eq., see WO2004/029050) in DMF (0.8 35 M) were added  $\text{K}_2\text{CO}_3$  (1.1 eq.) and 4-fluorobenzaldehyde (1.3 eq), and the reaction mixture was heated under MW conditions at 200 °C for 10 min. The reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine; dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the solvent gave (**C1**) which was purified by flash column chromatography from EtOAc: Petroleum Ether = 30:70 to 40:60.  $^1\text{H}$

NMR (400MHz, CDCl<sub>3</sub>, 300K) δ 10.08 (1H, s), 8.64 (1H, s), 8.20 (2H, d, J = 8.6 Hz), 8.16 (1H, d, J = 7.2 Hz), 8.05 (2H, d, J = 8.6 Hz), 7.96 (1H, d, J = 7.2 Hz), 7.21 (1H, t, J = 7.2 Hz), 4.06 (3H, s). MS (ES) C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> requires: 280, found: 281 (M+H)<sup>+</sup>.

5 **Step 2: Methyl 2-{4-[(Dimethylamino)methyl]phenyl}-2H-indazole-7-carboxylate (C2)**

(C1) was suspended in MeOH (0.1 M). Me<sub>2</sub>NH (8 eq., 2.0 M in MeOH) was added upon which the starting material dissolved. To this solution was added a solution of NaBH<sub>3</sub> (CN) (1.1 eq.) and ZnCl<sub>2</sub> (0.5 eq.) in MeOH (0.5 mL). The pH was adjusted to 6 with 1.25 M HCl in MeOH and the mixture stirred at RT for 3h. 6N HCl (0.1 mL) was added and the solvent was reduced in vacuo. Added sat. aq. NaHCO<sub>3</sub> 10 solution (5 mL) and the product extracted with DCM; dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave (C2) which was used in the next step without further purification. MS (ES) C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> requires: 309, found: 310 (M+H)<sup>+</sup>.

**Step 3: 2-{4-[(Dimethylamino)methyl]phenyl}-2H-indazole-7-carboxamide (C3)**

15 (C2) was heated in 7N NH<sub>3</sub> in MeOH (0.1 M) in a sealed tube overnight at 50°C. The solvents were reduced in vacuo and the residue was purified by flash column chromatography (DCM : MeOH = 90:10). <sup>1</sup>H NMR (300MHz, CD<sub>3</sub>CN, 300K) δ 8.85 (1H, s), 8.78 (1H, bs), 8.17 (1H, d, J = 8.0 Hz), 8.05-8.00 (3H, m), 7.56 (2H, d, J = 8.4 Hz), 7.28 (1H, t, J = 8.0 Hz), 6.36 (1H, bs), 3.56 (2H, s), 2.28 (6H, s). MS (ES) C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O requires: 294, found: 295 (M+H)<sup>+</sup>.

20

**EXAMPLE 4**

**2-{4-[(N,N-Dimethylglycyl)amino]phenyl}-2H-indazole-7-carboxamide (D4)**

**Step 1: Methyl 2-(4-nitrophenyl)-2H-indazole-7-carboxylate (D1)**

25 (D1) was prepared following the general procedure reported in Example 3 step 1 using 4-fluoronitrobenzene and the crude was purified by flash column chromatography from EtOAc: Petroleum Ether = 10:90 to 50:50. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>, 300K) δ 8.65 (1H, s), 8.44 (2H, d, J = 8.6 Hz), 8.23 (1H, d, J = 8.6 Hz), 8.19 (2H, d, J = 7.2 Hz), 7.98 (1H, d, J = 8.4 Hz), 7.24 (1H, m overlapped to solvent signal), 4.08 (3H, s). MS (ES) C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub> requires: 297, found: 298 (M+H)<sup>+</sup>.

30

**Step 2: 2-(4-Nitrophenyl)-2H-indazole-7-carboxamide (D2)**

(D2) was prepared following the general procedure reported in Example 3 step 3 and was used in the next step without further purification. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>, 300K) δ 9.52 (1H, s), 8.52-8.45 (5H, m), 8.10 (1H, d, J = 6.9 Hz), 8.05 (1H, d, J = 8.2 Hz), 7.94 (1H, bs), 7.30 (1H, dd, J = 8.2, 6.9 Hz). 35 MS (ES) C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub> requires: 282, found: 283 (M+H)<sup>+</sup>.

**Step 3: 4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzenaminium chloride (D3)**

To a suspension of (D2) in MeOH (0.1M) Pd/C (10% w/w) and 6N HCl solution (1.0 eq.) were added. The reaction mixture was stirred under hydrogen atmosphere at RT for 8 h. To the suspension 1.25 M HCl in MeOH was added and then the catalyst was filtered off through a pad of celite. The solvent was reduced in vacuo and the crude used in the next step without further purification. <sup>1</sup>H NMR (400MHz, DMSO-d6, 300K) δ 9.22 (1H, s), 8.56 (1H, bs), 8.08 (2H, d, J = 8.6 Hz), 8.05 (1H, d, J = 6.9 Hz), 8.01 (1H, d, J = 8.2 Hz), 7.87 (1H, bs), 7.30-7.23 (3H, m). MS (ES) C<sub>14</sub>H<sub>13</sub>ClN<sub>4</sub>O requires: 252, found: 253 (M+H)<sup>+</sup>.

**10 Step 4: 2-{4-[(N,N-Dimethylglycyl)amino]phenyl}-2H-indazole-7-carboxamide (D4)**

To a solution of N,N-dimethylglycine (1.5 eq.) in DMF (0.1M) HATU (1.5 eq.) and Et<sub>3</sub>N (1.5 eq.) were added and stirring was continued at RT for 30 min. Then, a solution of (D3) (1.0 eq.) and Et<sub>3</sub>N (1.0 eq.) in DMF (0.1M) was added and the reaction mixture was stirred for overnight at RT. Solvent was reduced in vacuo, the residue portioned between EtOAc and sat. aq. NaHCO<sub>3</sub> solution. Organic phase was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Crude was purified by flash column chromatography (DCM : MeOH = 95:5). <sup>1</sup>H NMR (400MHz, DMSO-d6, 300K) δ 10.01 (1H, bs), 9.25 (1H, s), 8.57 (1H, bs), 8.10 (2H, d, J = 9.0 Hz), 8.05 (1H, d, J 6.9 = Hz), 8.01 (1H, d, J = 8.2 Hz), 7.92 (2H, d, J = 9.0 Hz), 7.86 (1H, bs), 7.26 (1H, dd, J = 8.2, 6.9 Hz), 3.12 (2H, s), 2.30 (6H, s). MS (ES) C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub> requires: 337, found: 338 (M+H)<sup>+</sup>.

20

The following Examples were prepared according to the methods of Examples 1-4.

Example	Name	MWt	(M+H) <sup>+</sup>	Procedure of Example
5	2-benzyl-2H-indazole-7-carboxamide	251	252	1
6	2-(4-Chlorophenyl)-2H-indazole-7-carboxamide	271, 273	272, 274	2
7	2-(2-Chlorophenyl)-2H-indazole-7-carboxamide	271, 273	272, 274	2
8	{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N,N-dimethylmethanaminium chloride	294	295	3

Example	Name	MWt	(M+H) <sup>+</sup>	Procedure of Example
9	2-{4-[(4-Methylpiperazin-1-yl)methyl]phenyl}-2H-indazole-7-carboxamide	349	350	3
10	2-[4-(Morpholin-4-ylmethyl)phenyl]-2H-indazole-7-carboxamide	336	337	3
11	2-{4-[(Methylamino)methyl]phenyl}-2H-indazole-7-carboxamide	280	281	3
12	2-[4-(pyrrolidin-1-ylmethyl)phenyl]-2H-indazole-7-carboxamide	320	321	3
13	2-[4-(piperidin-1-ylmethyl)phenyl]-2H-indazole-7-carboxamide	334	335	3

#### EXAMPLE 14

#### 4-[(4-[(7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino)methyl]pyridinium trifluoroacetate (E3)

5

##### Step 1: 2-(4-Formylphenyl)-2H-indazole-7-carboxamide (E1)

(E1) was prepared following the general procedure reported in Example 3 step 1 using 2H-indazole-7-carboxamide and 4-fluorobenzaldehyde and the crude was purified by precipitation from MeOH/EtOAc. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 10.10 (s, 1H), 9.50 (s, 1H), 8.52 (br. s, 1H), 8.45 (d, J = 8.6 Hz, 2H), 8.15 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 7.2 Hz, 1H), 8.04 (d, J = 7.2 Hz, 1H), 7.92 (br. s, 1H), 7.30 (t, J = 7.0 Hz, 1H). MS (ES<sup>+</sup>) C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub> requires: 265, found: 266 (M+H)<sup>+</sup>.

##### Step 2: 4-[(7-(Aminocarbonyl)-2H-indazol-2-yl]benzoic acid (E2)

To a solution of (E1) (1.0 eq.) in *t*-BuOH/H<sub>2</sub>O (5:1, 0.2 M) was added 2-methyl-2-butene (10 eq., 2.0 M in THF) in THF, then NaH<sub>2</sub>PO<sub>4</sub> (7.0 eq.) followed by the addition of NaClO<sub>2</sub> (7.0 eq.) and the resulting mixture was stirred at RT O/N. Solvents were reduced under reduced pressure and (E2) was isolated by precipitation from 3N HCl. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 9.45 (s, 1H), 8.52 (br. s, 1H), 8.32 (d, J = 8.6 Hz, 2H), 8.16 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 7.7 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.92 (br. s, 1H), 7.30 (t, J = 7.0 Hz, 1H). MS (ES<sup>-</sup>) C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub> requires: 281, found: 280 (M-H)<sup>-</sup>.

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##### Step 3: 4-[(4-[(7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino)methyl]pyridinium trifluoroacetate (E3)

(**E2**) (1.0 eq.), HATU (1.5 eq.), Et<sub>3</sub>N (1.5 eq.) were dissolved in DMF and the mixture was left 30 min under stirring at RT. Then, 1-pyridin-4-ylmethanamine (1.5 eq.) was added and the mixture left under stirring O/N. Evaporation of the solvent gave a residue which was purified by reverse phase HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents, the desired fractions were 5 lyophilized to afford the titled compound (**E3**). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.45 (s, 1H), 9.42 (t, J = 5.8 Hz, 1H), 8.71 (d, J = 5.6 Hz, 2H), 8.54 (br. s, 1H), 8.34 (d, J = 8.6 Hz, 2H), 8.16 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 6.8 Hz, 1H), 8.04 (d, J = 6.8 Hz, 1H), 7.91 (br. s, 1H), 7.71 (d, J = 5.3 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 4.68 (d, J = 5.5 Hz, 2H). MS (ES) C<sub>21</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub> requires: 371, found: 372 (M+H)<sup>+</sup>.

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### EXAMPLE 15

#### 2-{4-[1-(Methylamino)ethyl]phenyl}-2H-indazole-7-carboxamide (F2)

##### Step 1: 2-(4-Acetylphenyl)-2H-indazole-7-carboxamide (F1)

(**F1**) was prepared following the general procedure reported in Example 3 step 1 using 2H-indazole-7-carboxamide and 1-(4-fluorophenyl)ethanone and was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 9.48 (s, 1H), 8.53 (br. s, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.09 (dd, J = 6.8, 0.8 Hz, 1H), 8.05 (dd, J = 8.4, 0.8 Hz, 1H), 7.92 (br. s, 1H), 7.30 (dd, J = 8.4, 7.2 Hz, 1H), 2.66 (s, 3H). MS (ES<sup>+</sup>) C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> requires: 279, found: 280 (M+H)<sup>+</sup>.

20

##### Step 2: 2-{4-[1-(Methylamino)ethyl]phenyl}-2H-indazole-7-carboxamide (F2)

(**F2**) was prepared following the general procedure reported in Example 3 step 2 using MeNH<sub>2</sub>.HCl and the crude was purified using an IST ISOLUTE<sup>®</sup> SPE column SCX, loading the reaction mixture as a MeOH solution and then eluting the desired compound with 3N NH<sub>3</sub> in MeOH. The titled compound was isolated after evaporation of the solvent under reduced pressure. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 300K) δ 9.05 (br. s, 1H), 8.49 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.46 (br. s, 1H), 3.77 (m, 1H), 2.56 (br. s, 1H), 2.35 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H). MS (ES<sup>+</sup>) C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O requires: 294, found: 295 (M+H)<sup>+</sup>.

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### EXAMPLE 16

#### N-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}cyclohexanaminium trifluoroacetate (G1)

To MP-Triacetoxyborohydride (5 eq, loading 2.5 mmol/g) a solution of Example 14, (**E1**) (1 eq) in DMF was added followed by cyclohexanamine (1.03 eq.) in DMF. The mixture was heated in the MW (10 min, 80 °C) and then purified by RP-HPLC (column Atlantis dC18 5μm, gradient A: H<sub>2</sub>O + 0.1% TFA; B: MeCN + 0.1% TFA) and the desired fractions were evaporated under reduced pressure to yield the desired compound. <sup>1</sup>H NMR (400 MHz, DMSO<sub>d</sub><sub>6</sub>, 300K) δ 9.35 (s, 1H), 8.77 (br. s, 2H), 8.53 (br. s, 1H), 8.26 (d, J = 8.6 Hz, 2H), 8.06 (d, J = 7.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.88 (bs, 1H), 7.73 (d, J

= 8.6 Hz, 2H), 7.28 (t, J = 7.1 Hz, 1H), 4.30-4.24 (m, 2H), 3.04 (br. s, 1H), 2.15-2.08 (m, 2H), 1.82-1.74 (m, 2H), 1.65-1.57 (m, 1H) 1.40-1.05 (m, 5H). MS (ES<sup>+</sup>) C<sub>21</sub>H<sub>24</sub>N<sub>4</sub>O requires: 348, found: 349 (M+H)<sup>+</sup>.

### EXAMPLE 17

5 **{4-[7-(aminocarbonyl)-4-chloro-2H-indazol-2-yl]phenyl}-N-methylmethanaminium trifluoroacetate (H5)**

**Step 1: Methyl 2-amino-4-chloro-3-methylbenzoate (H1)**

To a solution of 2-amino-4-chloro-3-methylbenzoic acid (1.0 eq., from Butt Park Ltd.) and 10 cesium carbonate (1.5 eq.) in DMF (0.25 M) at RT was added methyl iodide (1.0 eq.). After the mixture was stirred for 18 h, brine was added and the mixture was extracted with EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The yellow solid (**H1**) was used in the next step without further purification. <sup>1</sup>H NMR (400MHz, DMSO, 300K) δ 7.29 (1H, d, J = 8.6 Hz), 6.50 (2H, brs), 6.32 (1H, d, J = 8.6 Hz), 3.78 (3H, s), 2.17 (3H, s). MS (ES) C<sub>9</sub>H<sub>10</sub>ClNO<sub>2</sub> requires: 199, found: 168 (M-OCH<sub>3</sub>)<sup>+</sup>.  
15

**Step 2: Methyl 4-chloro-1H-indazole-7-carboxylate (H2)**

To a solution of the ester (**H1**) (1.0 eq.) in chloroform (0.02 M) was added Ac<sub>2</sub>O (2.3 eq.) and the mixture was stirred for two hours at RT. Then KOAc (0.3 eq.) and isoamyl nitrite (2.2 eq.) were added 20 and the solution was heated at reflux for 18 h. The mixture was cooled to RT and diluted with DCM. The organic phase was washed carefully with sat. aq. NaHCO<sub>3</sub> solution and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave (**H2**) as a brown solid which was used in the next step without purification. MS (ES) C<sub>9</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>2</sub> requires: 210, found: 211 (M+H)<sup>+</sup>.

25 **Step 3: 4-Chloro-1H-indazole-7-carboxamide (H3)**

A mixture of (**H2**) (1.0 eq.) and KOH (1.3 eq.) in dioxane/water (0.1 M) was stirred for 12 h at RT. Solvents were removed under reduced pressure. The carboxylic acid was dissolved in DMF (0.1 M) and TBTU (1.5 eq.) was added. After 15 min DIPEA (2.0 eq.) and ammonia (3.0 eq., 0.5 M in THF) were added and the solution was stirred for 36 h. The mixture was diluted with EtOAc and then the organic 30 phase was washed with sat. aq. NaHCO<sub>3</sub> solution and brine. Evaporation of the solvent gave (**H3**) as a yellow solid which was used in the next step without purification. <sup>1</sup>H NMR (300MHz, DMSO, 300K) δ 13.38 (1H, br. s), 8.19 (2H, br. s), 7.89 (1H, d, J = 7.9 Hz), 7.56 (1H, br. s), 7.27 (1H, d, J = 7.9 Hz). MS (ES) C<sub>8</sub>H<sub>6</sub>ClN<sub>3</sub>O requires: 195, found: 196 (M+H)<sup>+</sup>.

35 **Step 4: 4-Chloro-2-(4-formylphenyl)-2H-indazole-7-carboxamide (H4)**

(**H4**) was prepared following the procedure reported in Example 3 step 1. The reaction mixture was poured in water and the precipitation was filtered, washed with water and dried in vacuo. The yellow solid was used in the next step without purification. <sup>1</sup>H NMR (300MHz, DMSO, 300K) δ 10.09 (1H, s),

9.61 (1H, s), 8.51 (2H, d,  $J$  = 8.3 Hz), 8.37 (1H, br. s), 8.13 (2H, d,  $J$  = 8.3 Hz), 8.02 (1H, d,  $J$  = 7.5 Hz), 7.98 (1H, br. s), 7.38 (1H, d,  $J$  = 7.5 Hz). MS (ES)  $C_{15}H_{10}ClN_3O_2$  requires: 299, found: 300 ( $M+H$ )<sup>+</sup>.

**Step 5: {4-[7-(aminocarbonyl)-4-chloro-2*H*-indazol-2-yl]phenyl}-*N*-methylmethanaminium trifluoroacetate (H5)**

(H5) was prepared following the procedure reported in Example 3 step 2. After purification by preparative RP-HPLC (column: C18), using  $H_2O$  (0.1% TFA) and MeCN (+0.1% TFA) as eluents, the desired fractions were lyophilized to afford the titled compound (H5) as a yellow solid. <sup>1</sup>H NMR (300MHz, DMSO, 300K)  $\delta$  9.51 (1H, s), 8.87 (2H, brs), 8.39 (1H, brs), 8.35 (2H, d,  $J$  = 8.6 Hz), 8.02 (1H, d,  $J$  = 7.6 Hz), 7.98 (1H, brs), 7.71 (2H, d,  $J$  = 8.6 Hz), 7.38 (1H, d,  $J$  = 7.6 Hz), 4.23 (2H, s), 2.16 (3H, s). MS (ES)  $C_{16}H_{15}ClN_4O$  requires: 314, found: 315 ( $M+H$ )<sup>+</sup>.

**EXAMPLE 18**

**2-Phenyl-2*H*-1,2,3-benzotriazole-4-carboxamide (I4)**

**Step 1: Methyl 2,3-diaminobenzoate (I1)**  
A mixture of 2-amino-3-nitro-benzoic acid methyl ester (1.0 eq., from CHESS GmbH) and Pd/C (10% w/w) in MeOH (0.25 M) was stirred for 3 d at RT under  $H_2$  atmosphere (1 atm). The mixture was filtered through Celite® and then the solvent was evaporated under reduced pressure. The red solid (I1) was used in the next step without further purification. <sup>1</sup>H NMR (300MHz,  $CDCl_3$ , 300K)  $\delta$  7.46 (1H, dd,  $J$  = 8.1 Hz, 1.4 Hz), 6.84 (1H, dd,  $J$  = 7.5 Hz, 1.4 Hz), 6.59 (1H, dd,  $J$  = 8.1 Hz, 7.5 Hz), 3.87 (3H, s). MS (ES)  $C_8H_{10}N_2O_2$  requires: 166, found: 167 ( $M+H$ )<sup>+</sup>.

**Step 2: Methyl 3-amino-2-[phenyldiazenyl]benzoate (I2)**

A mixture of (I1) (1.0 eq.) and nitrosobenzene (1.1 eq.) in AcOH (0.1 M) was stirred for 3 h at RT. Evaporation of the solvent gave (I2) as a yellow solid which was used in the next step without purification. MS (ES)  $C_{14}H_{13}N_3O_2$  requires: 255, found: 256 ( $M+H$ )<sup>+</sup>.

**Step 3: Methyl 2-phenyl-2*H*-1,2,3-benzotriazole-4-carboxylate (I3)**

A mixture of (I2) (1.0 eq.) and copper (II) acetate (1.0 eq.) in DMF (0.4 M) was stirred for 90 min at 80°C while oxygen was bubbled through this solution. The mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine and dried ( $Na_2SO_4$ ). Evaporation of the solvent gave (I3) as a yellow oil which was used in the next step without purification. MS (ES)  $C_{14}H_{11}N_3O_2$  requires: 253, found: 276 ( $M+Na$ )<sup>+</sup>.

**Step 4: 2-Phenyl-2*H*-1,2,3-benzotriazole-4-carboxamide (I4)**  
A mixture of (I3) (1.0 eq.) and NaOH (1.5 eq.) in dioxane/water (0.1 M) was stirred for 5 h at RT. Solvents were removed under reduced pressure. The carboxylic acid was dissolved in DMF (0.1 M)

and HATU (1.5 eq.) was added. After 15 min DIEA (2.0 eq.) and ammonia (3.0 eq., 0.5 M in THF) were added and the mixture was stirred for 36 h. The mixture was diluted with EtOAc and then the organic phase was washed with sat. aq. NaHCO<sub>3</sub> solution and brine. Evaporation of the solvent gave a crude which was purified by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**I4**) as a yellow solid. <sup>1</sup>H NMR (300MHz, DMSO, 300K) δ 8.44 (2H, d, J = 8.0 Hz), 8.25 (1H, d, J = 8.5 Hz), 8.12 (2H, d, J = 7.1 Hz), 8.03 (1H, br. s), 7.72-7.56 (4H, m). MS (ES) C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>O requires: 238, found: 239 (M+H)<sup>+</sup>.

### EXAMPLE 19

#### 2-Benzyl-2H-1,2,3-benzotriazole-4-carboxamide (J3)

##### Step 1: Methyl 1H-1,2,3-benzotriazole-7-carboxylate (J1)

To a solution of Example 18, (**I1**) (1.0 eq.) in AcOH (0.4 M) at 0°C was slowly added NaNO<sub>2</sub> (1.1 eq.) in water (6 M). After 1 h the suspension was filtered and the precipitation was washed with water. The white solid (**J1**) was dried in vacuo and was used in the next step without further purification. <sup>1</sup>H NMR (300MHz, DMSO, 300K) δ 15.91 (1H, br. s), 8.36 (1H, d, J = 7.9 Hz), 8.10 (1H, d, J = 6.9 Hz), 7.50 (1H, dd, J = 7.9 Hz, 6.9 Hz), 3.92 (3H, s). MS (ES) C<sub>8</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> requires: 177, found: 178 (M+H)<sup>+</sup>.

##### Step 2: Methyl 2-benzyl-2H-1,2,3-benzotriazole-4-carboxylate (J2)

To a solution of (**J1**) and Cs<sub>2</sub>CO<sub>3</sub> (3.0 eq.) in DMF (0.1 M) was added benzyl bromide (1.2 eq.) and the mixture was stirred for 1 h at 80°C. The reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed under reduced pressure and the residue purified by flash column chromatography on silica using a gradient of EtOAc/Petroleum ether from 0:100 to 60:40 to yield the desired triazole (**J2**) as a white solid. MS (ES) C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> requires: 267, found: 268 (M+H)<sup>+</sup>.

##### Step 3: 2-Benzyl-2H-1,2,3-benzotriazole-4-carboxamide (J3)

(**J3**) was prepared from (**J2**) following the general procedure reported for Example 1 step 6. After purification by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents, the desired fractions were lyophilized to afford the titled compound (**J3**) as a white solid. <sup>1</sup>H NMR (400MHz, DMSO, 300K) δ 8.14 (1H, d, J = 8.6 Hz), 8.04 (1H, d, J = 7.0 Hz), 7.97 (1H, br. s), 7.94 (1H, br. s), 7.56 (1H, dd, J = 8.6 Hz, 7.0 Hz), 7.46-7.31 (5H, m), 6.05 (2H, s). MS (ES) C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O requires: 252, found: 253 (M+H)<sup>+</sup>.

**Step 1: methyl 3-((E)-{[3-(1,3-dioxolan-2-yl)phenyl]imino}methyl)-2-nitrobenzoate (K1)**

(K1) was prepared following the general procedure reported for Example 1 step 4 using methyl 3-formyl-2-nitrobenzoate (A3) and 3-aminobenzaldehyde ethylene acetal until TLC revealed completion of the reaction (Petroleum ether:EtOAc = 85:15) and was used in the next step without further purification.

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**Step 2: methyl 2-[3-(1,3-dioxolan-2-yl)phenyl]-2H-indazole-7-carboxylate (K2)**

(K2) was prepared following the general procedure reported for Example 1 step 5 and the crude was purified by flash column chromatography on silica using a gradient of 10-20% EtOAc/Petroleum ether 10 to yield the desired (K2) as an orange oil. MS (ES) C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> requires: 324, found: 325 (M+H)<sup>+</sup>.

**Step 3: methyl 2-(3-formylphenyl)-2H-indazole-7-carboxylate (K3)**

(K2) was stirred in a mixture of DCM:TFA:H<sub>2</sub>O (8:1:1, 0.1M) for 1 hr at RT. Evaporation of the solvent under reduced pressure yielded the desired (K3) as brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 300K) 15 δ 10.13 (1H, s), 8.63 (1H, s), 8.45 (1H, s), 8.34 (1H, d, J = 8.1 Hz), 8.16 (1H, d, J = 6.8 Hz), 7.98 (1H, d, J = 8.3 Hz), 7.96 (1H, d, J = 7.6 Hz), 7.73 (1H, t, J = 7.8 Hz), 7.30 (1H, dd, J = 8.3, 7.3 Hz), 4.06 (3H, s). MS (ES) C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> requires: 280, found: 281 (M+H)<sup>+</sup>.

**Step 4: methyl 2-{3-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxylate (K4)**

20 (K4) was prepared as described in Example 3 step 2 and the crude product was used in the next step without further purification. MS (ES) C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> requires: 295, found: 296 (M+H)<sup>+</sup>.

**Step 5: 2-{3-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide (K5)**

(K5) was prepared as described in Example 3 step 3 and the crude product was purified by 25 preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (K5) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 9.32 (1H, s), 8.96 (1H, br. s), 8.54 (1H, br. s), 8.33 (1H, s), 8.20 (1H, d, J = 8.0 Hz), 8.09 (1H, d, J = 7.1 Hz), 8.05 (1H, d, J = 8.2 Hz), 7.98 (1H, br. s), 7.71 (1H, t, J = 8.0 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.30 (1H, dd, J = 8.2, 7.1 Hz), 4.30 (2H, s), 2.64 (3H, s). MS (ES) C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O requires: 30 280, found: 281 (M+H)<sup>+</sup>.

**EXAMPLE 21****4-({3-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino)piperidinium trifluoroacetate****35 Step 1: methyl 3-((E)-{[3-(tert-butoxycarbonyl)phenyl]imino}methyl)-2-nitrobenzoate (L1)**

(L1) was prepared following the general procedure reported for Example 1 step 4 using methyl 3-formyl-2-nitrobenzoate (A3) and *tert*-butyl 3-aminobenzoate until TLC revealed completion of the reaction (Petroleum ether:EtOAc = 85:15) and was used in the next step without further purification.

**Step 2: methyl 2-[3-(*tert*-butoxycarbonyl)phenyl]-2H-indazole-7-carboxylate (L2)**

(**L2**) was prepared following the general procedure reported for Example 1 step 5 and the crude was purified by flash column chromatography on silica using a gradient of 10-20% EtOAc/Petroleum ether 5 to yield the desired (**L2**) as an orange solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 300K)  $\delta$  8.61 (1H, s), 8.49 (1H, s), 8.29 (1H, d,  $J$  = 8.1 Hz), 8.15 (1H, d,  $J$  = 6.8 Hz), 8.04 (1H, d,  $J$  = 7.8 Hz), 7.97 (1H, d,  $J$  = 8.3 Hz), 7.60 (1H, t,  $J$  = 7.9 Hz), 7.21 (1H, t,  $J$  = 7.7 Hz), 4.06 (3H, s), 1.64 (9H, s). MS (ES)  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$  requires: 352, found: 353 ( $\text{M}+\text{H}$ ) $^+$ .

10 **Step 3: *tert*-butyl 3-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoate (L3)**

(**L3**) was prepared as described in Example 3 step 3 and the crude product was used in the next step without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 300K)  $\delta$  9.10 (1H, br. s), 8.61 (1H, s), 8.47 (1H, s), 8.32 (1H, d,  $J$  = 7.1 Hz), 8.13 (1H, d,  $J$  = 8.1 Hz), 8.07 (1H, d,  $J$  = 7.6 Hz), 7.93 (1H, d,  $J$  = 8.3 Hz), 7.63 (1H, t,  $J$  = 7.9 Hz), 7.28 (1H, dd,  $J$  = 8.1, 7.3 Hz), 6.26 (1H, br. s), 1.65 (9H, s). MS (ES) 15  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3$  requires: 337, found: 338 ( $\text{M}+\text{H}$ ) $^+$ .

**Step 4: 3-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoic acid (L4)**

(**L3**) was stirred in a mixture of DCM:TFA (9:1, 0.1M) at RT overnight. The solvent was evaporated under reduced pressure, the residue taken up with EtOAc, washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) 20 and concentrated under reduced pressure affording (**L4**) as a pale brown solid which was used in the next step without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ , 300K)  $\delta$  9.45 (1H, s), 8.62 (1H, s), 8.53 (1H, br. s), 8.44 (1H, d,  $J$  = 8.1 Hz), 8.10-8.00 (3H, m), 7.91 (1H, br. s), 7.77 (1H, t,  $J$  = 7.9 Hz), 7.29 (1H, dd,  $J$  = 8.1, 7.1 Hz). MS (ES)  $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$  requires: 295, found: 296 ( $\text{M}+\text{H}$ ) $^+$ .

25 **Step 5: *tert*-butyl 4-({3-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino) piperidine-1-carboxylate (L5)**

(**L5**) was prepared as described in Example 4, step 4 and the crude product was purified by preparative RP-HPLC (column: C18), using  $\text{H}_2\text{O}$  (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**L5**) as a white solid. MS (ES) 30  $\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_4$  requires: 463, found: 464 ( $\text{M}+\text{H}$ ) $^+$ .

**Step 6: 4-({3-[7-(aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino)piperidinium trifluoroacetate (L6)**

(**L5**) was stirred in a mixture of MeCN:TFA = 9:1 (0.1M) for 24 hr at RT. Solvent was evaporated under reduced pressure, the residue dissolved in a mixture of MeCN: $\text{H}_2\text{O}$  = 1:1 and 35 lyophilized to afford the title compound (**L6**) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ , 300K)  $\delta$  9.38 (1H, s), 8.69 (1H, d,  $J$  = 7.3 Hz), 8.60 (1H, br. s), 8.57-8.51 (2H, m), 8.40 (1H, br. s), 8.34 (1H, d,  $J$  = 8.1 Hz), 8.09 (1H, d,  $J$  = Hz), 8.05 (1H, d,  $J$  = 7.1 Hz), 7.97 (1H, d,  $J$  = 8.3 Hz), 7.92 (1H, br. s), 7.73 (1H, t,  $J$  = 7.9 Hz), 7.29 (1H, dd,  $J$  = 8.3, 7.2 Hz), 4.18-4.06 (1H, m), 3.40-3.28 (2H, m overlapped to  $\text{H}_2\text{O}$

signal), 3.14-2.98 (2H, m), 2.09-1.99 (2H, m), 1.83-1.69 (2H, m). MS (ES)  $C_{20}H_{21}N_5O_2$  requires: 363, found: 364 ( $M+H$ )<sup>+</sup>.

The following examples were prepared according to the methods of the previous examples.

5

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
22	{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylmethanaminium chloride	280	281	3
23	2-{3-Chloro-4-[(dimethylamino)methyl]phenyl}-2H-indazole-7-carboxamide	328	329	3
24	1-[2-(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]-2-oxoethyl]-4-methylpiperazin-1-ium trifluoroacetate	392	393	4
25	2-(4-[(4-Pyrrolidin-1-ylpiperidin-1-yl)acetyl]amino)phenyl)-2H-indazole-7-carboxamide	446	447	4
26	2-{4-[(Pyrrolidin-1-ylacetyl)amino]phenyl}-2H-indazole-7-carboxamide	363	364	4
27	2-{4-[(Piperidin-1-ylacetyl)amino]phenyl}-2H-indazole-7-carboxamide	377	378	4
28	2-{4-[(Morpholin-4-ylacetyl)amino]phenyl}-2H-indazole-7-carboxamide	379	380	4
29	4-[2-(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]-2-oxoethyl]morpholin-4-ium chloride	379	380	4
30	2-{4-[(Ethylamino)methyl]phenyl}-2H-indazole-7-carboxamide	294	295	3
31	2-{4-[(Isopropylamino)methyl]phenyl}-2H-indazole-7-carboxamide	308	309	3
32	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}propan-2-aminium chloride	308	309	3

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
33	2-(4-{{(2-Fluoroethyl)amino]methyl}phenyl)-2H-indazole-7-carboxamide	312	313	3
34	2-(4-{{(2,2-Difluoroethyl)amino]methyl}phenyl)-2H-indazole-7-carboxamide	330	331	3
35	2-{{4-[(Cyclopropylamino)methyl]phenyl}-2H-indazole-7-carboxamide	306	307	3
36	4-{{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzoyl}-1,4-diazepan-1-ium trifluoroacetate	363	364	5
37	2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino)-N,N-dimethylethanaminium trifluoroacetate	351	352	5
38	4-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzoyl}amino)methyl]piperidinium trifluoroacetate	377	378	5
39	N-{{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-N,N',N'-trimethylethane-1,2-diaminium dichloride	351	352	3
40	4-{{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzoyl}-1-methylpiperazin-1-ium trifluoroacetate	363	364	5
41	3-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]azetidinium trifluoroacetate	335	336	4
42	(2S)-2-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylpyrrolidinium trifluoroacetate	363	364	4
43	3-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylpiperidinium trifluoroacetate	377	378	4
44	4-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]-1-methylpiperidinium trifluoroacetate	377	378	4

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
45	4-( $\{4-[7-(\text{Aminocarbonyl})-2H-\text{indazol-2-yl}]benzoyl\}\text{amino}$ )-1-benzylpiperidinium trifluoroacetate	453	454	5
46	2-{4-[ $(\text{Pyridin-4-yl})\text{amino}$ ]carbonyl}phenyl}-2H-indazole-7-carboxamide	357	358	5
47	2-{4-[ $(4-\text{Phenyl})\text{piperazin-1-yl}$ ]carbonyl}phenyl}-2H-indazole-7-carboxamide	425	426	5
48	2-(4-{ $[\text{Methyl}(\text{quinoxalin-6-ylmethyl})\text{amino}]$ carbonyl}phenyl)-2H-indazole-7-carboxamide	436	437	5
49	2-(4-Formylphenyl)-2H-indazole-7-carboxamide	265	266	5
50	1-[2-( $\{4-[7-(\text{Aminocarbonyl})-2H-\text{indazol-2-yl}]benzoyl\}\text{amino}$ )ethyl]pyrrolidinium trifluoroacetate	377	378	5
51	1-[2-( $\{4-[7-(\text{Aminocarbonyl})-2H-\text{indazol-2-yl}]benzoyl\}\text{amino}$ )ethyl]piperidinium trifluoroacetate	391	392	5
52	4-[2-( $\{4-[7-(\text{Aminocarbonyl})-2H-\text{indazol-2-yl}]benzoyl\}\text{amino}$ )ethyl]morpholin-4-ium trifluoroacetate	393	394	5
53	4-( $\{4-[7-(\text{Aminocarbonyl})-2H-\text{indazol-2-yl}]benzoyl\}\text{amino}$ )-1-methylpiperidinium trifluoroacetate	377	378	5
54	2-[4-[ $(4-\text{methylpiperazin-1-yl})\text{methyl}$ ]-3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide	417	418	3
55	2-[4-[ $(\text{methylamino})\text{methyl}$ ]-3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide	348	349	3
56	1-{4-[ $7-(\text{aminocarbonyl})-2H-\text{indazol-2-yl}]phenyl\}$ -N-methylethanaminium chloride	294	295	6

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
57	2-[4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide	388	389	3
58	2-[4-(piperidin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide	402	403	3
59	2-[4-[(ethylamino)methyl]-3-(trifluoromethyl)phenyl]-2H-indazole-7-carboxamide	362	363	3
60	4-{4-[7-(Aminocarbonyl)-4-chloro-2H-indazol-2-yl]benzyl}-1-methylpiperazin-1-ium trifluoroacetate	383	384	8
61	1-[2-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]ethyl]piperidinium bis(trifluoroacetate)	377	378	7
62	4-[2-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]ethyl]morpholin-4-ium bis(trifluoroacetate)	379	380	7
63	1-[2-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio]ethyl]pyrrolidinium bis(trifluoroacetate)	363	364	7
64	4-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio)-1-methylpiperidinium bis(trifluoroacetate)	363	364	7
65	4-(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio)-1-benzylpiperidinium bis(trifluoroacetate)	439	440	7
66	1-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-phenylpiperazinium bis(trifluoroacetate)	411	412	7
67	<i>N</i> -{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-(dimethylamino)-2-oxoethanaminium trifluoroacetate	351	352	7

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
68	2-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]pyridinium bis(trifluoroacetate)	357	358	7
69	4-[(4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]pyridinium bis(trifluoroacetate)	357	358	7
70	<i>N</i> -{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-methylpropan-2-aminium trifluoroacetate	322	323	7
71	<i>N</i> <sup>+</sup> -{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}- <i>N,N</i> -dimethylethane-1,2-diaminium bis(trifluoroacetate)	337	338	7
72	{4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl}- <i>N</i> -(1,3-oxazol-2-ylmethyl)methanaminium trifluoroacetate	347	348	7

**EXAMPLE 73****7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium chloride (M1)**

5 (M1) was obtained following the general procedure reported in Example 1. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 9.54 (2H, br. s), 9.30 (1H, s), 8.43 (1H, br. s), 8.05-7.98 (4H, m), 7.90 (1H, br. s), 7.47 (1H, d, J = 8.3 Hz), 7.27 (1H, dd, J = 8.2, 7.2 Hz), 4.45-4.35 (2H, m), 3.47-3.37 (2H, m), 3.14-3.04 (2H, m). MS (ES) C<sub>17</sub>H<sub>17</sub>ClN<sub>4</sub>O requires: 292, found: 293 (M+H)<sup>+</sup>.

10

**EXAMPLE 74****6-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium chloride (N1)**

15 (N1) was obtained following the general procedure reported in Example 1. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 9.43-9.28 (3H, m), 8.53 (1H, br. s), 8.12-8.00 (4H, m), 7.89 (1H, br. s), 7.48 (1H, d, J = 8.3 Hz), 7.28 (1H, dd, J = 8.2, 7.2 Hz), 4.40-4.33 (2H, m), 3.55-3.35 (2H, m overlapped to the H<sub>2</sub>O signal), 3.20-3.12 (2H, m). MS (ES) C<sub>17</sub>H<sub>17</sub>ClN<sub>4</sub>O requires: 292, found: 293 (M+H)<sup>+</sup>.

**EXAMPLE 75****5-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate (O1)**

20

(**O1**) was obtained following the general procedure reported in Example 1. The crude product was purified by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**O1**) as a white powder.

5 <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 9.30-9.10 (2H, m), 8.90 (1H, s), 8.38 (1H, br. s), 8.13-8.03 (2H, m), 7.90 (1H, br. s), 7.64-7.48 (3H, m), 7.32 (1H, dd, J = 8.2, 7.2 Hz), 4.48-4.38 (2H, m), 3.40-3.28 (2H, m partially overlapped to the H<sub>2</sub>O signal), 2.90-2.80 (2H, m). MS (ES) C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub> requires: 292, found: 293 (M+H)<sup>+</sup>.

10

### EXAMPLE 76

#### 3-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]azetidinium trifluoroacetate (P4)

##### Step 1: 5-Fluoro-2-(4-nitrophenyl)-2H-indazole-7-carboxamide (P1)

15 (**P1**) was prepared following the general procedure reported for Example 4 step 1 using Example 88, (**DD2**) and 4-fluoronitrobenzene. Solvent was evaporated under reduced pressure, the residue was portioned between EtOAc and H<sub>2</sub>O and the precipitate filtered off giving the titled compound (**P1**) as yellow solid. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>, 300K) δ 9.47 (1H, s), 8.53-8.42 (5H, m), 8.12 (1H, br. s), 7.90-7.80 (2H, m). MS (ES) C<sub>14</sub>H<sub>9</sub>FN<sub>4</sub>O<sub>3</sub> requires: 300, found: 301 (M+H)<sup>+</sup>.

20

##### Step 2: 4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzenaminium chloride (P2)

25 (**P2**) was prepared from (**P1**) following the general procedure reported for Example 4 step 3 and the crude product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 9.12 (1H, s), 8.57 (1H, br. s), 8.04 (1H, br. s), 7.95 (2H, d, J = 8.4 Hz), 7.83-7.73 (2H, m), 7.05 (2H, d, J = 8.4 Hz). MS (ES) C<sub>14</sub>H<sub>12</sub>ClFN<sub>4</sub>O requires: 270, found: 271 (M+H)<sup>+</sup>.

##### Step 3: tert-Butyl 3-[(4-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]azetidine-1-carboxylate (P3)

30 A solution of 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (1.3 eq) and HATU (1.3 eq) in DMF (0.2M) was stirred at RT for 30 min, then a solution of (**P2**) (1.0 eq) and DMAP (1.0 eq) in DMF (0.2 M) was added and stirring was continued at RT for O/N. Solvent was evaporated under reduced pressure, the residue was portioned between EtOAc and H<sub>2</sub>O and the precipitate filtered off giving the titled compound (**P3**) as pale brown solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 10.33 (1H, br. s), 9.20 (1H, s), 8.56 (1H, br. s), 8.11 (2H, d, J = 9.0 Hz), 8.05 (1H, br. s), 7.87-7.76 (4H, m), 4.10-3.90 (5H, m), 1.39 (9H, s). MS (ES) C<sub>23</sub>H<sub>24</sub>FN<sub>5</sub>O<sub>4</sub> requires: 453, found: 454 (M+H)<sup>+</sup>.

##### Step 4: 3-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]azetidinium trifluoroacetate (P4)

To a stirred solution of (**P3**) (1.0 eq) in DCM (0.1 M) TFA (10.0 eq) was added and the reaction mixture was stirred at RT for 2h. Solvent was evaporated under reduced pressure and the crude product was purified by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**P4**) as a yellow powder.

5 <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 10.44 (1H, br. s), 9.23 (1H, s), 8.75 (2H, br. s), 8.54 (1H, br. s), 8.15 (2H, d, J = 9.0 Hz), 8.09 (1H, br. s), 7.89-7.77 (4H, m), 4.20-4.05 (4H, m), 3.85-3.73 (1H, m). MS (ES) C<sub>20</sub>H<sub>17</sub>F<sub>4</sub>N<sub>5</sub>O<sub>4</sub> requires: 353, found: 354 (M+H)<sup>+</sup>.

### EXAMPLE 77

10 **2-(4-{|(Azetidin-3-ylcarbonyl)(methyl)amino|methyl}phenyl)-2H-indazole-7-carboxamide**  
**(Q2)**

**Step 1: *tert*-Butyl 3-{|{4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl|(methyl)amino|carbonyl}azetidine-1-carboxylate (Q1)}**

15 A solution of 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (1.3 eq) and TBTU (1.3 eq) in DMF (0.2M) was stirred at RT for 30 min, then a solution of 2-{|[(methylamino)methyl]phenyl|-2H-indazole-7-carboxamide (prepared following the general procedure reported in Example 3 for (**C3**)) (1.0 eq) and Et<sub>3</sub>N (1.3 eq) in DMF (0.2M) was added and stirring was continued at RT for O/N. Solvent was reduced *in vacuo*, the residue dissolved in EtOAc, washed with saturated NaHCO<sub>3</sub> solution, brine, dried 20 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Crude product was purified by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**Q1**) as a yellow powder. MS (ES) C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub> requires: 463, found: 464 (M+H)<sup>+</sup>.

25 **Step 2: 2-(4-{|(Azetidin-3-ylcarbonyl)(methyl)amino|methyl}phenyl)-2H-indazole-7-carboxamide (Q2)**

(**Q2**) was prepared following the general procedure reported for Example 21 step 6 and the crude product was purified by ISOLUTE<sup>®</sup> HM-N SCX cartridge to yield the titled compound (**Q2**) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 9.30 (1H, s), 8.55 (1H, br. s), 8.11 (2H, d, J = 8.5 Hz), 30 8.06 (1H, d, J = 7.2 Hz), 8.02 (1H, d, J = 8.2 Hz), 7.90 (1H, br. s), 7.47 (1H, d, J = 8.5 Hz), 7.27 (1H, dd, J = 8.2, 7.2 Hz), 7.01 (1H, br. s), 4.65-4.57 (2H, m), 4.25-3.95 (5H, m), 2.82 (3H, s). MS (ES) C<sub>20</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub> requires: 363, found: 364 (M+H)<sup>+</sup>.

### EXAMPLE 78

35 **3-{|(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl|amino|carbonyl|azetidinium trifluoroacetate (R4)}**

**Step 1: 2-{4-[(Hydroxyimino)methyl]phenyl}-2H-indazole-7-carboxamide (R1)**

To a stirred suspension of Example 14, **E1** (1.0 eq) and hydroxylamine hydrochloride (4.0 eq) in dry CH<sub>3</sub>CN (0.035 M) was added Et<sub>3</sub>N (4.0 eq). The reaction mixture was stirred at reflux for 3h, and then cooled to RT. The titled compound (**R1**) was isolated by precipitation from the reaction mixture and used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 11.45 (1H, s), 9.37 (1H, s), 8.55 (1H, br. s), 8.30-8.18 (3H, m), 8.06 (1H, d, J = 6.8 Hz), 8.02 (1H, d, J = 8.3 Hz), 7.89 (1H, br. s), 7.83 (2H, d, J = 8.2 Hz), 7.27 (1H, t, J = 7.5 Hz). MS (ES) C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> requires: 280, found: 281 (M+H)<sup>+</sup>.

**Step 2: {4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}methanaminium chloride (R2)**

To a suspension of (**R1**) in MeOH (0.1M) Pd/C (10% w/w) and 6N HCl solution (1.0 eq.) were added. The reaction mixture was stirred at RT under hydrogen atmosphere O/N. To the suspension 1.25 M HCl in MeOH was added and then the catalyst was filtered off through a pad of Celite. The solvent was reduced *in vacuo* and the crude product used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) 9.37 (1H, s), 8.64 (3H, br. s), 8.55 (1H, br. s), 8.23 (2H, d, J = 8.5 Hz), 8.06 (1H, d, J = 6.8 Hz), 8.02 (1H, d, J = 8.2 Hz), 7.87 (1H, br. s), 7.76 (2H, d, J = 8.2 Hz), 7.28 (1H, dd, J = 6.8, 8.1 Hz), 4.15-4.08 (2H, m). MS (ES) C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O requires: 267, found: 268 (M+H)<sup>+</sup>.

**Step 3: *tert*-Butyl 3-[({4-[7-(aminocarbonyl)-2H-indazol-2-yl]benzyl}amino)carbonyl]azetidine-1-carboxylate (R3)**

(**R3**) was prepared following the general procedure reported for Example 77 step 1 and the crude product was purified by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**R3**) as a yellow powder. MS (ES) C<sub>24</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> requires: 449, found: 450 (M+H)<sup>+</sup>.

**Step 4: 3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}amino)carbonyl]azetidinium trifluoroacetate (R4)**

(**R4**) was prepared following the general procedure reported for Example 21 step 6. <sup>1</sup>H NMR (400 MHz, DMSO-d6, 300K) δ 9.30 (1H, s), 8.77-8.64 (3H, m), 8.55 (1H, br. s), 8.11 (2H, d, J = 8.5 Hz), 8.06 (1H, d, J = 7.1 Hz), 8.02 (1H, d, J = 8.2 Hz), 7.90 (1H, br. s), 7.51 (2H, d, J = 8.5 Hz), 7.27 (1H, dd, J = 8.2, 7.1 Hz), 4.45-4.38 (2H, m), 4.15-3.98 (5H, m). MS (ES) C<sub>21</sub>H<sub>20</sub>F<sub>3</sub>N<sub>5</sub>O<sub>4</sub> requires: 349, found: 350 (M+H)<sup>+</sup>.

**EXAMPLE 79**

**2-(4-Bromophenyl)-5-fluoro-2H-indazole-7-carboxamide (U1)**

To a solution of Example 88, **DD2** (1.0 eq) in DMF (0.2 M) K<sub>2</sub>CO<sub>3</sub> (1.3 eq) and 4-bromofluorobenzene (10.0 eq) were added and the reaction mixture was heated under MW conditions at 180 °C for 20 min. The reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine; dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave (**U1**) which was purified by

chromatography on silica gel eluting with 50-70% EtOAc/Petroleum ether to obtain the title compound as a yellow powder.  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>, 300K)  $\delta$  9.34 (1H, s), 8.50 (1H, br. s), 8.17 (2H, d,  $J$  = 9.0 Hz), 8.03 (1H, br. s), 7.90-7.80 (4H, m). MS (ES $^+$ ) C<sub>14</sub>H<sub>9</sub>BrFN<sub>3</sub>O requires: 334/336, found: 335/337 (M+H) $^+$ .

5

### EXAMPLE 80

#### **5-Fluoro-2-(4-pyridin-3-ylphenyl)-2H-indazole-7-carboxamide (U2)**

A mixture of (U1) from Example 79 (1.0 eq) and pyridine-3-boronic acid (1.3 eq) in DMF (1.0 M) together with 2N Na<sub>2</sub>CO<sub>3</sub> solution (2.0 eq) was degassed with a stream of Ar for 30 min.  $^1\text{Bu}_3\text{PH}^+$  BF<sub>4</sub> $^-$  (0.05 eq) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.05 eq) were added and the reaction mixture was heated at 90  $^{\circ}\text{C}$  for 48 h. The mixture was cooled to RT, DCM was added and the organic phase was washed with sat. aq. NaHCO<sub>3</sub> solution, brine, dried (Na<sub>2</sub>SO<sub>4</sub>). The solution was concentrated under reduced pressure and the residue was purified by chromatography on silica gel eluting with 50-90% EtOAc/Petroleum ether then 10%MeOH/DCM to obtain the title compound as a yellow powder.  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>, 300K)  $\delta$  9.40 (1H, s), 9.01 (1H, d,  $J$  = 1.6 Hz), 8.63 (1H, dd,  $J$  = 4.8, 1.6 Hz), 8.57 (1H, br. s), 8.32 (2H, d,  $J$  = 8.8 Hz), 8.20 (1H, d,  $J$  = 7.8 Hz), 8.10 (1H, br. s), 8.01 (2H, d,  $J$  = 8.8 Hz), 7.88-7.82 (2H, m), 7.54 (1H, dd,  $J$  = 7.8, 4.8 Hz). MS (ES) C<sub>19</sub>H<sub>13</sub>FN<sub>4</sub>O requires: 332, found: 333 (M+H) $^+$ .

### EXAMPLE 81

#### **2-(4-Pyridin-3-ylphenyl)-2H-indazole-7-carboxamide (V2)**

##### **Step 1: 2-(4-Bromophenyl)-2H-indazole-7-carboxamide (V1)**

(V1) was prepared following the general procedure reported in Example 3 step 1 using 2H-indazole-7-carboxamide and 4-bromofluorobenzene and the crude was purified by chromatography on silica gel eluting with 80-90% EtOAc/Petroleum ether to obtain the title compound as a yellow powder. MS (ES $^+$ ) C<sub>14</sub>H<sub>10</sub>BrN<sub>3</sub>O requires: 315/317, found: 316/318 (M+H) $^+$ .

##### **Step 2: 2-(4-Pyridin-3-ylphenyl)-2H-indazole-7-carboxamide (V2)**

(V2) was prepared following the general procedure reported in Example 80 using (V1) and pyridine-3-boronic acid and the crude was purified by chromatography on silica gel eluting with 90% EtOAc/Petroleum ether then 10%MeOH/DCM to obtain the title compound as a yellow powder.  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>, 300K)  $\delta$  9.42 (1H, s), 9.01 (1H, d,  $J$  = 2.0 Hz), 8.63 (1H, dd,  $J$  = 4.8, 1.5 Hz), 8.58 (1H, br. s), 8.31 (2H, d,  $J$  = 8.6 Hz), 8.19 (1H, d,  $J$  = 7.8 Hz), 8.10-8.03 (2H, m), 8.01 (2H, d,  $J$  = 8.6 Hz), 7.89 (1H, br. s), 7.56-7.50 (1H, m), 7.35-7.25 (1H, m). MS (ES) C<sub>19</sub>H<sub>14</sub>N<sub>4</sub>O requires: 314 found: 315 (M+H) $^+$ .

### EXAMPLE 82

#### **4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-1-methylpiperazin-1-ium trifluoroacetate (W1)**

(**W1**) was prepared following the general procedure reported in Example 1 using methyl 3-formyl-2-nitrobenzoate and 4-(4-methylpiperazin-1-yl)aniline and the product was isolated by reverse phase RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, the desired fractions were lyophilized to afford the titled compound (**W1**) as a white powder. <sup>1</sup>H NMR (400MHz, DMSO, 300K) δ 10.11 (1H, br. s), 9.22 (1H, s), 8.58 (1H, s), 8.10-7.90 (4H, m), 7.86 (1H, br. s), 7.30-7.20 (3H, m), 4.10-3.90 (2H, m), 3.60-3.50 (2H, m), 3.30-3.00 (4H, m), 2.88 (3H, s). MS (ES) C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub> requires: 335, found: 336 (M+H<sup>+</sup>).

### EXAMPLE 83

#### 4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}piperidinium trifluoroacetate (X1)

(**X1**) was prepared following the general procedure reported in Example 1 using methyl 3-formyl-2-nitrobenzoate and *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate and the product was isolated by reverse phase RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, the desired fractions were lyophilized to afford the titled compound (**X1**) as a white powder. <sup>1</sup>H NMR (400MHz, DMSO, 300K) δ 9.30 (1H, s), 8.60-8.50 (2H, br. s), 8.40-8.30 (1H, br. s), 8.12 (2H, d, J = 8.6 Hz), 8.10-8.00 (2H, m), 7.91 (1H, br. s), 7.48 (2H, d, J = 8.6 Hz), 7.30-7.25 (1H, m), 3.50-3.40 (2H, m), 3.10-2.90 (2H, m), 2.10-2.00 (2H, m), 1.90-1.80 (2H, m). MS (ES) C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O requires: 320, found: 321 (M+H<sup>+</sup>).

20

### EXAMPLE 84

#### 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylethanaminium trifluoroacetate (Y3)

##### Step 1: 2-[4-(2-Oxoethyl)phenyl]-2H-indazole-7-carboxamide (Y1)

25 To a suspension of (methoxymethyl)triphenylphosphonium chloride (2.0 eq) in dry Et<sub>2</sub>O:THF (1:1, 0.2 M) under Ar at -78 °C was added t-BuOK (2.0 eq). The reaction mixture was stirred for 30 min at -78 °C, then 30 min at 0 °C, cooled again to -78 °C and Example 14, (**E1**) (1.0 eq) was added and the resulting solution was stirred O/N at RT. The reaction mixture was diluted with EtOAc, washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave the intermediate enol ether which was used in the next step without further purification. MS (ES) C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> requires: 293, found: 294 (M+H<sup>+</sup>).

30 The enol ether (1.0 eq) was dissolved in THF:Et<sub>2</sub>O (1:1, 0.1 M) and HCl (3.0 eq, 2.0 M in Et<sub>2</sub>O) was added and the solution was stirred at RT for 3h. The reaction mixture was quenched by the addition of sat. aq. NaHCO<sub>3</sub> solution until pH ~5 and stirred at RT for 5 min. Organic layer was separated, washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave the aldehyde intermediate (**Y1**) which was used in the next step without further purification. MS (ES) C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> requires: 279, found 280 (M+H)<sup>+</sup>.

##### Step 2: 2-(4-{2-[Benzyl(methyl)amino]ethyl}phenyl)-2H-indazole-7-carboxamide (Y2)

(**Y1**) was dissolved in MeOH (0.1 M) and benzaldehyde (1.0 eq) was added followed by a solution of NaBH<sub>3</sub>CN (1.1 eq) and ZnCl<sub>2</sub> (0.5 eq) in MeOH (0.5 mL). The pH was adjusted to ~ 6 with 1.25 M HCl in MeOH and the mixture stirred at RT for 1h after which the formation of 2-{4-[2-(benzylamino)ethyl]phenyl}-2H-indazole-7-carboxamide was observed (MS (ES) C<sub>23</sub>H<sub>22</sub>N<sub>4</sub>O requires: 5 370, found: 371 (M+H)<sup>+</sup>). Then, formaldehyde (1.0 eq) was added and the reaction mixture stirred for additional 1h after which the formation of (**Y2**) was observed (MS (ES) C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O requires: 384, found: 10 385 (M+H)<sup>+</sup>). 6N HCl (0.1 mL) was added and the solvent was removed under reduced pressure. The reaction mixture was diluted with DCM, washed with sat. aq. NaHCO<sub>3</sub> solution, then brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent under reduced pressure gave (**Y2**) which was used in the next step 10 without further purification.

**Step 3: 2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylethanaminium trifluoroacetate (**Y3**)**

To a solution of (**Y2**) (1.0 eq) in MeOH (0.1M) were added Pd/C (10% w/w) and 6N HCl 15 solution (1.0 eq). The reaction mixture was stirred under H<sub>2</sub> atmosphere (1 atm) O/N. The catalyst was filtered through a pad of Celite and solvent was removed under vacuum and the crude was purified by reverse phase RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, the desired fractions were lyophilized to afford the titled compound as a white powder. <sup>1</sup>H NMR (400MHz, DMSO, 330K) δ 9.25 (1H, s), 8.51 (2H, br. s), 8.10 (2H, d, J = 8.6 Hz), 8.05 (2H, m), 7.94 (1H, br. s), 20 7.53 (2H, d, J = 8.6 Hz), 7.30-7.25 (1H, m, overlapped with TFA signal), 3.00-2.80 (4H, m), 2.59 (3H, s). MS (ES) C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O requires: 294, found: 295 (M+H)<sup>+</sup>.

**EXAMPLE 85**

**2-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl)amino]carbonyl]azetidinium trifluoroacetate (**Z1**)**

To a solution of 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (1 eq) in DMF/DCM (3:2, 0.05 M)) was added PL-Mukaiyama resin (1.9 eq), 2-(4-aminophenyl)-2H-indazole-7-carboxamide (free 30 base of Example 4, **D3**) (0.83 eq), TEA (4 eq) and PS-DMAP (0.19 eq). The mixture was stirred at RT for 24 hours, filtered through a silica-carbonate cartridge (2 g) and evaporated. Purification by RP-HPLC (column XBridge C18 5μm, 19X100mm, gradient A: H<sub>2</sub>O + 0.1% TFA; B: MeCN + 0.1% TFA) and evaporation of the desired fractions yield the desired compound. <sup>1</sup>H NMR (300 MHz, DMSO<sub>d</sub><sub>6</sub>+ TFA, 300K) δ 10.70 (1H, s), 9.26 (1H, s), 9.14 (1H, br. s), 8.93 (1H, br. s), 8.54 (1H, br. s), 8.18 (2H, d, J = 8.8 Hz), 8.20 (2H, dd, J<sub>1</sub> = 7.1 Hz, J<sub>2</sub> = 8.2 Hz), 7.93-7.78 (3H, m), 7.25 (1H, t, J = 8.0 Hz), 5.18-5.02 (1H, m), 4.10-3.75 (2H, m), 2.85-2.50 (2H, m). MS (ES<sup>+</sup>) C<sub>18</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub> requires: 335, found: 336 (M+H)<sup>+</sup>.

**EXAMPLE 86**

**2-{5-[(Methylamino)methyl]pyridin-2-yl}-2H-indazole-7-carboxamide (**AA2**)**

**Step 1: 2-(5-Formylpyridin-2-yl)-2H-indazole-7-carboxamide (AA1)**

(AA1) was prepared following the general procedure reported in Example 3 step 1 using 6-bromonicotinaldehyde and 2H-indazole-7-carboxamide. The crude was purified by precipitation by adding water to the reaction mixture followed by filtration.  $^1\text{H}$  NMR (300 MHz, DMSO $_{\delta}$ , 300K)  $\delta$  10.18 (1H, s), 9.55 (1H, s), 9.13 (1H, br. s), 8.66 (1H, d,  $J$  = 8.4 Hz), 8.55 (1H, dd,  $J_1$  = 2.0 Hz,  $J_2$  = 8.4 Hz), 8.49 (1H, s), 8.13-8.05 (2H, m), 7.94 (1H, s), 7.25 (1H, dd,  $J_1$  = 7.0 Hz,  $J_2$  = 8.4 Hz), MS (ES $^+$ )  $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_2$  requires: 266, found: 268 ( $\text{M}+2\text{H}$ ) $^+$ .

10 **Step 2: 2-{5-[(Methylamino)methyl]pyridin-2-yl}-2H-indazole-7-carboxamide (AA2)**

(AA2) was prepared from AA1 following the general procedure reported in Example 3 step 2 and the crude was purified by RP- HPLC (column: C18), using H<sub>2</sub>O (+0.1% TFA) and MeCN (+0.1% TFA) as eluents, and the desired fractions were lyophilized to afford the titled compound.  $^1\text{H}$  NMR (300 MHz, DMSO $_{\delta}$ , 300K)  $\delta$  9.43 (1H, s), 8.53 (2H, br. s), 8.38 (1H, d,  $J$  = 8.2 Hz), 8.09 – 8.03 (3H, m), 7.89 (1H, s), 7.30–7.25 (1H, m), 3.76 (2H, s), 2.30 (3H, s), MS (ES $^+$ )  $\text{C}_{15}\text{H}_{15}\text{N}_5\text{O}$  requires: 281, found: 282 ( $\text{M}+\text{H}$ ) $^+$ .

**EXAMPLE 87**20 **5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide (BB2)****Step 1: 5-Fluoro-2-(3-fluoro-4-formylphenyl)-2H-indazole-7-carboxamide (BB1)**

(BB1) was prepared following the general procedure reported in Example 3 step 1 using 2,4-difluorobenzaldehyde and Example 88, (DD2). The crude was purified by precipitation by adding water to the reaction mixture followed by filtration. The crude solid was taken forward without further purification. MS (ES $^+$ )  $\text{C}_{15}\text{H}_9\text{F}_2\text{N}_3\text{O}_2$  requires: 301, found: 302 ( $\text{M}+\text{H}$ ) $^+$ .

**Step 2: 5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide (BB2)**

30 (BB2) was prepared from BB1 following the general procedure reported in Example 3 step 2 and the crude was purified by RP- HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, and the desired fractions were lyophilized to afford the titled compound.  $^1\text{H}$  NMR (300 MHz, DMSO $_{\delta}$ , 300K)  $\delta$  9.40 (1H, s), 9.02 (1H, br. s), 8.50 (1H, s), 8.34 (1H, dd,  $J_1$  = 2.0 Hz,  $J_2$  = 10.8 Hz), 8.20 (1H, dd,  $J_1$  = 2.0 Hz,  $J_2$  = 8.3 Hz), 8.07 (1H, s), 7.90-7.80 (3H, m), 4.28 (2H, s), 2.60 (3H, s), MS (ES $^+$ )  $\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_4\text{O}$  requires: 316, found: 317 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATIVE EXAMPLE A****Step 1: 5-Fluoro-3-methyl-2-nitrobenzoic acid (CC1)**

To a solution of 3-fluoro-5-methylbenzoic acid (1.0 eq.) in conc.  $\text{H}_2\text{SO}_4$  was added slowly  $\text{KNO}_3$  (1.1 eq.) at 0°C. The mixture was stirred at RT for 1 h and then slowly poured into iced water. After stirring to until the ice has completely melted, the white precipitation was filtered, washed with cold water and dried under reduced pressure. The white solid was used without further purification for the next 5 step.  $^1\text{H}$  NMR (400 MHz, DMSO, 300K)  $\delta$  14.08 (1H, br. s), 7.65 (2H, m), 2.30 (3H, s).

#### Step 2: Methyl 5-fluoro-3-methyl-2-nitrobenzoate (CC2)

(CC2) was prepared following the general procedure reported in Example 17 step 1. The yellow solid was used in the next step without purification.  $^1\text{H}$  NMR (400 MHz, DMSO, 300K)  $\delta$  7.63 (2H, m), 10 3.83 (3H, s), 2.29 (3H, s).

#### Step 3: Methyl 2-amino-5-fluoro-3-methylbenzoate (CC3)

(CC3) was prepared following the general procedure reported in Example 18 step 1. The white solid was used without further purification in the subsequent step.  $^1\text{H}$  NMR (400 MHz, DMSO, 300K)  $\delta$  15 7.29 (1H, dd,  $J$  = 9.5 Hz,  $J$  = 3.0 Hz), 7.12 (1H, dd,  $J$  = 9.5 Hz,  $J$  = 3.0 Hz), 6.36 (2H, br. s), 3.78 (3H, s), 2.11 (3H, s).

#### Step 4: Methyl 2,5-difluoro-3-methylbenzoate (CC4)

To a solution of (CC3) (1.0 eq.) in dry DCM (0.4 M) at 0°C was added nitrosonium 20 tetrafluoroborate (1.3 eq.) portionwise. After 1 h at 0°C dry dichlorobenzene (120 eq.) was added and the reaction was slowly heated to 160°C while DCM was distilled off. After 3 hrs, the mixture was cooled to RT, EtOAc was added and the organic phase was washed with brine (2x). After drying over  $\text{MgSO}_4$ , the solvents were removed under reduced pressure. The crude was purified by flash chromatography 1-10% EtOAc/petroleum ether to yield (CC4) as a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 300K)  $\delta$  25 7.42 (1H, m), 7.06 (1H, m), 3.92 (3H, s), 2.30 (3H, d,  $J$  = 2.3 Hz).

#### Step 5: Methyl 2,5-difluoro-3-formylbenzoate (CC5)

(CC5) was prepared from CC4 following the general procedure reported in Example 1 step 2 and 3. The crude was purified by flash chromatography 1-20% EtOAc/petroleum ether to yield a white solid. 30  $^1\text{H}$  NMR (300 MHz, DMSO, 300K)  $\delta$  10.19 (1H, d,  $J$  = 2.4 Hz), 7.98 (1H, m), 7.86 (1H, m), 3.89 (3H, s). MS ( $\text{ES}^+$ )  $\text{C}_9\text{H}_6\text{F}_2\text{O}_3$  requires: 200, found: 201 ( $\text{M}+\text{H}$ )<sup>+</sup>.

**EXAMPLE 88****5-Fluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate (DD3)****Step 1: Methyl 5-fluoro-1H-indazole-7-carboxylate (DD1)**

5 To a solution of Preparative Example A, **CC3** (1.0 eq.) in 1,2-dichloroethane (0.1 M) was added AcCl (5 eq.) and heated at 55°C for 2h. Afterwards the solvent was removed under reduced pressure.

10 The white solid was dissolved in toluene/water (5/1, 0.1 M). The solution was cooled to 0°C and HCl (10 eq., 37%) was added. Then slowly and in portions NaNO<sub>2</sub> (10 eq.) was added and the mixture was stirred for 3h at 0°C. The organic phase was washed with water (3x), dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure.

15 The yellow solution in toluene (0.1 M) was then heated for 2 h at 90°C. Evaporation of toluene yielded the desired product as a red solid. <sup>1</sup>H NMR (400 MHz, DMSO, 300K) δ 13.37 (1H, s), 8.23 (1H, s), 7.63 (1H, dd, J = 8.6 Hz, J = 2.5 Hz), 7.48 (1H, dd, J = 8.6 Hz, J = 2.5 Hz), 3.66 (3H, s). MS (ES<sup>+</sup>) C<sub>9</sub>H<sub>7</sub>FN<sub>2</sub>O<sub>2</sub> requires: 194, found: 195 (M+H)<sup>+</sup>.

**Step 2: 5-Fluoro-1H-indazole-7-carboxamide (DD2)**

20 **(DD1)** was solved in dioxane/water (1/1, 0.1 M) and KOH (1.5 eq.) was added. After stirring 12 h at RT the solvents were removed under reduced pressure. The white solid was used without purification for the coupling.

25 The carboxylic acid was dissolved in DMF (0.1 M) and TBTU (1.5 eq.) was added at 0°C. After 15 min DIEA (2.0 eq.) and ammonia (3.0 eq., 0.5 M in dioxane) were added and the mixture was stirred 36h at RT. EtOAc was added and the organic phase was washed with sat. aq. NaHCO<sub>3</sub> solution (3x) and brine (2x). The organic phase was dried and evaporated under reduced pressure. The crude was purified by flash chromatography 1-20% MeOH/DCM to yield **(DD2)** as a white solid. MS (ES<sup>+</sup>) C<sub>8</sub>H<sub>6</sub>FN<sub>3</sub>O requires: 179, found: 180 (M+H)<sup>+</sup>.

**Step 3: 5-Fluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate (DD3)**

30 **(DD3)** was prepared from **DD2** following the general procedure reported in Example 3 step 1 and 2 and the crude was purified by RP- HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, and the desired fractions were lyophilized to afford the titled compound. <sup>1</sup>H NMR (400 MHz, DMSO, 300K) δ 9.43 (2H, s), 9.33 (1H, s), 8.52 (1H, s), 8.24 (2H, dd, J = 8.6 Hz), 8.08 (1H, s), 7.88-7.71 (4H, m), 4.20 (2H, t, J = 5.6 Hz), 2.55 (3H, t, J = 5.6 Hz). MS (ES<sup>+</sup>) C<sub>16</sub>H<sub>15</sub>FN<sub>4</sub>O requires: 299, found: 300 (M+H)<sup>+</sup>.

**EXAMPLE 89****2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylpropan-2-aminium trifluoroacetate  
(EE4)****5 Step 1: 2-(4-Acetylphenyl)-2H-indazole-7-carboxamide (EE1)**

(EE1) was prepared following the general procedure reported in Example 3 step 1 using 1*H*-indazole-7-carboxamide and 1-(4-fluorophenyl)ethanone. The product was obtained as a white solid by precipitation from the reaction mixture by adding MeOH/EtOAc (5/1). <sup>1</sup>H NMR (400 MHz, DMSO, 300K) δ 9.46 (1H, s), 8.51 (1H, s), 8.34 (2H, d, J = 8.8 Hz), 8.17 (2H, d, J = 8.8 Hz), 8.07 (1H, d, J = 7.2 Hz), 8.03 (1H, d, J = 7.2 Hz), 7.91 (1H, s), 7.28 (1H, dd, J = 8.3 Hz, J = 6.8 Hz), 2.65 (3H, s). MS (ES<sup>+</sup>) C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> requires: 279, found: 280 (M+H)<sup>+</sup>.

**Step 2: 2-[4-(1-Hydroxy-1-methylethyl)phenyl]-2*H*-indazole-7-carboxamide (EE2)**

To a solution of (EE1) (1.0 eq.) in THF (0.05 M) at 0°C was added slowly MeMgBr (1.5 eq., 3 M in THF). The mixture was stirred overnight at RT. H<sub>2</sub>O was added and then mixture was extracted with EtOAc. The combined organic phase was dried over MgSO<sub>4</sub> and evaporated under reduced pressure to yield the product (EE2) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO, 300K) δ 9.27 (1H, s), 8.57 (1H, s), 8.06 (4H, m), 7.87 (1H, s), 7.68 (2H, d, J = 8.6 Hz), 7.25 (1H, m), 1.47 (6H, s). MS (ES<sup>+</sup>) C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> requires: 295, found: 296 (M+H)<sup>+</sup>.

**20 Step 3: 2-{4-[1-(Formylamino)-1-methylethyl]phenyl}-2*H*-indazole-7-carboxamide (EE3)**

To a solution of (EE2) (1.0 eq.) and NaCN (1.0 eq.) in DCM (0.12 M) was added conc. H<sub>2</sub>SO<sub>4</sub> (5.0 eq.) and the mixture was stirred for 24h at RT. Sat. aq. NaHCO<sub>3</sub> solution was added and the mixture was extracted with EtOAc. The combined organic phase was dried over MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by reverse phase HPLC (column: C18) to afford the titled compound (EE3) a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO, 300K) δ 9.26 (1H, s), 8.56 (1H, s), 8.42 (1H, s), 8.05 (5H, m), 7.86 (1H, s), 7.56 (2H, d, J = 8.8 Hz), 7.26 (1H, dd, J = 8.4 Hz, J = 7.1 Hz), 1.61 (6H, s). MS (ES<sup>+</sup>) C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub> requires: 322, found: 323 (M+H)<sup>+</sup>.

**30 Step 4: 2-{4-[7-(Aminocarbonyl)-2*H*-indazol-2-yl]phenyl}-N-methylpropan-2-aminium trifluoroacetate (EE4)**

To a solution of (EE3) (1.0 eq.) in THF (0.03 M) was added BH<sub>3</sub>-THF (1.5 eq., 1 M in THF) and the mixture was stirred for 24h at RT. Then sat. aq. NaHCO<sub>3</sub> solution was added and the mixture was extracted with EtOAc. The combined organic phase was dried over MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by reverse phase HPLC (column: C18) to afford the titled compound (EE4) a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO, 300K) δ 9.38 (1H, s), 9.14 (1H, s), 8.53 (1H, s), 8.27 (2H, d, J = 8.7 Hz), 8.04 (2H, s), 7.88 (1H, s), 7.79 (2H, d, J = 8.7 Hz), 7.28 (1H, dd, J = 8.2 Hz, J = 8.2 Hz), 2.36 (3H, s), 1.73 (6H, s). MS (ES<sup>+</sup>) C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O requires: 308, found: 309 (M+H)<sup>+</sup>.

**EXAMPLE 90****2-(6-Phenylpyridin-3-yl)-2H-indazole-7-carboxamide (FF1)**

5 (FF1) was prepared following the general procedure reported in Example 3 step 1, using 3-chloro-6-phenylpyridazine and 1*H*-indazole-7-carboxamide as starting materials. The product was obtained as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO, 300K)  $\delta$  9.69 (1H, s), 8.85 (1H, d,  $J$  = 9.2 Hz), 8.54 (1H, d,  $J$  = 9.2 Hz), 8.52 (1H, s), 8.24 (2H, d,  $J$  = 6.8 Hz), 8.11 (2H, m) 7.91 (1H, s), 7.59 (3H, m), 7.32 (1H, dd,  $J$  = 7.7 Hz,  $J$  = 7.7 Hz). MS (ES $^+$ )  $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}$  requires: 315, found: 316 ( $\text{M}+\text{H}$ ) $^+$ .

10

**EXAMPLE 91****{4-[7-(Aminocarbonyl)-5-fluoro-2*H*-indazol-2-yl]phenyl}-N-[(1-[hydroxymethyl)cyclohexyl]methyl}methanaminium trifluoroacetate (GG1)**

15 To MP-Triacetoxyborohydride (5 eq, loading 2.5 mmol/g) a solution of 5-fluoro-2-(4-formylphenyl)-2*H*-indazole-7-carboxamide (Intermediate in preparation of Example 88, (DD3) (1 eq) and [1-(aminomethyl)cyclohexyl]methanol (1.2 eq.) in DMF (0.132 M) was added. The mixture was heated in the MW apparatus (10 min, 80 °C) and then purified by RP-HPLC (column Symmetry RP18 7 $\mu\text{m}$ , 19x300mm, gradient A:  $\text{H}_2\text{O} + 0.1\%$  TFA; B: MeCN + 0.1% TFA) and the pooled fractions were 20 evaporated under reduced pressure to yield the title compound.  $^1\text{H}$  NMR (300 MHz, DMSO $\text{d}_6$ , 300K)  $\delta$  9.30 (1H, s), 8.54 (3H, br. s), 8.25 (2H, d,  $J$  = 8.6 Hz), 8.05 (1H, br. s), 7.88-7.80 (1H, m), 7.75 (3H, d,  $J$  = 8.3 Hz), 4.28-4.20 (2H, m), 3.39 (2H, s), 2.90-2.83 (2H, m), 1.45-1.25 (10H, m). MS (ES $^+$ )  $\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_2$  requires: 410, found: 411 ( $\text{M}+\text{H}$ ) $^+$ .

25 The following examples were prepared according to the methods of the previous examples:

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u><math>\text{M}+\text{H}^+</math></u>	<u>Procedure of Example</u>
92	5-Chloro-2-(4-formylphenyl)-2 <i>H</i> -indazole-7-carboxamide	299/301	300/302	17
93	2-{3-Methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}-2 <i>H</i> -indazole-7-carboxamide	379	380	17
94	2-{3-Methoxy-4-[(methylamino)methyl]phenyl}-2 <i>H</i> -indazole-7-carboxamide	310	311	3

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
95	5-Chloro-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-2H-indazole-7-carboxamide	383/385	384/386	17
96	5-Chloro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide	314/316	315/317	17
97	{4-[7-(Aminocarbonyl)-4-fluoro-2H-indazol-2-yl]phenyl}-N-methylmethanaminium chloride	298	299	17
98	{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-N-methylmethanaminium chloride	298	299	88
99	1-{4-[7-(Aminocarbonyl)-4-fluoro-2H-indazol-2-yl]benzyl}-4-methylpiperazin-1-ium chloride	367	368	3
100	1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-4-methylpiperazin-1-ium chloride	367	368	3
101	1-{3-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-methylpiperazinediium bis(trifluoroacetate)	349	350	20
102	2-[4-(1-Hydroxy-1-methylethyl)phenyl]-2H-indazole-7-carboxamide	295	296	89
103	2-(4-Acetylphenyl)-2H-indazole-7-carboxamide	279	280	15
104	3-{{[4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}(methyl)amino]carbonyl}-1-methylpiperidinium trifluoroacetate	405	406	77
105	2-{4-[1-(Formylamino)-1-methylethyl]phenyl}-2H-indazole-7-carboxamide	322	323	89
106	2-[3-(1,4-Diazepan-1-ylcarbonyl)phenyl]-2H-indazole-7-carboxamide	363	364	21
107	3-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl)amino]carbonyl]-1-methylpiperidinium trifluoroacetate	391	392	78

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
108	(2S)-2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium trifluoroacetate	349	350	4
109	3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium trifluoroacetate	349	350	4
110	(2R)-2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium trifluoroacetate	349	350	4
111	3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidinium trifluoroacetate	363	364	4
112	(3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpyrrolidinium trifluoroacetate	363	364	4
113	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium trifluoroacetate	377	378	4
114	4-Chloro-2-(4-formylphenyl)-2H-indazole-7-carboxamide	299/301	300/302	17
115	(3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpyrrolidinium trifluoroacetate	363	364	4
116	(R)-1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylethanaminium chloride	294	295	Separated by SFC
117	(S)-1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-methylethanaminium chloride	294	295	Separated by SFC
118	2-{3-Fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide	298	299	3
119	{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]-2-fluorophenyl}-N-methanaminium trifluoroacetate	298	299	3
120	2-{4-[1-Methyl-1-(methylamino)ethyl]phenyl}-2H-indazole-7-carboxamide	308	309	89

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
121	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]-2-hydroxybenzyl}-4-methylpiperazin-1-ium trifluoroacetate	365	366	3
122	(3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium chloride	377	378	4
123	(3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium chloride	377	378	4
124	1-(2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}ethyl)-4-methylpiperazinediium bis(trifluoroacetate)	363	364	84
125	{4-[7-(Aminocarbonyl)-4-hydroxy-2H-indazol-2-yl]phenyl}-N-methylmethanaminium trifluoroacetate	296	297	3
126	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-phenylpyrrolidinium trifluoroacetate	425	426	85
127	(1R,3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopentanaminium trifluoroacetate	363	364	85
128	(1R,3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopentanaminium trifluoroacetate	363	364	85
129	(1S,3R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopentanaminium trifluoroacetate	363	364	85
130	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-2-methylazetidinium trifluoroacetate	349	350	85
131	4-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]-1-methylpiperidinium trifluoroacetate	391	392	85

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
132	9-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]-3-azoniaspiro[5.5]undecane trifluoroacetate	445	446	85
133	4-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)-2-oxoethyl]-4-phenylpiperidinium trifluoroacetate	453	454	85
134	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridinium trifluoroacetate	357	358	85
135	4-{3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridin-2-yl}piperazin-1-ium trifluoroacetate	441	442	85
136	3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridinium trifluoroacetate	357	358	85
137	4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyridinium trifluoroacetate	357	358	85
138	4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]quinolinium trifluoroacetate	407	408	85
139	4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]isoquinolinium trifluoroacetate	407	408	85
140	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylazepanium trifluoroacetate	391	392	85
141	3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-2-methyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate	425	426	85
142	2-{4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidin-1-yl}pyrimidin-1-ium trifluoroacetate	441	442	85
143	1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-4-methylpiperazin-1-ium chloride	367	368	85

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
144	5-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-3-oxooctahydroindolizin-2-aminium trifluoroacetate	432	433	85
145	2-{3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]piperidin-1-yl}pyridinium trifluoroacetate	440	441	85
146	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-methylmorpholin-4-ium trifluoroacetate	379	380	85
147	(1R,4R)-N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-1'-(methylsulfonyl)-1',2'-dihydrospiro[cyclohexane-1,3'-indole]-4-carboxamide	543	544	85
148	1-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]octahydro-1H-isoindolium trifluoroacetate	403	404	85
149	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-benzylmorpholin-4-ium trifluoroacetate	455	456	85
150	(3S,4R)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-4-(methoxycarbonyl)pyrrolidinium trifluoroacetate	407	408	85
151	4-{(2S)-2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]pyrrolidinium-1-yl}piperidinium bis(trifluoroacetate)	432	433	85
152	(1S,3S)-3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]cyclopentanaminium trifluoroacetate	363	364	85
153	3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpyrrolidinium trifluoroacetate	363	364	85

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
154	2-{4-[{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino]carbonyl}piperidin-1-yl}pyrimidin-1-ium trifluoroacetate	397	398	16
155	2-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}pyrrolidinium-3-yl)pyridinium bis(trifluoroacetate)	397	398	16
156	3-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}pyrrolidinium-3-yl)pyridinium bis(trifluoroacetate)	397	398	16
157	(3S,4S)-1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,4-difluoropyrrolidinium trifluoroacetate	356	357	16
158	3-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-6-ammonio-3-azoniabicyclo[3.1.0]hexane bis(trifluoroacetate)	347	348	16
159	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-7-methyl-2,7-diazoniaspiro[4.4]nonane bis(trifluoroacetate)	389	390	16
160	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3-[4-(dimethylammonio)phenyl]pyrrolidinium bis(trifluoroacetate)	439	440	16
161	5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-methyl-1,2,4,5,6,6a-hexahydropyrrolo[3,4-b]pyrrolediium bis(trifluoroacetate)	373	374	16
162	3-{{[4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}(methyl)ammonio]methyl}-1-methylpiperidinium bis(trifluoroacetate)	391	392	16
163	(1R,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-oxa-5-azoniabicyclo[2.2.1]heptane trifluoroacetate	348	349	16
164	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-hydroxy-2-methylpropan-1-aminium trifluoroacetate	338	339	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
165	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,3-difluorocyclobutanaminium trifluoroacetate	356	357	16
166	4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-6-fluoro-1,4-diazepan-1-ium trifluoroacetate	367	368	16
167	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-pyrimidin-1-ium-2-yl-1,4-diazepan-1-ium bis(trifluoroacetate)	427	428	16
168	3-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)-1-benzylpyrrolidinium bis(trifluoroacetate)	425	426	16
169	3-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio)methyl]-1-methylpyrrolidinium bis(trifluoroacetate)	363	364	16
170	3-[(4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl)ammonio)methyl]-1-benzylpyrrolidinium bis(trifluoroacetate)	439	440	16
171	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-7-benzyl-2,7-diazoniaspiro[4.4]nonane bis(trifluoroacetate)	465	466	16
172	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-8-benzyl-2,8-diazoniaspiro[5.5]undecane bis(trifluoroacetate)	493	494	16
173	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,6-diazoniaspiro[3.3]heptane bis(trifluoroacetate)	347	348	16
174	7-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,7-diazoniaspiro[3.5]nonane bis(trifluoroacetate)	375	376	16
175	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,6-diazoniaspiro[3.5]nonane bis(trifluoroacetate)	375	376	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
176	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,8-diazoniaspiro[5.5]undecane bis(trifluoroacetate)	403	404	16
177	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,8-diazoniaspiro[4.5]decane bis(trifluoroacetate)	389	390	16
178	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,7-diazoniaspiro[4.5]decane bis(trifluoroacetate)	389	390	16
179	8-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2,8-diazoniaspiro[4.5]decane bis(trifluoroacetate)	389	390	16
180	3-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,9-diazoniaspiro[5.5]undecane bis(trifluoroacetate)	403	404	16
181	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}octahydropyrrolo[3,4-c]pyrrolediium bis(trifluoroacetate)	361	362	16
182	5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}octahydropyrrolo[3,4-b]pyrrolediium bis(trifluoroacetate)	361	362	16
183	4-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)octahydrocyclopenta[c]pyrrolidinium bis(trifluoroacetate)	375	376	16
184	N <sup>2</sup> -{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-N <sup>1</sup> ,N <sup>1</sup> -dimethyl-1-pyridin-2-ylethane-1,2-diaminium bis(trifluoroacetate)	414	415	16
185	7-(Aminocarbonyl)-2-[4-({[2-(2,3-dihydro-1H-indol-1-yl)ethyl]ammonio}methyl)phenyl]-2H-indazol-1-ium bis(trifluoroacetate)	411	412	16
186	(3S,4S)-1-[2-({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)ethyl]-3,4-difluoropyrrolidinium bis(trifluoroacetate)	399	400	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
187	5-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{amino}\}$ )-1,3-benzothiazol-3-ium trifluoroacetate	399	400	16
188	1-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio}\}$ )-8-azoniaspiro[4.5]decane bis(trifluoroacetate)	403	404	16
189	4-[ $(\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio})\text{methyl}\}$ ]-1-methylpiperidinium bis(trifluoroacetate)	377	378	16
190	N- $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{-2-hydroxyethanaminium}$ trifluoroacetate	310	311	16
191	7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate	292	293	73
192	3-[2-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{phenyl}\}\text{amino}\}$ )-2-oxoethyl]azetidinium trifluoroacetate	349	350	4
193	4-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio}\}$ piperidinium bis(trifluoroacetate)	349	350	16
194	(3R,4R)-4-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio}\}$ )-3-fluoropiperidinium bis(trifluoroacetate)	367	368	16
195	(3S,4R)-4-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio}\}$ )-3-benzyl-1-methylpiperidinium bis(trifluoroacetate)	453	454	16
196	N- $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{-1-isobutyrylpiperidin-4-aminium}$ trifluoroacetate	419	420	16
197	2-[4-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio}\}$ piperidin-1-yl]-3-methylpyridinium bis(trifluoroacetate)	440	441	16
198	3-( $\{\{4-[7-(\text{Aminocarbonyl})-2\text{H-indazol-2-yl}]\text{benzyl}\}\text{ammonio}\}$ piperidinium bis(trifluoroacetate)	349	350	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
199	3-( $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ ammonio)-1-benzylpiperidinium bis(trifluoroacetate)	439	440	16
200	5- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -5-aza-2-azoniabicyclo[2.2.2]octane trifluoroacetate	361	362	16
201	(1S,4S)-2- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -5-methyl-2,5-diaza-1-azoniabicyclo[2.2.1]heptane bis(trifluoroacetate)	361	362	16
202	1- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -4-(pyridin-2-ylmethyl)piperazinium bis(trifluoroacetate)	426	427	16
203	5- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -2-benzyl-5-aza-2-azoniabicyclo[2.2.2]octane trifluoroacetate	451	452	16
204	8- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -3-benzyl-8-aza-3-azoniabicyclo[3.2.1]octane trifluoroacetate	451	452	16
205	(1S,4S)-5- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -2-benzyl-5-aza-2-azoniabicyclo[2.2.1]heptane trifluoroacetate	437	438	16
206	3-( $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ ammonio)pyrrolidinium bis(trifluoroacetate)	335	336	16
207	6- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ ammonio)-3-azoniabicyclo[3.1.0]hexane bis(trifluoroacetate)	347	348	16
208	(3S,4S)-N- $\{\text{4-}[\text{7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}\}$ -4-hydroxytetrahydrothiophen-3-aminium 1,1-dioxide trifluoroacetate	400	401	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
209	4-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}ammonio)methyl]-4-hydroxy-1-methylpiperidinium bis(trifluoroacetate)	393	394	16
210	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-cyclopropyl-2-hydroxyethanaminium trifluoroacetate	350	351	16
211	{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-{{1-(hydroxymethyl)cyclopentyl}methyl}methanaminium trifluoroacetate	378	379	16
212	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1,2,3,4-tetrahydro-2,7-naphthyridinium bis(trifluoroacetate)	383	384	16
213	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3-[(dimethylammonio)methyl]piperidinium bis(trifluoroacetate)	391	392	16
214	4-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}piperidinium-4-yl)thiomorpholin-4-ium bis(trifluoroacetate)	435	436	16
215	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-[(methylsulfonyl)amino]piperidinium trifluoroacetate	427	428	16
216	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(1H-imidazol-3-ium-1-ylmethyl)piperidinium bis(trifluoroacetate)	414	415	16
217	7-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-1-oxa-7-azoniaspiro[4.5]decane trifluoroacetate	390	391	16
218	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(1-hydroxy-1-methylethyl)piperidinium trifluoroacetate	392	393	16
219	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-benzylpiperidinium trifluoroacetate	453	454	4

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
220	2-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-ethylpiperidinium trifluoroacetate	391	392	4
221	3-[({4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-ethylpiperidinium trifluoroacetate	391	392	4
222	2-[3-(1,4-Diazepan-1-ylcarbonyl)-4-fluorophenyl]-2H-indazole-7-carboxamide trifluoroacetate	381	382	21
223	tert-Butyl {4-[7-(aminocarbonyl)-4-chloro-2H-indazol-2-yl]benzyl}methylcarbamate	414/416	415/417	3
224	6-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate	292	293	74
225	2-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}pyrrolidinium trifluoroacetate	306	307	1
226	6-Fluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide	298	299	17
227	5-Fluoro-2-{2-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide	316	317	17
228	2-{3-Hydroxy-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate	296	297	3
229	2-(4-{[Formyl(methyl)amino]methyl}-3-hydroxyphenyl)-2H-indazole-7-carboxamide	324	325	3
230	2-{2-Chloro-4-[(methylamino)methyl]phenyl}-5-fluoro-2H-indazole-7-carboxamide	332/334	333/335	17
231	5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate	316	317	87
232	2-{2,5-Difluoro-4-[(methylamino)methyl]phenyl}-5-fluoro-2H-indazole-7-carboxamide trifluoroacetate	334	335	17

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
233	2-(4-Bromophenyl)-2H-indazole-7-carboxamide	315/317	316/318	81
234	(3R)-3-[({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium chloride	395	396	76
235	(3R)-3-[({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylpiperidinium trifluoroacetate	395	396	76
236	2-(1,2,3,4-Tetrahydroisoquinolin-7-yl)-2H-indazole-7-carboxamide	292	293	73
237	(R)-2-[4-({3-[(Dimethylamino)methyl]piperidin-1-yl}methyl)phenyl]-2H-indazole-7-carboxamide	391	392	Separated by SFC
238	(S)-2-[4-({3-[(Dimethylamino)methyl]piperidin-1-yl}methyl)phenyl]-2H-indazole-7-carboxamide	391	392	Separated by SFC
239	3-({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)-2-(chloromethyl)-3-oxopropan-1-aminium trifluoroacetate	389/391	390/392	76
240	5-Fluoro-2-{3-fluoro-4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide hydrochloride	316	317	87
241	2-{4-[(Dimethylamino)methyl]-3-fluorophenyl}-5-fluoro-2H-indazole-7-carboxamide trifluoroacetate	330	331	87
242	2-{4-[(Azetidin-3-ylcarbonyl)amino]phenyl}-5-fluoro-2H-indazole-7-carboxamide	353	354	76
243	2-[4-(2,7-Diazaspiro[4.5]dec-2-ylmethyl)phenyl]-2H-indazole-7-carboxamide	389	390	16
244	(1S,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-(4-chlorobenzyl)-5-aza-2-azoniabicyclo[2.2.1]heptane trifluoroacetate	471/473	472/474	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
245	(1S,4S)-5-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-(3-chlorobenzyl)-5-aza-2-azoniabicyclo[2.2.1]heptane trifluoroacetate	471/473	472/474	16
246	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-[(methylamino)carbonyl]piperazin-1-ium trifluoroacetate	392	393	16
247	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-hydroxy-2-pyridin-3-ylethanaminium trifluoroacetate	387	388	16
248	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-cyclohexyl-2-hydroxyethanaminium trifluoroacetate	392	393	16
249	4-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-6-(hydroxymethyl)-1,4-oxazepan-4-ium trifluoroacetate	380	381	16
250	{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-{[1-(hydroxymethyl)cyclobutyl]methyl}methanaminium trifluoroacetate	364	365	16
251	{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]phenyl}-N-{[1-(hydroxymethyl)cyclohexyl]methyl}methanaminium trifluoroacetate	392	393	16
252	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-(5-methyl-1H-benzimidazol-2-yl)piperidinium trifluoroacetate	464	465	16
253	2-(1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-4-hydroxypiperidinium-4-yl)pyridinium bis(trifluoroacetate)	427	428	16
254	1-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-3,3-difluoropyrrolidinium trifluoroacetate	356	357	16
255	2-(4-{{(2R)-2-(Fluoromethyl)pyrrolidin-1-yl}methyl}phenyl)-2H-indazole-7-carboxamide	352	353	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
256	N-{4-[7-(Aminocarbonyl)-2H-indazol-2-yl]benzyl}-2-oxopyrrolidin-3-aminium trifluoroacetate	349	350	16
257	5-Fluoro-2-(4-formylphenyl)-2H-indazole-7-carboxamide	283	284	88
258	3-[({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}amino)carbonyl]-1-methylazetidinium trifluoroacetate	367	368	76
259	1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-3-[(dimethylammonio)methyl]piperidinium bis(trifluoroacetate)	409	410	16
260	3-[({4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorophenyl}amino)carbonyl]azetidinium trifluoroacetate	371	372	77
261	2-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl}-2,7-diazoniaspiro[4.5]decane bis(trifluoroacetate)	407	408	16
262	4,5-Difluoro-2-{4-[(methylamino)methyl]phenyl}-2H-indazole-7-carboxamide trifluoroacetate	316	317	3
263	5-Fluoro-2-(3-fluoro-4-[(1-methylazetidin-3-yl)carbonyl]amino)phenyl)-2H-indazole-7-carboxamide trifluoroacetate	385	386	77
264	5-Fluoro-2-(3-fluoro-4-formylphenyl)-2H-indazole-7-carboxamide	301	302	87
265	5-Fluoro-2-(5-fluoro-2-formylphenyl)-2H-indazole-7-carboxamide	301	302	87
266	{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorophenyl}-N-{{[1-(hydroxymethyl)cyclopentyl]methyl}methanaminium trifluoroacetate	414	415	16

<u>Example</u>	<u>Name</u>	<u>MW</u>	<u>M+H<sup>+</sup></u>	<u>Procedure of Example</u>
267	5-Fluoro-2-[3-fluoro-4-({[(3R)-1-methylpiperidin-3-yl]carbonyl}amino)phenyl]-2H-indazole-7-carboxamide trifluoroacetate	413	414	77
268	1-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorobenzyl}-4-methylpiperazinium bis(trifluoroacetate)	367	368	16
269	4-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzyl)ammonio)methyl]-1-methylpiperidinium bis(trifluoroacetate)	395	396	16
270	4-[(4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-2-fluorobenzyl)ammonio)methyl]-1-methylpiperidinium bis(trifluoroacetate)	413	414	16

### EXAMPLE 271

#### 7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-methyl-1,2,3,4-tetrahydroisoquinolinium trifluoroacetate (HH2)

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##### Step 1: 2-(3,4-Dihydroisoquinolin-7-yl)-2H-indazole-7-carboxamide (HH1)

To a stirred solution of Example 73, (M1) (1.0 eq) and Et<sub>3</sub>N (1.0 eq) in DMSO (0.15M) was added IBX (1.1 eq) and reaction mixture was stirred at RT for 1h, then quenched with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. Reaction mixture was partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub> solution, and separated. The aqueous phase was extracted with EtOAc several times. Recombined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Crude product was purified by SCX cartridge to remove traces of DMSO affording a yellow solid which was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 300K) δ 9.30 (1H, s), 8.58 (1H, br. s), 8.50 (1H, br. s), 8.24 (1H, s), 8.17 (1H, d, J = 8.1 Hz), 8.07 (1H, d, J = 6.8 Hz), 8.03 (1H, d, J = 8.3 Hz), 7.86 (1H, br. s), 7.48 (1H, d, J = 8.3 Hz), 7.28 (1H, dd, J = 8.1, 7.3 Hz), 4.05-3.96 (2H, m), 3.28-3.19 (2H, m). MS (ES) C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O requires: 290, found: 291 (M+H)<sup>+</sup>.

##### Step 2: 7-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-methyl-1,2,3,4-tetrahydro isoquinolinium trifluoroacetate (HH2)

(HH1) (1.0 eq) was dissolved in dry THF (0.05 M) under Argon atmosphere and cooled to -78°C. To this solution boron trifluoride etherate (2.0 eq) and methylmagnesium bromide (2.0

eq) were added. Reaction mixture was stirred overnight warming to RT and was then quenched by adding sat. aq. NH<sub>4</sub>Cl solution. EtOAc was added and the layers were separated. The aqueous phase was extracted with EtOAc, and the recombined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Crude product was purified by preparative RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (+0.1% TFA) as eluents. The desired fractions were lyophilized to afford the titled compound (**HH2**) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN, 300K) δ 8.85 (1H, s), 8.76 (1H, br. s), 8.17 (1H, d, J = 6.8 Hz), 8.02 (1H, d, J = 8.3 Hz), 7.98-7.92 (2H, m), 7.44 (1H, d, J = 8.1 Hz), 7.27 (1H, dd, J = 8.1, 7.1 Hz), 6.42 (1H, br. s), 4.82-4.74 (1H, m), 3.63-3.53 (1H, m), 3.51-3.42 (1H, m), 3.29-3.09 (2H, m), 1.78 (3H, d, J = 6.8 Hz). MS (ES) C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub> requires: 306, found: 307 (M+H)<sup>+</sup>.

### EXAMPLE 272

#### 3-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-1-ethylpiperidinium trifluoroacetate (**II3**)

**Step 1:** 3-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-1-ethylpyridinium iodide (**II1**)

To a solution of Example 80, (**U2**) (1.0 eq) in dry CH<sub>3</sub>CN (0.2 M) iodoethane (1.3 eq) was added dropwise at RT and the reaction mixture was refluxed for 3h. Then, the mixture was cooled to RT.

Evaporation of the solvent gave **II1** which was used in the next step without further purification. MS (ES) C<sub>21</sub>H<sub>18</sub>FN<sub>4</sub>OI requires: 361, found: 362 (M+H<sup>+</sup>).

**Step 2:** 2-[4-(1-Ethyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl]-5-fluoro-2H-indazole-7-carboxamide (**II2**)

To a stirred solution of (**II1**) in dry MeOH (0.2 M), NaBH<sub>4</sub> (3.0 eq) was added portionwise at RT and the reaction mixture was stirred at RT O/N. Then, the mixture was quenched with sat. aq. NH<sub>4</sub>Cl solution. MeOH was concentrated under reduced pressure and EtOAc was added. The organic phase separated and was washed with sat. aq. NaHCO<sub>3</sub> solution, brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave **II2** which was used in the next step without further purification. MS (ES) C<sub>21</sub>H<sub>21</sub>FN<sub>4</sub>O requires: 364, found: 365 (M+H<sup>+</sup>).

**Step 3:** 3-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}-1-ethylpiperidinium trifluoroacetate (**II3**)

To a solution of (**II2**) (1.0 eq) in MeOH (0.2 M) were added 10 % Pd/C (0.35 eq) and HCl (1.0 eq) and the reaction mixture was stirred under H<sub>2</sub> atmosphere (1 atm) for 48 h. Then, the mixture was filtered through Celite and solvent was removed under reduced pressure affording a residue which was purified by reverse phase RP-HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, the desired fractions were lyophilized to afford the titled compound (**II3**) as a white powder.

<sup>1</sup>H NMR (400MHz, DMSOd<sub>6</sub>, 300K) δ 9.30 (1H, s), 8.53 (1H, br. s), 8.16 (2H, d, J = 8.3 Hz), 8.11 (1H, br. s), 7.90-7.70 (2H, m), 7.55 (2H, d, J = 8.3 Hz), 3.60-3.40 (2H, m), 3.20-3.00 (4H, m),, 3.00-2.80 (1H, m), 2.00-1.90 (2H, m), 1.80-1.70 (2H, m), 1.30-1.20 (3H, m), MS (ES) C<sub>21</sub>H<sub>23</sub>FN<sub>4</sub>O requires: 366, found: 367 (M+H<sup>+</sup>).

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### EXAMPLE 273

#### 2-(4-Cyanophenyl)-5-fluoro-2H-indazole-7-carboxamide (JJ1)

The desired compound was prepared following the general procedure reported in Example 3, 10 step 1 using 5-fluoro-1H-indazole-7-carboxamide and 4-fluorobenzonitrile. The crude was purified by precipitation by adding water to the reaction mixture followed by filtration. <sup>1</sup>H NMR (300 MHz, DMSOd<sub>6</sub>, 300K) δ 9.42 (1H, s), 8.47 (3H, m), 8.11 (3H, d, J = 8.4 Hz), 7.82 (2H, m). MS (ES<sup>+</sup>) C<sub>15</sub>H<sub>9</sub>FN<sub>4</sub>O requires: 280, found: 281 (M+H)<sup>+</sup>.

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### EXAMPLE 274

#### 5-fluoro-2-[4-(1H-tetrazol-5-yl)phenyl]-2H-indazole-7-carboxamide (KK1)

To a solution of Example 273, **JJ1** in DMF (0.8 M) were added sodium azide (12.0 eq.) and ammonium chloride (12.0 eq), and the reaction mixture was heated under MW conditions at 200 °C for 20 min. The 20 crude was purified by precipitation by adding water to the reaction mixture followed by filtration. <sup>1</sup>H NMR (300 MHz, DMSOd<sub>6</sub>, 300K) δ 9.31 (1H, s), 8.8.61 (1H, br. s), 8.18 (4H, s), 8.07 (1H, br. s), 7.77-7.87 (2H, m), MS (ES<sup>+</sup>) C<sub>15</sub>H<sub>10</sub>FN<sub>7</sub>O requires: 323, found: 324 (M+H)<sup>+</sup>.

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### EXAMPLE 275

#### 2-(4-Aminophenyl)-5-fluoro-2H-indazole-7-carboxamide hydrochloride (LL2)

##### Step 1: 5-Fluoro-2-(4-nitrophenyl)-2H-indazole-7-carboxamide (LL1)

The desired compound prepared following the general procedure reported in Example 3 step 1 30 using 5-fluoro-1H-indazole-7-carboxamide and 1-fluoro-4-nitrobenzene. The crude was purified by precipitation by adding water to the reaction mixture followed by filtration. MS (ES<sup>+</sup>) C<sub>14</sub>H<sub>9</sub>FN<sub>4</sub>O<sub>3</sub> requires: 300, found: 301 (M+H)<sup>+</sup>.

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##### Step 2: 2-(4-Aminophenyl)-5-fluoro-2H-indazole-7-carboxamide hydrochloride (LL2)

(**LL1**) was dissolved in DMF (0.2 M) and PtO<sub>2</sub> (0.5 eq) and 1N HCl (1 eq) were added. The mixture was stirred under H<sub>2</sub> atmosphere for 24 hr. Then the mixture was filtered and solvent was removed under reduced pressure affording a residue which was crude was purified by RP- HPLC (column: C18), using H<sub>2</sub>O (0.1% TFA) and MeCN (0.1% TFA) as eluents, and the desired

fractions were lyophilized to afford the titled compound.  $^1\text{H}$  NMR (300 MHz, DMSO<sub>d</sub><sub>6</sub>, 300K)  $\delta$  9.05 (1H, s), 8.58 (1H, br. s), 8.10 (1H, s), 7.73-7.83 (4H, m), 6.8 (2H, d,  $J$ = 8.8). MS (ES<sup>+</sup>) C<sub>14</sub>H<sub>11</sub>FN<sub>4</sub>O requires: 270, found: 271 (M+H)<sup>+</sup>.

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### EXAMPLE 276

#### **tert-Butyl 3-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]pyrrolidine-1-carboxylate (MM3)**

##### **Step 1: tert-Butyl 3-{|2,5-difluoro-3-(methoxycarbonyl)phenyl|methylene}amino pyrrolidine-1-carboxylate (MM1).**

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A mixture of methyl 2,5-difluoro-3-formylbenzoate (Preparative Example A, **CC5**) (1.0 eq.) and tert-butyl 3-aminopyrrolidine-1-carboxylate (1.05 eq.) in EtOH (0.2 M) was heated at reflux for 2 hr until TLC revealed reaction completion (25% EtOAc/Hexane). Evaporation of the solvent gave the title imine which was used in the next step without further purification.  $^1\text{H}$  NMR (d6 DMSO, 300K, 300MHz)  $\delta$  (ppm) 8.63 (1H, s), 7.88-7.73 (2H, m); 4.22-4.10 (1H, m); 3.87 (3H, s); 3.58-3.12 (6H, m); 2.20-2.03 (1H, m); 1.93-1.77 (1H, m); 1.40 (9H, s).

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##### **Step 2: Methyl 2-[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]-5-fluoro-2H-indazole-7-carboxylate (MM2).**

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A mixture of (**MM1**) (1.0 eq.) and NaN<sub>3</sub> (2 eq.) in dry DMF (0.6 M) was irradiated in a microwave oven in a sealed tube (110 °C 3h, then 140 °C 40min). The crude was filtered through a silica pad and reduced under reduced pressure. The residue was purified by flash column chromatography on silica using a gradient of 18-100% EtOAc/Petroleum ether to yield the desired compound as a brown oil. 1H NMR (D6 DMSO + 5% TFA, 300K, 300 MHz):  $\delta$  (ppm) 8.58 (1H, s); 7.82-7.69 (2H, m); 5.40-5.29 (1H, m); 3.88 (3H, s); 3.86-3.79 (1H, m); 3.72-3.53 (2H, m); 3.51-3.39 (1H, m); 2.46-2.35 (2H, m, partially overlapped by DMSO); 1.39 (9H, s).  $^{19}\text{F}$  NMR (D6 DMSO + 5% TFA, 300K, 283 MHz):  $\delta$  (ppm) -122.82. MS (ES) C<sub>18</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> requires: 363, found: 364 (M+H)<sup>+</sup>.

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##### **Step 3: tert-Butyl 3-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]pyrrolidine-1-carboxylate (MM3).**

30

A solution of (**MM2**) in 7N ammonia/MeOH (100 eq.) was irradiated at microwave in a sealed tube (120 °C, 1h 40min). After evaporation of solvent under reduced pressure, the residue was taken into EtOAc and filtered over a silica pad, eluting with EtOAc. After evaporation of the solvent, the title compound was isolated as a pale yellow foam.  $^1\text{H}$  NMR (D6 DMSO+ 5%TFA, 300K, 300 MHz):  $\delta$  (ppm) 8.64 (1H, s); 8.42 (1H, br. s); 8.00 (1H, br. s); 7.80-7.67 (2H, m); 5.43-5.32 (1H, m); 3.89-3.67 (2H, m); 3.63-3.39

35

(2H, m); 2.47-2.37 (2H, m, partially overlapped by DMSO); 1.39 & 1.37 (9H, 2s).  $^{19}\text{F}$  NMR (D6 DMSO + 5%TFA, 300K, 283 MHz):  $\delta$  (ppm) -121.80. MS (ES)  $\text{C}_{17}\text{H}_{21}\text{FN}_4\text{O}_3$  requires: 348, found: 349 ( $\text{M}+\text{H}$ ) $^+$ .

### EXAMPLE 277

#### 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]pyrrolidinium trifluoroacetate (NN1).

A solution of Example 276, (MM3) in TFA / DCM 1:1 (0.1 M) was stirred at room temperature for 20 min. After evaporation of solvent under reduced pressure, and treatment with  $\text{Et}_2\text{O}$ , the title compound was isolated as a yellowish solid.  $^1\text{H}$  NMR (D6 DMSO, 300K, 600 MHz):  $\delta$  (ppm) 9.32 (2H, br. s), 8.74 (1H, s), 8.36 (1H, s), 8.03 (1H, s), 7.80 (2H, dd,  $J_1=16\text{Hz}$ ,  $J_2=3\text{Hz}$ ), 5.64-5.59 (1H, m), 3.79 (2H, d,  $J=4\text{Hz}$ ), 3.59-3.52 (1H, m), 3.48-3.41 (1H, m), 2.61-2.53 (1H, m), 2.48-2.41 (1H, m).  $^{13}\text{C}$  NMR (D6 DMSO, 300K, 150 MHz):  $\delta$  (ppm) 164.31, 157.72, 156.15, 142.79, 126.22 (d,  $J=8\text{Hz}$ ), 123.65 (d,  $J=8\text{Hz}$ ), 121.76 (d,  $J=11\text{Hz}$ ), 118.99 (d,  $J=30\text{Hz}$ ), 107.94 (d,  $J=24\text{Hz}$ ), 60.84, 49.90, 44.85, 31.86.  $^{19}\text{F}$  NMR (D6 DMSO, 300K, 283 MHz):  $\delta$  (ppm) -76.60, -123.17. MS (ES)  $\text{C}_{12}\text{H}_{13}\text{FN}_4\text{O}$  requires: 248, found: 249 ( $\text{M}+\text{H}$ ) $^+$ .

### EXAMPLE 278

#### 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-methylpyrrolidinium trifluoroacetate (OO1)

To a solution of Example 277, (NN1) in  $\text{MeOH}$  (0.06 M),  $\text{AcOH}$  (5 eq.), formaldehyde (37% in water, 2.8 eq.) and Silica-supported cyanoborohydride (3 eq.) were added and the mixture was stirred at room temperature overnight. After filtration, the filtrate was passed through a SCX cartridge, eluting with  $\text{MeOH}$  then with 1N  $\text{NH}_3/\text{MeOH}$ . The solvent was evaporated, a mixture of DCM/TFA 1:1 was added and the title compound was isolated after evaporation of the solvents.  $^1\text{H}$  NMR (D6 DMSO, 300K, 300 MHz):  $\delta$  (ppm) 10.19 (1H, br. s), 8.72 (1H, s), 8.38 (1H, br. s), 8.03 (1H, br. s), 7.84-7.72 (2H, m), 5.73-5.57 (1H, m), 4.30-3.55 (4H, m, partially overlapped by water), 2.96 (3H, s), 2.88-2.61 (1H, m), 2.60-2.53 (1H, m, partially overlapped by DMSO).  $^{19}\text{F}$  NMR (D6 DMSO, 300K, 283 MHz):  $\delta$  (ppm) -76.60, -123.27. MS (ES)  $\text{C}_{13}\text{H}_{15}\text{FN}_4\text{O}$  requires: 262, found: 263 ( $\text{M}+\text{H}$ ) $^+$ .

### EXAMPLE 279

#### 3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-ethylpyrrolidinium trifluoroacetate (PP1)

The title compound was prepared according to the procedure for Example 278, substituting acetaldehyde for formaldehyde, and isolated by RP-HPLC.  $^{19}\text{F}$  NMR (D6 DMSO, 300K, 283 MHz):  $\delta$  (ppm) -76.60, -122.36. MS (ES)  $\text{C}_{14}\text{H}_{17}\text{FN}_4\text{O}$  requires: 276, found: 277 ( $\text{M}+\text{H}$ ) $^+$ .

**EXAMPLE 280****3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-propylpyrrolidinium trifluoroacetate (QQ1)**

5 The title compound was prepared according to the procedure for Example 278, substituting propionaldehyde for formaldehyde. Compound at NMR was present as a mixture of 2 rotamers.  $^1\text{H}$  NMR (D6 DMSO, 300K, 400 MHz):  $\delta$  (ppm) 10.21 (0.4H, br. s), 10.04 (0.6H, br. s), 8.77-8.72 (1H, m), 8.41 (0.6H, br. s), 8.30 (0.4H, br. s), 8.06 (1H, br. s), 7.83-7.74 (2H, m), 5.71-5.54 (1H, m), 4.25-4.09 (1H, m), 3.91-3.68 (2H, m), 3.55-3.43 (0.4H, m), 3.35-3.14 (2.6H, m), 2.84-2.73 (0.6H, m), 2.62-2.51 (1.4H, m, 10 partially overlapped under water), 1.74-1.62 (2H, m), 0.93 (3H, t,  $J$ = 7 Hz).  $^{19}\text{F}$  NMR (D6 DMSO, 300K, 376 MHz):  $\delta$  (ppm) -76.60, -122.52, -122.55. MS (ES)  $\text{C}_{15}\text{H}_{19}\text{FN}_4\text{O}$  requires: 290, found: 291 ( $\text{M}+\text{H}$ ) $^+$ .

**EXAMPLE 281****3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-isopropylpyrrolidinium trifluoroacetate (RR1)**

15

The title compound was prepared according to the procedure for Example 278, substituting acetone for formaldehyde. Compound at NMR was present as a mixture of 2 rotamers.  $^1\text{H}$  NMR (D6 DMSO, 300K, 400 MHz):  $\delta$  (ppm) 10.15 (0.5 H, br. s), 10.02 (0.5H, br. s), 8.75 (1H, s), 8.42 (0.5H, br. s), 8.31 (0.5H, br. s), 8.09 (0.5H, br. s), 8.03 (0.5H, br. s), 7.83-7.75 (2H, m), 5.68-5.53 (1H, m), 4.22-4.12 (1H, m), 3.87-3.70 (2H, m), 3.68-3.33 (2H, m), 2.82-2.70 (0.6H, m), 2.62-2.52 (1.4H, m), 1.37-1.26 (6H, m).  $^{19}\text{F}$  NMR (D6 DMSO, 300K, 376 MHz):  $\delta$  (ppm) -76.60, -122.66. MS (ES)  $\text{C}_{15}\text{H}_{19}\text{FN}_4\text{O}$  requires: 290, found: 291 ( $\text{M}+\text{H}$ ) $^+$ .

**EXAMPLE 282****3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-cyclohexylpyrrolidinium trifluoroacetate (SS1)**

25 The title compound was prepared according to the procedure for Example 278, substituting cyclohexanone for formaldehyde. MS (ES)  $\text{C}_{18}\text{H}_{23}\text{FN}_4\text{O}$  requires: 330, found: 331 ( $\text{M}+\text{H}$ ) $^+$ .

**EXAMPLE 283****3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-cyclobutylpyrrolidinium trifluoroacetate (TT1)**

35

The title compound was prepared according to the procedure for Example 278, substituting cyclobutanone for formaldehyde. MS (ES)  $\text{C}_{16}\text{H}_{19}\text{FN}_4\text{O}$  requires: 302, found: 303 ( $\text{M}+\text{H}$ ) $^+$ .

**EXAMPLE 284****tert-Butyl 4-[7-(aminocarbonyl)-2H-indazol-2-yl]-4-methylpiperidine-1-carboxylate (UU3)****5    Step 1: *tert-Butyl 4-{|3-(methoxycarbonyl)-2-nitrobenzylidene|amino}-4-methylpiperidine-1-carboxylate (UU1).***

10    A mixture of methyl 3-formyl-2-nitrobenzoate Example 1, (A3) (1.0 eq.) and tert-butyl 4-amino-4-methylpiperidine-1-carboxylate (WO 2005/101989)(1.05 eq.) in EtOH (0.2 M) was stirred at reflux for 24 hr. Evaporation of the solvent gave the title imine which was used in the next step without further 10 purification.

**Step 2: Methyl 2-[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]-5-fluoro-2H-indazole-7-carboxylate (UU2).**

15    A mixture of (UU1) (1.0 eq.) and NaN<sub>3</sub> (2 eq.) in dry DMF (0.25 M) was irradiated in a microwave oven in a sealed tube (140 °C 40min). The title compound was isolated as described in Example 276, step 2 for (MM2). <sup>1</sup>H NMR (D6 DMSO + 5% TFA, 300K, 400 MHz): δ (ppm) 8.67 (1H, s); 7.97 (1H, d, J= 8 Hz); 7.90 (1H, d, J= 7 Hz); 7.12 (1H, t, J= 8 Hz); 3.88 (3H, s); 3.57-3-47 (2H, m); 3.34-3.25 (2H, m); 2.55.2.50 (2H, m, partially hidden under DMSO); 2.20-1.93 (2H, m); 1.61 (3H, s); 1.40 (9H, s). MS (ES) 20    C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub> requires: 373, found: 374 (M+H)<sup>+</sup>.

**Step 3: *tert-Butyl 4-[7-(aminocarbonyl)-2H-indazol-2-yl]-4-methylpiperidine-1-carboxylate (UU3).***

25    A solution of (UU2) in 7N ammonia/MeOH (100 eq.) was irradiated at microwave in a sealed tube (130 °C, 1h 14 h). Evaporation of the solvent provided the title compound. <sup>1</sup>H NMR (D6 DMSO + 5% TFA, 300K, 400 MHz): δ (ppm) 8.77 (1H, s); 8.53 (1H, br. s); 7.98 (1H, d, J= 7 Hz); 7.92 (1H, d, J= 8 Hz); 7.74 (1H, br. s); 7.22-7.14 (1H, m); 3.58-3.46 (2H, m); 3.32-3.19 (2H, m); 2.50-2.49 (2H, m, partially hidden under DMSO); 2.07-1.96 (2H, m); 1.60 (3H, s); 1.38 (9H, s). MS (ES) C<sub>19</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub> requires: 358, 30    found: 359 (M+H)<sup>+</sup>.

**EXAMPLE 285****4-[7-(Aminocarbonyl)-2H-indazol-2-yl]-4-methylpiperidinium trifluoroacetate (VV1)**

35    A solution of Example 284, (UU3) in TFA / DCM 1:1 (0.1 M) was stirred at room temperature for 20 min. After evaporation of solvent under reduced pressure and treatment with Et<sub>2</sub>O, the title compound was isolated as a yellowish solid. <sup>1</sup>H NMR (D6 DMSO, 300K, 600 MHz): δ (ppm) 8.85 (1H, s); 8.57 (1H, br. s); 8.45 (2H, br. s); 8.01 (1H, d, J= 6 Hz); 7.96 (1H, d, J= 8 Hz); 7.85 (1H, br. s); 7.25-7.19 (1H, m);

3.34-3.23 (2H, m); 3.07-2.94 (2H, m); 2.85-2.73 (2H, m); 2.26-2.15 (2H, m); 1.65 (3H, s). MS (ES)  $C_{14}H_{18}N_4O$  requires: 258, found: 259 ( $M+H$ )<sup>+</sup>.

The following examples were prepared according to the methods of the previous examples:

5

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
286	2-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}pyrrolidinium trifluoroacetate	324	325	Example 1 using Preparative Example A, CC5
287	2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-5-fluoro-2H-indazole-7-carboxamide trifluoroacetate	323	324	Example 1 using Preparative Example A, CC5
288	6-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1,2,3,4-tetrahydroisoquinolinium chloride	310	311	Example 1 using Preparative Example A, CC5
289	2-{4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]phenyl}piperidinium chloride	338	339	Example 1 using Preparative Example A, CC5
290	5-Fluoro-2-[4-(1H-pyrazol-1-yl)phenyl]-2H-indazole-7-carboxamide	321	322	Example 1 using Preparative Example A, CC5
291	2-[4-(Aminosulfonyl)phenyl]-5-fluoro-2H-indazole-7-carboxamide	334	335	Example 1 using Preparative Example A, CC5

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
292	5-Fluoro-2-(5,6,7,8-tetrahydro-1,7-naphthyridin-3-yl)-2H-indazole-7-carboxamide	311	312	Example 1 using Preparative Example A, CC5
293	5-Fluoro-2-(4-piperazin-2-ylphenyl)-2H-indazole-7-carboxamide	339	339	Example 1 using Preparative Example A, CC5
294	Methyl 4-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]benzoate	313	313	273
295	5-Fluoro-2-(1-methylpiperidin-3-yl)-2H-indazole-7-carboxamide	276	277	278
296	5-Fluoro-2-(1-ethylpiperidin-3-yl)-2H-indazole-7-carboxamide	290	291	279
297	5-Fluoro-2-(1-propylpiperidin-3-yl)-2H-indazole-7-carboxamide	304	305	280
298	5-Fluoro-2-(1-isopropylpiperidin-3-yl)-2H-indazole-7-carboxamide	304	305	281
299	2-(1-Cyclohexylpiperidin-3-yl)-5-fluoro-2H-indazole-7-carboxamide	344	345	282
300	5-Fluoro-2-(1-methylpiperidin-4-yl)-2H-indazole-7-carboxamide	276	277	278
301	5-Fluoro-2-(1-ethylpiperidin-4-yl)-2H-indazole-7-carboxamide	290	291	279
302	5-Fluoro-2-(1-propylpiperidin-4-yl)-2H-indazole-7-carboxamide	304	305	280
303	5-Fluoro-2-(1-isopropylpiperidin-4-yl)-2H-indazole-7-carboxamide	304	305	281
304	2-(1-Cyclohexylpiperidin-4-yl)-5-fluoro-2H-indazole-7-carboxamide	344	345	282
305	2-(1-Cyclobutylpiperidin-4-yl)-5-fluoro-2H-indazole-7-carboxamide	316	317	283
306	2-(1-Cyclobutylpiperidin-3-yl)-2H-indazole-7-carboxamide	298	299	283

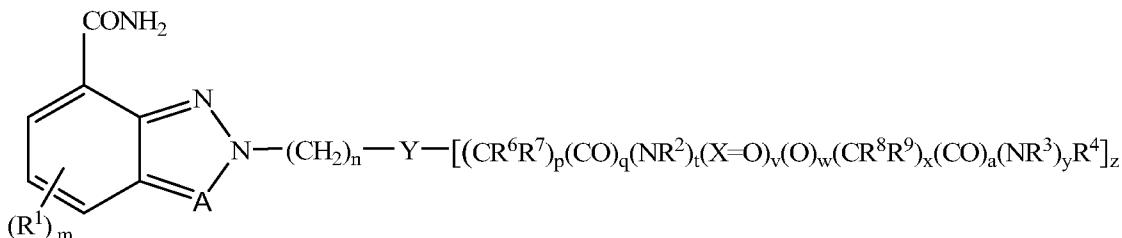
<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
307	2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-N,N-dimethylethanaminium trifluoroacetate	250	251	278
308	2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-N,N-diethylethanaminium trifluoroacetate	278	279	279
309	N-{2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl}propan-2-aminium trifluoroacetate	264	265	281
310	N-{2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl}cyclohexanaminium trifluoroacetate	304	305	282
311	2-[2-(Dicyclobutylamino)ethyl]-5-fluoro-2H-indazole-7-carboxamide	330	331	283
312	tert-Butyl 3-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidine-1-carboxylate	362	363	276
313	tert-Butyl 4-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidine-1-carboxylate	362	363	276
314	3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidinium trifluoroacetate	262	263	277
315	4-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]piperidinium trifluoroacetate	262	263	277
316	tert-Butyl 3-[7-(aminocarbonyl)-2H-indazol-2-yl]piperidine-1-carboxylate	344	345	276
317	tert-Butyl {2-[7-(aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl} carbamate	322	323	276
318	2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethanaminium trifluoroacetate	222	223	277
319	3-[7-(Aminocarbonyl)-2H-indazol-2-yl]piperidinium trifluoroacetate	244	245	277
320	3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-methylpiperidinium trifluoroacetate	258	259	278
321	3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-ethylpiperidinium trifluoroacetate	272	273	279
322	3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-propylpiperidinium trifluoroacetate	286	287	280
323	3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-isopropylpiperidinium trifluoroacetate	286	287	281
324	3-[7-(Aminocarbonyl)-2H-indazol-2-yl]-1-cyclohexylpiperidinium trifluoroacetate	326	327	282

<u>Example</u>	<u>Name</u>	<u>MWt</u>	<u>(M+H)<sup>+</sup></u>	<u>Procedure of Example</u>
325	3-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]-1-cyclobutylpiperidinium trifluoroacetate	316	317	283
326	<i>N</i> -{2-[7-(Aminocarbonyl)-5-fluoro-2H-indazol-2-yl]ethyl}- <i>N</i> -propylpropan-1-aminium trifluoroacetate	306	307	280

CLAIMS

1. A compound of formula I:

5



(I)

wherein:

a is 0 or 1;

m is 0, 1, 2 or 3;

10 n is 0, 1, 2, 3, 4, 5 or 6;

each p is independently 0, 1, 2, 3, 4, 5 or 6;

each q is independently 0 or 1;

each t is independently 0 or 1;

each v is independently 0 or 1;

15 each w is independently 0 or 1;

each x is independently 0, 1, 2, 3, 4, 5 or 6;

each y is independently 0 or 1;

z is 1, 2 or 3;

A is CH or N;

20 each R<sup>1</sup> is independently hydroxy, halogen, cyano, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or haloC<sub>1-6</sub>alkoxy;

Y is a direct bond or a ring which is: a C<sub>3-5</sub>cycloalkyl, a 4 membered saturated heterocycle containing one N atom, a 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S, a 5 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from O, N and S, but not more than one of which is O or S, a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms, a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring or a 8-13 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S;

30 each R<sup>2</sup> is independently hydrogen, C<sub>1-6</sub>alkyl or C<sub>3-10</sub>cycloalkyl;

each X is independently C or SO;

each R<sup>3</sup> is independently hydrogen or C<sub>1-6</sub>alkyl;

each  $R^4$  is independently hydrogen, hydroxy, cyano, halogen,  $C_{1-6}$ alkyl,  $C_{2-10}$ alkenyl, halo $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl,  $C_{1-6}$ alkoxy, halo $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxycarbonyl, carboxy, nitro or a ring which is:  $C_{6-10}$ aryl;  $C_{6-10}$ aryloxy;  $C_{6-10}$ arylcarbonyl;  $C_{3-10}$ cycloalkyl; a 4 membered saturated heterocyclic ring containing one N atom; a 5 or 6 membered saturated or partially saturated 5 heterocyclic ring containing one, two or three atoms independently selected from N, O and S; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-15 membered unsaturated, partially saturated or saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being 10 optionally substituted by one or more groups independently selected from  $(CH_2)_bR^5$ ;

each  $b$  is independently 0, 1, 2, 3, 4, 5 or 6;

each  $R^5$  is independently hydroxy, oxo, cyano, halogen,  $C_{1-6}$ alkyl,  $C_{2-10}$ alkenyl, halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl,  $C_{1-6}$ alkoxy, halo $C_{1-6}$ alkoxy, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxycarbonyl, carboxy,  $NR^aR^b$ ,  $CONR^aR^b$ ,  $S(O)_rR^c$  or a ring which is:  $C_{6-10}$ aryl;  $C_{6-10}$ aryl $C_{1-6}$ alkyl; a 4 membered saturated heterocyclic 15 ring containing one N atom; a 5, 6 or 7 membered saturated or partially saturated heterocyclic ring containing one, two or three atoms independently selected from N, O and S; a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 20 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{2-10}$ alkenyl, halo $C_{1-6}$ alkyl, amino,  $C_{1-6}$ alkylamino and di( $C_{1-6}$ alkyl)amino;

each of  $R^a$  and  $R^b$  is independently hydrogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl, halo $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl,  $S(O)_rR^c$  or  $S(O)_rN(R^d)_2$ ; or 25

$R^a$  and  $R^b$  together with the N atom to which they are attached form a 4 membered saturated heterocycle containing one N atom or a 5, 6 or 7 membered saturated or partially saturated heterocycle containing one, two or three N atoms and zero or one O atom, the ring being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{2-10}$ alkenyl and halo $C_{1-6}$ alkyl;

30  $r$  is 0, 1 or 2;

$R^c$  is  $C_{1-6}$ alkyl,  $C_{6-10}$ aryl, a 5 membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, not more than one heteroatom of which is O or S; a 6 membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; or a 7-10 membered unsaturated or partially 35 saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S; any of which rings being optionally substituted by one or more groups independently selected from hydroxy, cyano, halogen,  $C_{1-6}$ alkyl,  $C_{2-10}$ alkenyl and halo $C_{1-6}$ alkyl;

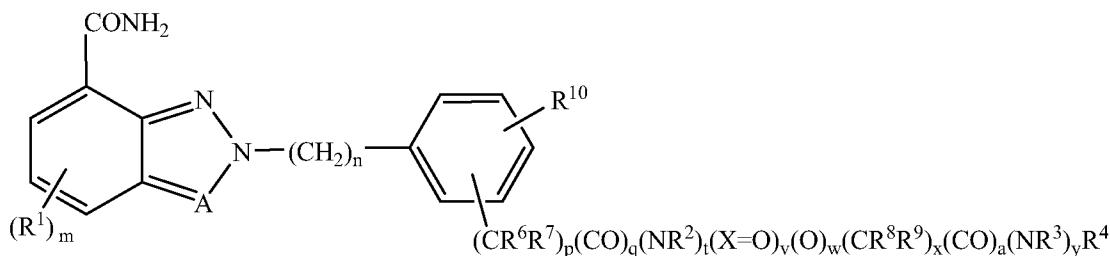
each  $R^d$  is independently hydrogen or  $C_{1-6}$ alkyl;

each of  $R^6$  and  $R^7$  is independently hydrogen or  $C_{1-6}$ alkyl;

each of R<sup>8</sup> and R<sup>9</sup> is independently hydrogen, C<sub>1-6</sub>alkyl, hydroxy, haloC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, amino, C<sub>1-6</sub>alkylamino or di(C<sub>1-6</sub>alkyl)amino;  
or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

5 2. A compound of claim 1 wherein Y is a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms, a 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring or a 8-13 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S.

10 3. A compound of claim 1 of formula II:



(II)

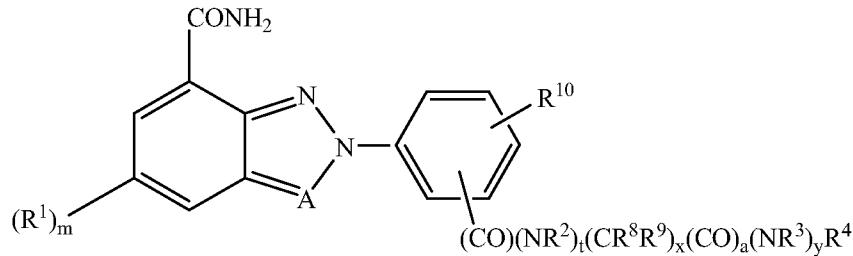
wherein:

a, m, n, p, q, t, v, w, x, y, A,  $R^1, R^2, R^3, R^4, R^6, R^7, R^8$  and  $R^9$  are as defined in claim 1;

15 R<sup>10</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl or haloC<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

4. A compound of claim 1 formula IV:



20

wherein:

$m$ ,  $A$ ,  $R^1, R^2, R^3, R^4, R^8$  and  $R^9$  are as defined in claim 1;

a is 0 or 1;

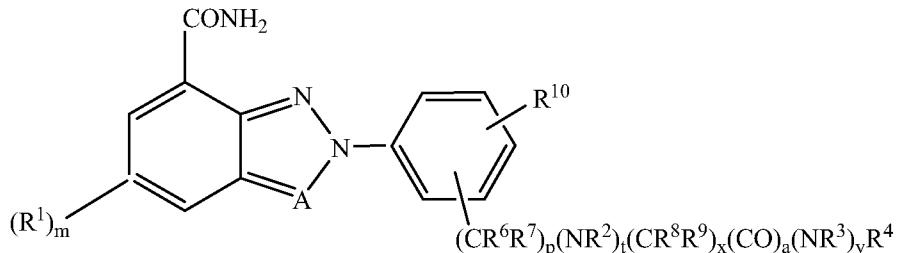
$t$  is 0 or 1;

25 x is 0, 1 or 2;

y is 0 or 1;

$R^{10}$  is hydrogen, halogen,  $C_{1-6}$ alkyl or  $haloC_{1-6}$ alkyl;  
or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof

5. A compound of claim 1 of formula V:



(V)

wherein:

a, m, t, y, A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are as defined in claim 1;

p is 1 or 2;

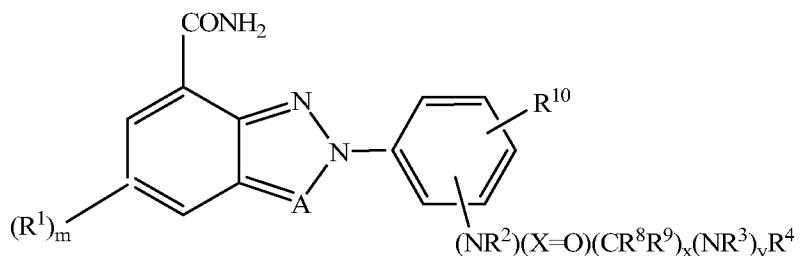
10 x is 0, 1 or 2;

$R^{10}$  is hydrogen, halogen,  $C_{1-6}$ alkyl or  $haloC_{1-6}$ alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof

6. A compound of claim 1 of formula VI:

15



(VI)

wherein:

m, y, A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^8$ ,  $R^9$  and X are as defined in claim 1;

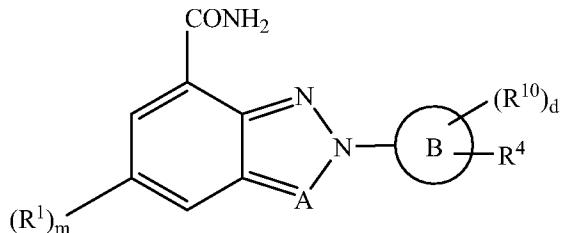
x is 0, 1 or 2;

20  $R^{10}$  is hydrogen, halogen,  $C_{1-6}$ alkyl or  $haloC_{1-6}$ alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof

7. A compound of claim 1 of formula VII:

25



(VII)

wherein:

m, A, R<sup>1</sup> and R<sup>4</sup> are as defined in claim 1;

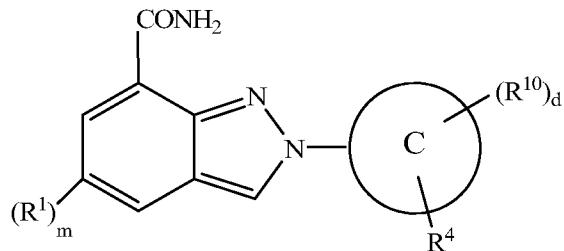
5 d is 0, 1 or 2;

B is a 6 membered unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms, 6-13 membered saturated, partially saturated or unsaturated hydrocarbon ring or a 8-13 membered unsaturated or partially saturated heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S;

R<sup>10</sup> is halogen or C<sub>1-6</sub>alkyl;

10 or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

8. A compound of claim 1 of formula VIII:



(VIII)

15 wherein m, R<sup>1</sup> and R<sup>4</sup> are as defined in claim 1;

d is 0, 1 or 2;

C is a 4 membered saturated heterocycle containing one N atom or a 5, 6 or 7 membered saturated or partially saturated heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S;

20 R<sup>10</sup> is halogen or C<sub>1-6</sub>alkyl;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

9. A compound of any previous claim wherein:

R<sup>4</sup> is hydrogen, hydroxy, halogen, C<sub>1-4</sub>alkyl, haloC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, cyano or a ring selected 25 from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl, oxazolyl, pyridinyl, quinoxalinyl, phenyl, azoniaspiro[5.5]undecanyl, quinolinyl,

isoquinoliny, azepanyl, tetrahydroisoquinoliny, octahydroindoliziny, morpholiny, 1'2'-dihydrospirocyclohexane-1,3'-indolyl, octahydroisoindolyl, azoniabicyclo[3.1.0]hexanyl, diazoniaspiro[4.4]nonanyl, hexahydropyrrolo[3,4-b]pyrrolyl, oxaazoniabicyclo[2.2.1]heptanyl, diazoniaspiro[5.5]undecanyl, diazoniaspiro[3.3]heptanyl, diazoniaspiro[3.5]nonanyl,

5 diazoniaspiro[4.5]decanyl, octahydropyrrolo[3,4-c]pyrrolyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydrocyclopenta[c]pyrrolyl, dihydroindolyl, benzothiazolyl, azoniaspiro[4.5]decanyl, diazoniabicyclo[2.2.2]octanyl, diazoniabicyclo[2.2.1]heptanyl, diazoniabicyclo[3.2.1]octanyl, diazoniabicyclo[2.2.1]heptanyl, azoniabicyclo[3.1.0]hexanyl, tetrahydrothiophenyl, tetrahydronaphthyridiny, oxaazoniaspiro[4.5]decanyl, oxazepanyl, tetrazolyl, cyclobutyl,

10 10 dihydroimidazolyl and pyrazolyl, the ring being optionally substituted by one or more independently selected  $(CH_2)_bR^5$  groups;

b is 0 or 1;

$R^5$  is  $C_{1-6}$ alkyl,  $NR^aR^b$ , oxo,  $S(O)_rR^c$ ,  $C_{1-6}$ alkoxycarbonyl, halogen, hydroxy,  $C_{1-6}$ alkylcarbonyl, hydroxy $C_{1-6}$ alkyl,  $CONR^aR^b$ , halo $C_{1-6}$ alkyl or an optionally substituted ring selected from  $C_{6-10}$ aryl,  $C_{6-10}$ arylc $C_{1-6}$ alkyl, pyrrolidinyl, piperazinyl, pyrimidinyl, pyridinyl, piperidinyl, thiomorpholiny, imidazolyl and benzimidazolyl;

15 r is 1 or 2;

each of  $R^a$  and  $R^b$  is independently hydrogen,  $C_{1-6}$ alkyl or  $S(O)_2R^c$ ; and

$R^c$  is  $C_{1-6}$ alkyl.

20 10. A pharmaceutical composition comprising a compound of any previous claim, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof in association with a pharmaceutically acceptable carrier.

25 11. A compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof and an anti-cancer agent for simultaneous, separate or sequential administration.

12. A compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or tautomer, for use in therapy.

30 13. The use of a compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof for the manufacture of a medicament for the treatment or prevention of conditions which can be ameliorated by the inhibition of poly(ADP-ribose) polymerase (PARP).

35 14. The use of a compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof for the manufacture of a medicament for the treatment or prevention of cancer, inflammatory diseases, reperfusion injuries, ischemic conditions, stroke, renal failure,

cardiovascular diseases, vascular diseases other than cardiovascular diseases, diabetes, neurodegenerative diseases, retroviral infection, retinal damage or skin senescence and UV-induced skin damage.

15. The use of a compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt,

5 stereoisomer or tautomer, as a chemo- or radiosensitizer for cancer treatment.

16. A method of treating or preventing cancer, inflammatory diseases, reperfusion injuries, ischemic conditions, stroke, renal failure, cardiovascular diseases, vascular diseases other than cardiovascular diseases, diabetes, neurodegenerative diseases, retroviral infection, retinal damage or skin senescence and

10 UV-induced skin damage, which method comprises administration to a patient in need thereof of an effective amount of a compound of claim 1 or a composition comprising a compound of claim 1.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2007/050177

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07D231/56 A61K31/416 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
C07D

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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/26192 A (BASF AG [DE]; LUBISCH WILFRIED [DE]; KOCK MICHAEL [DE]; HOEGER THOMAS) 11 May 2000 (2000-05-11) examples 1-62 -----	1-16
A	WO 2005/066136 A (LILLY CO ELI [US]; CONNER SCOTT EUGENE [US]; MANTLO NATHAN BRYAN [US];) 21 July 2005 (2005-07-21) examples ----- -/-	1-16

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document 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

4 September 2007

Date of mailing of the international search report

11/09/2007

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No PCT/GB2007/050177
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## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ISHIDA ET AL: "4-Phenyl-1,2,3,6-tetrahydropyridine, an excellent fragment to improve the potency of PARP-1 inhibitors" BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 15, no. 19, 1 October 2005 (2005-10-01), pages 4221-4225, XP005038878 ISSN: 0960-894X examples</p> <p>-----</p>	1-16
A	<p>PARVEEN I ET AL: "2-nitroimidazol-5-ylmethyl as a potential bioreductively activated prodrug system: reductively triggered release of the PARP inhibitor 5-bromoisoquinolinone" BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 14, 19 July 1999 (1999-07-19), pages 2031-2036, XP004171631 ISSN: 0960-894X examples</p> <p>-----</p>	1-16

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2007/050177

### Box 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:  

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box 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 an additional fee, this Authority did not invite payment of any additional fee.
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.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No

PCT/GB2007/050177

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WO 2005066136	A 21-07-2005	EP 1706386 A1		04-10-2006
		JP 2007520471 T		26-07-2007