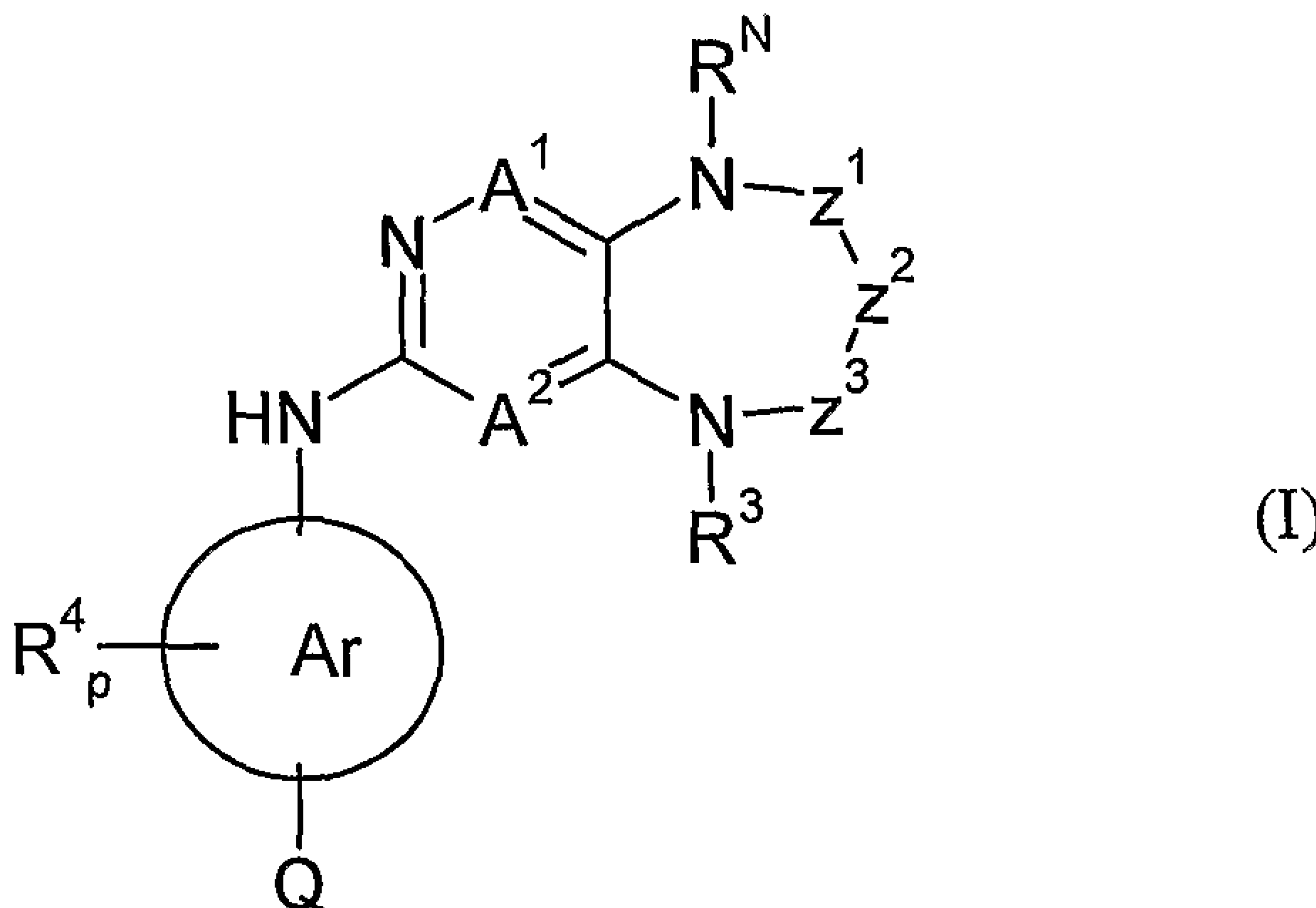




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There is provided a compound of formula (I); processes for the manufacture thereof, pharmaceutical compositions thereof and uses in therapy.



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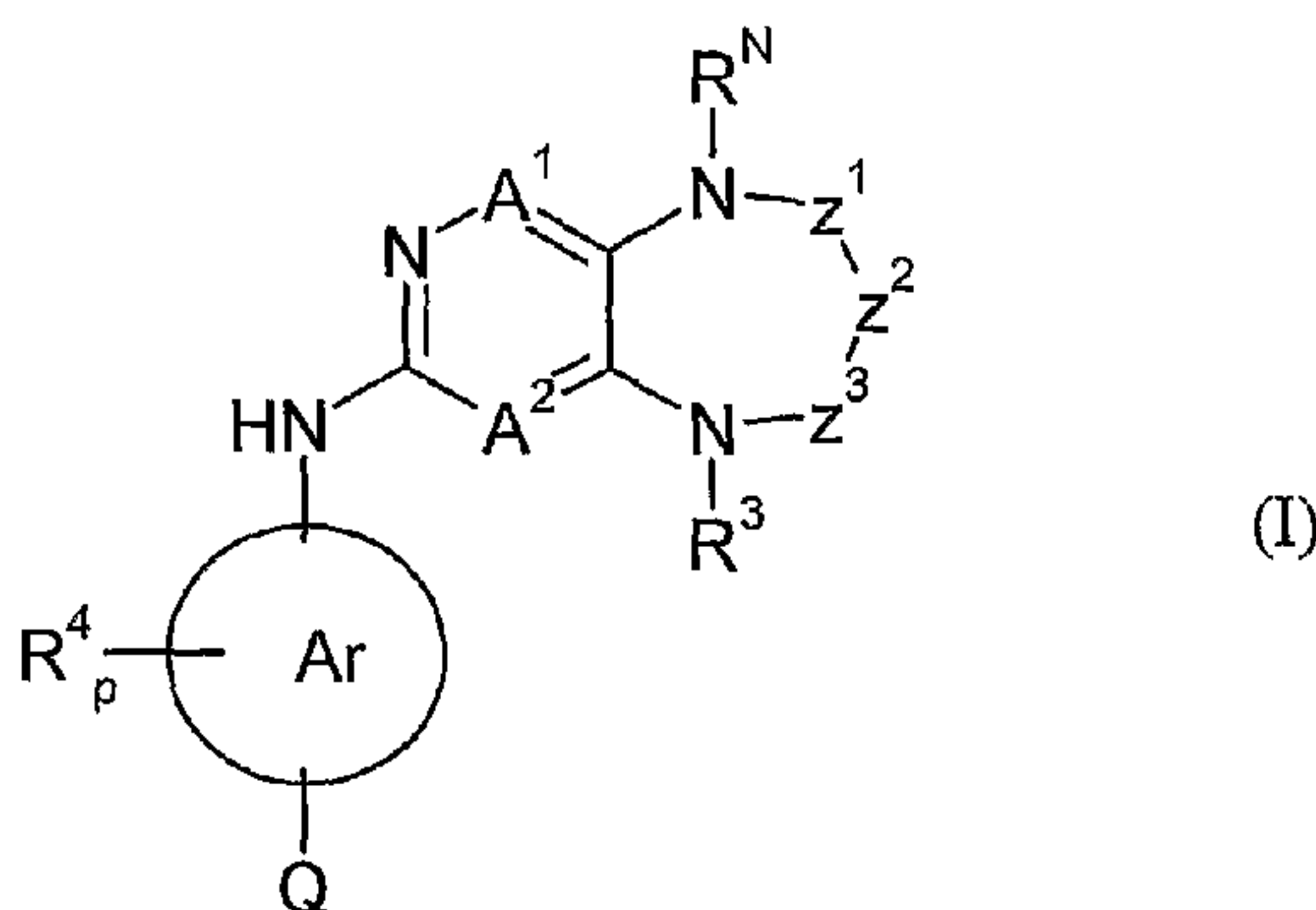
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(57) Abstract: There is provided a compound of formula (I); processes for the manufacture thereof, pharmaceutical compositions thereof and uses in therapy.

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NOVEL COMPOUNDS

The present invention relates to pyrimidine derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy and the treating of conditions mediated by polo-like kinases.

Many of the current treatment regimes for cell proliferation diseases such as cancer and psoriasis utilise compounds that inhibit DNA synthesis. Compounds that inhibit DNA synthesis may often prove to be toxic to many types of cells. However, the marked toxic effect on rapidly dividing cells such as tumour cells is often seen to offer a benefit in light of the general toxic nature of such compounds. Therefore, alternative antiproliferative agents that act by mechanisms other than the inhibition of DNA synthesis may offer the potential for selective targeting of the proliferating cells.

The Cyclin dependent kinase family (Cdks) have long been considered the master regulators of the cell cycle but an increasing number of diverse protein kinases are emerging as critical components of cell cycle progression. Among these are the polo-like kinase family (Plks), serine/threonine kinases that play multiple roles in regulating progress through cell cycle. In man, four distinct family members have been identified. These are Plk1, Plk2 (Snk), Plk3 (Fnk, Prk) and Plk4 (Sak).

The best characterized family member is Plk1 which is conserved from yeast to man and has been implicated in numerous mitotic processes including activation of Cdc25C and Cdk1/Cyclin B at the G2-M transition, centrosome maturation, spindle formation and assembly (Glover et al. 1998, Genes Dev. 12:3777-87; Barr et al 2004, Nat. Rev. Mol. Cell Biol 5:429-441). In the later stages of mitosis Plk1 is involved in separation of sister chromatids, activation of components of the anaphase-promoting complex and septin regulation during cytokinesis (van Vugt & Medema 2005, Oncogene 24:2844-2859).

Plk1 is overexpressed in a broad spectrum of cancer types including breast, colorectal, endometrial, oesophageal, ovarian, prostate, pancreatic, non small cell lung cancers and melanomas (Wolf et al. 1997, Oncogene 14:543-549; Knecht et al. 1999, Cancer Res. 59:2794-2797; Wolf et al. 2000, Pathol. Res. Pract. 196:753-759; Takahashi et al. 2003, Cancer Sci. 94:148-152). The expression of Plk1 often correlates with poor patient prognosis.

The conclusion that Plk1 elevation is a cause and not a consequence of oncogenesis resulted from a study demonstrating that overexpression or constitutive expression of Plk1 induces malignant transformation of mammalian cells, causing tumour formation in nude mice (Smith et al 1997, Biochem. Biophys. Res. Commun 234:397-405)

5 Therapeutic potential for Plk1 inhibition has been demonstrated in studies employing both antisense oligonucleotides (ASO) and small molecule RNA (siRNA). Reduction in the level of Plk1 results in the inhibition of proliferation of tumour cells and loss of cell viability both *in vivo* and *in vitro* but does not inhibit proliferation of primary cells (Spankuch-Schmitt et al 2002, Oncogene 21: 3162-3171; Elez et al 2003, Oncogene 22:69-80). Microinjection of
10 anti-Plk1 antibodies induced mitotic catastrophe in HeLa tumour cells. These cells displayed abnormal distribution of chromatin and monoastal microtubules while normal fibroblast cells arrested transiently in G2 phase of cell cycle as single mononucleated cells (Lane & Nigg 1996 J.Cell Biol. 135:1701-1713). These results suggest that Plk1 inhibition specifically targets cancer cells with checkpoint defects while cells with intact checkpoint pathways are
15 less affected.

Although the exact functions of the other family members remains largely unknown, silencing of Plk2 in the presence of taxol or nocodazole significantly increases apoptosis suggesting Plk2 may prevent mitotic catastrophe following spindle damage (Burns et al. 2003, Mol Cell Biol 23: 5556-5571). Likewise silencing of Plk4 in mammalian cells induces
20 apoptosis (Li et al. 2005, Neoplasia 7: 312-323) and plk4 null mouse embryos arrest with an increase in mitotic and apoptotic cells (Hudson et al. 2001, Curr Biol 11: 441-446).

Plk3 also appears to play roles in mitosis, like Plk1 it has been reported to phosphorylate Cdc25C, regulate microtubule dynamics and is involved in centrosome function. Overexpression of Plk3 has been observed in both breast and ovarian carcinomas,
25 with little or no expression in adjacent normal tissue. Increased protein level was associated with enhanced mitosis and was significantly linked to reduced median survival time of patients (Weichert et al. 2005, Virchows Arch 446: 442-450; Weichert et al. 2004 Br. J.Cancer 90:815-821).

These findings suggest that pharmacological inhibitors of Plk family members should
30 be of therapeutic value for treatment of proliferative disease including solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In addition Plk

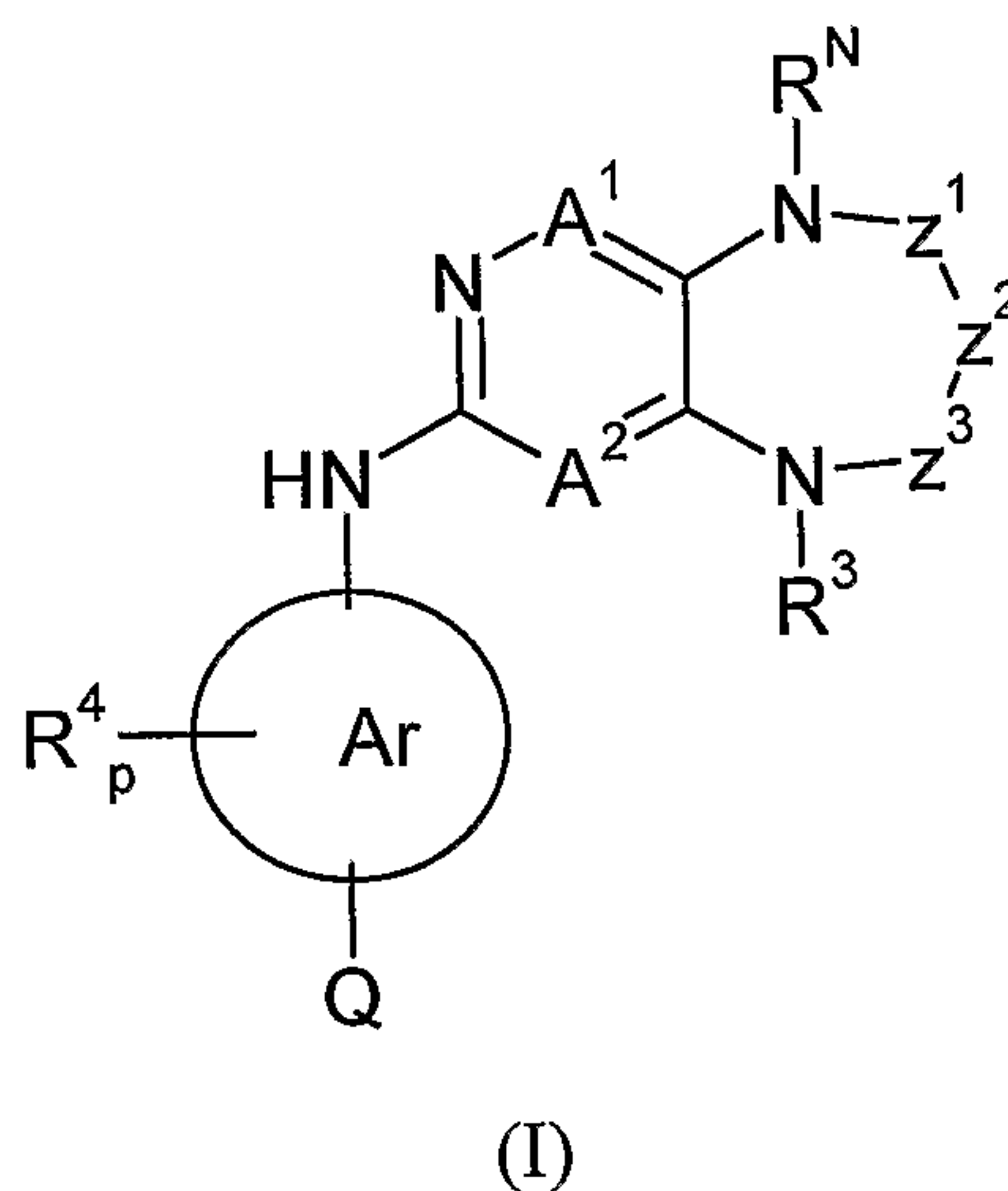
inhibitors should be useful in the treatment of other disorders associated with uncontrolled cellular proliferation.

Pteridinone derivatives are known from the prior art as active substances with an antiproliferative activity. WO 01/019825 and WO 03/020722 describe the use of pteridinone
5 derivatives for the treatment of tumoural diseases.

The resistance of many types of tumours calls for the development of new pharmaceutical compositions for combating tumours.

The aim of the present invention is to provide new compounds having an antiproliferative activity.

10 According to a first aspect of the present invention there is provided a compound of formula (I):



15 wherein

R³ represents hydrogen, an optionally substituted C₁₋₁₂alkyl group, an optionally substituted C₂₋₁₂alkenyl group, an optionally substituted C₂₋₁₂alkynyl group, an optionally substituted C₆₋₁₄aryl group, an optionally substituted C₃₋₁₂cycloalkyl group, an optionally substituted C₃₋₁₂cycloalkenyl group, an optionally substituted C₇₋₁₂polycycloalkyl group, an optionally substituted C₇₋₁₂polycycloalkenyl group, an
20 optionally substituted C₅₋₁₂spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2

heteroatoms, or an optionally substituted heteroaryl ring comprising 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen or sulphur;

R^4 each independently represent $-\text{CN}$, hydroxy, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-\text{NH}_2$, $-\text{OH}$, $-\text{CN}$, $-\text{C}=\text{CH}$, $-\text{C}(=\text{O})\text{NH}_2$, C_{1-3} alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{1-3} alkyloxy, C_{1-3} alkylcarbonyl, $-\text{CHO}$, or $-\text{SO}_2\text{Me}$

p is 0, 1 or 2;

Q is $-\text{C}(=\text{X}^1)-\text{NR}^a\text{R}^b$, $-\text{S}(\text{O})_2-\text{NR}^{a2}\text{R}^{b2}$, $-(\text{optionally substituted } \text{C}_{1-3}\text{alkyl})_g-\text{NR}^{a3}\text{R}^{b3}$, $-\text{S}(\text{O})_k-\text{R}^{a8}$, $-\text{C}(=\text{X}^2)-\text{OR}^{a9}$, $-\text{OR}^{a10}$ or $-(5\text{- or } 6\text{-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur})-\text{L}_n-\text{R}_m^5$;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted C_{1-6} alkyl group, and R^b represents $-\text{L}_n-\text{R}_m^5$, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b2} represents $-\text{L}_n-\text{R}_m^5$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b3} represents $-\text{L}_n-\text{R}_m^5$, $-\text{SO}_2\text{NR}^{a4}\text{R}^{b4}$, $-\text{C}(=\text{O})\text{NR}^{a5}\text{R}^{b5}$, $-\text{SO}_2\text{R}^{a6}$, $-\text{C}(=\text{O})\text{OR}^{a7}$, or R^{a3} and R^{b3} together

with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b4} represents $-L_n-R^5_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached

form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b5} represents $-L_n-R^5_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached

form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a6} represents $-L_n-R^5_m$;

R^{a7} represents $-L_n-R^5_m$;

R^{a8} represents $-L_n-R^5_m$;

R^{a9} represents $-L_n-R^5_m$;

R^{a10} represents $-L_n-R^5_m$;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{7-12} polycycloalkyl group, optionally substituted C_{7-12} polycycloalkenyl group, optionally substituted C_{5-12} spirocycloalkyl group and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatane, optionally substituted oxogranatane and $-NR^8R^9$;

R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group;

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

X^1 is O or S;

X^2 is O, S or H_2 ;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur; and

A^1 , A^2 each independently represents N or CH;

and wherein

when Z^1 is C=O, Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2 ;

R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group; or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d , or R^1 and R^e together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

or when Z^2 is $C=O$, Z^1 is $CR^{f2}R^{g2}$ and Z^3 is CR^1R^2 ;

5 R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

10 R^{f2} , R^{g2} each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^{f2} and R^{g2} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^1 and R^3 , or R^2 and R^3 together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

15 or when Z^3 is $C=O$, Z^2 is $CR^{c3}R^{d3}$ or NR^{e3} and Z^1 is $CR^{f3}R^{g3}$;

R^{c3} , R^{d3} each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^{c3} and R^{d3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

20 R^{e3} represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group;

R^{f3} , R^{g3} each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^{f3} and R^{g3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

25 optionally one of R^{c3} and R^{f3} , or R^{d3} and R^{g3} , or R^{e3} and R^{f3} together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom

or when Z^1 is CR^fR^g , Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2 ;

30 R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the

carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group;

R^f , R^g each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d , or R^1 and R^{e3} together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom,

or pharmacologically acceptable salts thereof.

The term alkyl group, including alkyl groups which are a part of other groups, unless otherwise stated, includes branched and unbranched alkyl groups with 1 to 12 carbon atoms. Examples of C_{1-12} alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and dodecyl groups. Unless otherwise stated, the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and dodecyl include all the possible isomeric forms. For example, the term propyl includes the two isomeric groups n-propyl and iso-propyl, the term butyl includes n-butyl, iso-butyl, sec-butyl and tert-butyl, the term pentyl includes isopentyl, neopentyl, etc.

In the above mentioned alkyl groups, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, alkyl groups may be substituted by the following substituents groups: =O; OH; NO_2 ; CN; $-NH_2$; halogen, for example fluorine or chlorine; optionally substituted C_{1-10} alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted $-OC_{1-3}$ alkyl, for example OMe, OEt, $-OCHF_2$, $-OCF_3$; $-COOH$; $-COO-C_{1-4}$ alkyl, for example $-COOMe$ or $-COOEt$; or $-CONH_2$. " $=O$ " denotes an oxygen atom linked via a double bond. All the hydrogen atoms of the alkyl group may optionally be

replaced by substituent groups, for example a trifluoromethyl group is a methyl group wherein all the hydrogen atoms have been replaced with fluorine atoms.

The term alkyl bridge, unless otherwise stated, includes branched and unbranched alkyl bridging groups with 1 to 5 carbon atoms, for example methylene, ethylene, propylene, butylene and pentylene bridges. Unless otherwise stated, the terms propylene, butylene and pentylene include all the possible isomeric forms. In the aforementioned alkyl bridges, 1 or 2 C-atoms may optionally be replaced by one or more heteroatoms selected from among oxygen, nitrogen or sulphur.

The term alkenyl groups (including those which are a part of other groups), unless otherwise stated, includes branched and unbranched alkylene groups with 2 to 10 carbon atoms comprising at least one carbon-carbon double bond. Examples of C₂₋₁₀alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl groups. Unless otherwise stated, the abovementioned terms propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl also include all the possible isomeric forms. For example, the term butenyl includes 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl and 1-ethyl-1-ethenyl.

In the above mentioned alkenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, alkenyl groups may be substituted by the following substituents groups: =O; OH; NO₂; CN; -NH₂; halogen, for example fluorine or chlorine; optionally substituted C₁₋₁₀alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC₁₋₃alkyl, for example OMe, OEt, -OCHF₂, -OCF₃; -COOH; -COO-C₁₋₄alkyl, for example -COOMe or -COOEt; or -CONH₂. "=O" denotes an oxygen atom linked via a double bond. All the hydrogen atoms of the alkenyl group may optionally be replaced, for example a trifluoroethylene group is an ethylene group wherein all the hydrogen atoms have been replaced with fluorine atoms.

The term alkynyl groups (including those which are a part of other groups), unless otherwise stated, includes branched and unbranched alkynyl groups with 2 to 10 carbon atoms comprising at least one triple bond. Examples of C₂₋₁₀alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl groups. Unless otherwise stated, the terms propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl

and decynyl also include all the possible isomeric forms. For example, the term butynyl includes 1-butyne, 2-butyne, 3-butyne and 1-methyl-2-propyne.

In the above mentioned alkynyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, alkynyl groups may be substituted by the following substituents groups: =O; OH; NO₂; CN; -NH₂; halogen, for example fluorine or chlorine; optionally substituted C₁₋₁₀alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC₁₋₃alkyl, for example OMe, OEt, -OCHF₂, -OCF₃; -COOH; -COO-C₁₋₄alkyl, for example -COOMe or -COOEt; or -CONH₂. "=" denotes an oxygen atom linked via a double bond. All the hydrogen atoms of the alkynyl group may optionally also be replaced.

The term aryl includes aromatic ring systems with 6 to 14 carbon atoms, said aromatic ring systems comprising one or more rings having from 6 to 14 ring atoms wherein at least one ring is aromatic. Examples of C₆₋₁₄aryl groups include phenyl (C₆), indenyl (C₉), naphthyl (C₁₀), fluorenyl (C₁₃), anthracenyl (C₁₄), and phenanthryl (C₁₄). In the above mentioned aryl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, aryl groups may be substituted by the following substituents groups: OH; NO₂; CN; NH₂; halogen, for example fluorine or chlorine; optionally substituted C₁₋₁₀alkyl, for example methyl, ethyl, propyl or CF₃; optionally substituted -OC₁₋₃alkyl, for example -OMe, -OEt, -OCHF₂, or -OCF₃; -COOH, -COO-C₁₋₄alkyl, for example -COOMe or -COOEt, or -CONH₂.

The term heteroaryl comprising 1 or 2 nitrogen atoms includes heteroaromatic ring systems with 5 to 14 ring atoms, said heteroaromatic ring systems comprising one or more rings having from 5 to 14 ring atoms wherein at least one ring is aromatic and wherein one or two of the ring atoms are replaced by nitrogen atoms the remaining ring atoms being carbon atoms. Examples of heteroaryl groups wherein up to two carbon atoms are replaced by one or two nitrogen atoms comprising one ring include pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl and pyrimidinyl groups. Each of the aforementioned examples of heteroaryl rings may optionally also be annellated by a further ring, for example a benzene ring. Examples of heteroaryl groups wherein up to two carbon atoms are replaced by one or two nitrogen atoms comprising two rings include indolyl, benzimidazolyl, quinolyl, isoquinolyl and quinazolinyl. In the above mentioned heteroaryl groups, unless otherwise stated, one or more

hydrogen atoms may optionally be replaced by other substituent groups. For example, heteroaryl groups may be substituted by the following substituents groups: F; Cl; Br; OH; OMe; Me; Et; CN; NH₂; CONH₂; optionally substituted phenyl; and optionally substituted heteroaryl, for example optionally substituted pyridyl.

5 The term optionally substituted heteroaryl ring comprising 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen or sulphur includes heteroaromatic ring systems with 5 to 14 ring atoms, said heteroaromatic ring systems comprising one or more rings having from 5 to 14 ring atoms wherein at least one ring is aromatic and wherein one, two or three of the ring atoms are replaced by nitrogen, oxygen or sulphur atoms the
10 remaining ring atoms being carbon atoms. Examples of heteroaryl rings wherein up to three carbon atoms are replaced by nitrogen, oxygen or sulphur comprising one ring include furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiazolyl, thienyl and triazolyl groups. Each of the aforementioned examples of heteroaryl rings may optionally also be anellated by a further ring, for example a
15 benzene ring. Examples of heteroaryl rings wherein up to three carbon atoms are replaced by nitrogen, oxygen or sulphur atoms comprising two rings include indolyl, benzimidazolyl, benzoxazolyl, benzioxazolyl, quinolinyl, isoquinolinyl and quinazolinyl. In the above mentioned heteroaryl rings, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, heteroaryl groups may be
20 substituted by the following substituents groups: F; Cl; Br; OH; OMe; Me; Et; CN; NH₂; CONH₂; optionally substituted phenyl; and optionally substituted heteroaryl, for example optionally substituted pyridyl.

The term cycloalkyl groups, unless otherwise stated, includes cycloalkyl groups comprising 1 ring with 3-12 carbon atoms. Examples of C₃₋₁₂cycloalkyl groups include
25 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl groups. In the abovementioned cycloalkyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, cycloalkyl groups may be substituted by the following substituents groups: =O; OH; NO₂; CN; -NH₂; halogen, for example fluorine or chlorine;
30 optionally substituted C₁₋₁₀alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC₁₋₃alkyl, for example OMe, OEt, -OCHF₂, -OCF₃; -COOH;

-COO-C₁₋₄alkyl, for example -COOMe or -COOEt; or -CONH₂. "=O" denotes an oxygen atom linked via a double bond.

The term cycloalkenyl, unless otherwise stated, includes cycloalkenyl groups with 3-12 carbon atoms comprising one ring, said ring comprising at least one carbon-carbon double bond. Examples of C₃₋₁₂cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl, cycloundecenyl and cyclododecenyl groups. In the abovementioned cycloalkenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, cycloalkenyl groups may be substituted by the following substituent groups: =O; OH; NO₂; CN; -NH₂; halogen, for example fluorine or chlorine; optionally substituted C₁₋₁₀alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC₁₋₃alkyl, for example OMe, OEt, -OCHF₂, -OCF₃; -COOH; -COO-C₁₋₄alkyl, for example -COOMe or -COOEt; or -CONH₂. "=O" denotes an oxygen atom linked via a double bond.

The terms heterocycloalkyl and heterocycloalkenyl, unless otherwise described in the definitions, includes 3- to 12-membered, for example 5-, 6- or 7-membered, heterocycles which may contain 1 to 4 heteroatoms selected from nitrogen, oxygen or sulphur. Heterocycloalkyl denotes a saturated heterocycle, and heterocycloalkenyl denotes an unsaturated heterocycle. Examples of heterocycloalkyl or heterocycloalkenyl groups include tetrahydrofuran, tetrahydrofuranone, *gamma*-butyrolactone, *alpha*-pyran, *gamma*-pyran, dioxolane, tetrahydropyran, dioxane, dihydrothiophene, thiolan, dithiolan, pyrroline, pyrrolidine, pyrazoline, pyrazolidine, imidazoline, imidazolidine, tetrazole, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, tetrazine, morpholine, thiomorpholine, diazepam, oxazine, tetrahydro-oxazinyl, isothiazole, and pyrazolidine. In the abovementioned heterocycloalkyl or heterocycloalkenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, heterocycloalkyl or heterocycloalkenyl groups may be substituted by the following substituents groups: =O; OH; CN; -NH₂; halogen, for example fluorine or chlorine; optionally substituted C₁₋₄alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC₁₋₃alkyl, for example OMe, OEt, -OCHF₂, -OCF₃; -COOH; -COO-C₁₋₄alkyl, for example -COOMe or -COOEt; or -CONH₂. "=O" denotes an oxygen atom linked via a double bond.

The term polycycloalkyl, unless otherwise stated, includes cycloalkyl groups comprising 3 to 12 carbon atoms and comprising 2 or more rings. Examples of polycycloalkyl groups include optionally substituted, bi-, tri-, tetra- or pentacyclic cycloalkyl groups, for example pinane, 2,2,2-octane, 2,2,1-heptane or adamantane.

5 The term polycycloalkenyl, unless otherwise stated, includes cycloalkenyl groups comprising 7 to 12 carbon atoms and comprising 2 or more rings wherein at least one ring comprises a carbon-carbon double bond. Examples of polycycloalkenyl groups are optionally bridged and/or substituted bi-, tri-, tetra- or pentacyclic cycloalkenyl groups, for example bicycloalkenyl or tricycloalkenyl groups having at least one double bond, such as norbornene.

10 The term spirocycloalkyl unless otherwise stated, includes spirocycloalkyl groups comprising 5 to 12 carbon atoms and comprising 2 or more rings wherein two rings are joined at a spiro carbon centre. Examples of spirocycloalkyl groups include spiro[4.4]nonyl and spiro[3.4]octyl.

The term 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at
15 least one ring heteroatom selected from nitrogen, oxygen and sulphur is a fully unsaturated, aromatic monocyclic ring containing 5 or 6 atoms of which one or more ring atoms is optionally a heteroatom selected from nitrogen, oxygen or sulphur, with the remaining ring atoms being carbon. Examples of a 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and
20 sulphur include furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl thiazolyl, thienyl and triazolyl rings.

The term 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms includes optionally substituted C₃₋₆cylcoalkyl and optionally substituted C₃₋₆cylcoalkenyl groups, and optionally substituted 3- to 6-membered heterocylcoalkyl and
25 optionally substituted 3- to 6-membered heterocylcoalkenyl groups each with 1 or 2 heteroatoms.

The term halogen includes fluorine, chlorine, bromine or iodine.

The terms alkyloxy (-OR wherein R is an alkyl), alkenyloxy (-OR wherein R is an alkenyl), alkynyloxy (-OR wherein R is an alkynyl), cycloalkyloxy (-OR wherein R is a
30 cycloalkyl) and heterocycloalkoxy (-OR wherein R is a heterocycloalkyl) denote an -OR

group wherein the respective alkyl, alkenyl, alkynyl, cycloalkyl or heterocycloalkyl group is as hereinbefore described above.

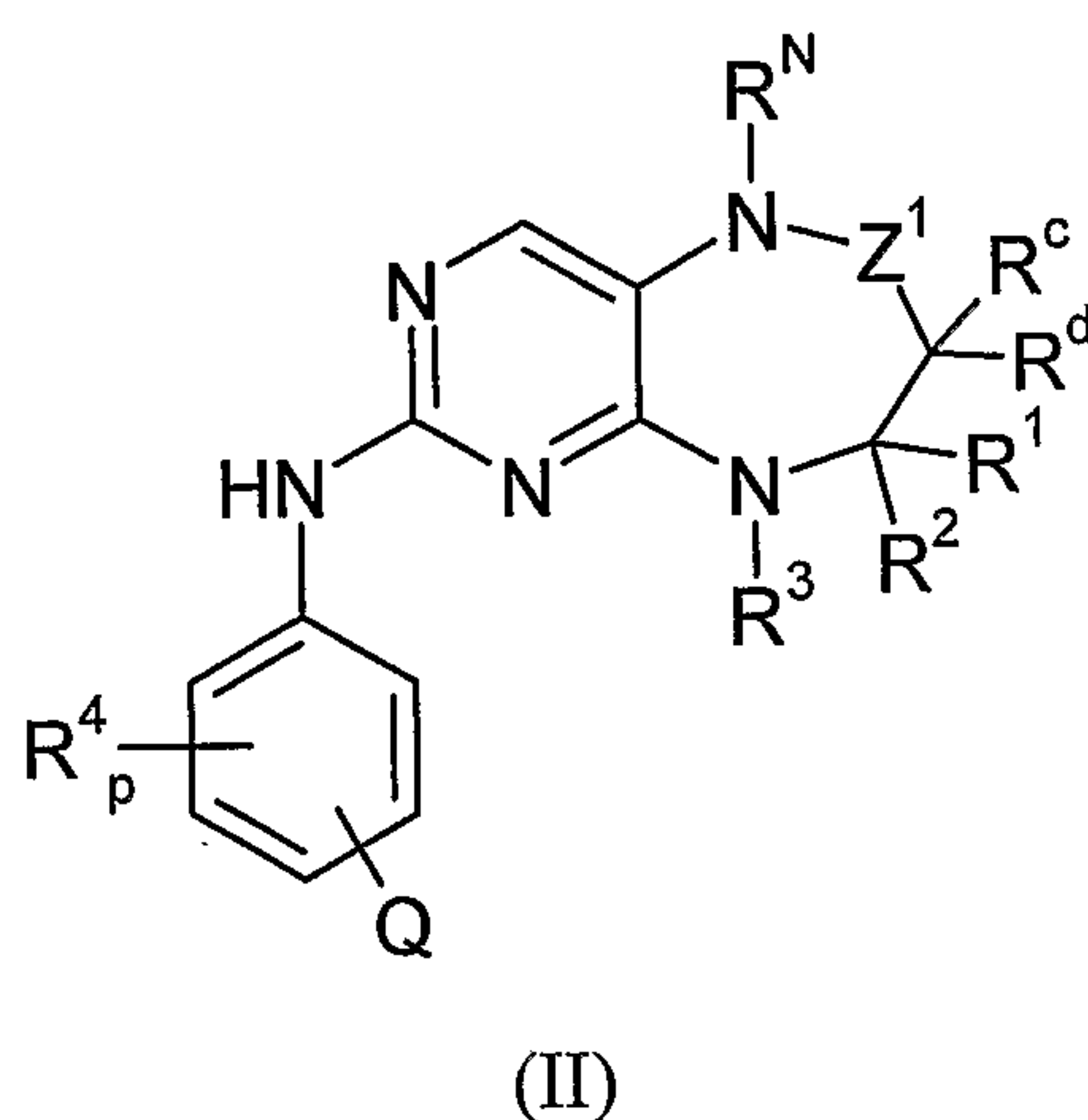
The terms alkylthio, alkylsulphoxo and alkylsulphono denotes an $-S(O)_xR$ group wherein $x=0, 1$ or 2 respectively and R is an alkyl group as hereinbefore described above.

5 The term $-alkyl-aryl$ refers to an alkyl group with an aryl substituent. The term $-alkyl-cycloalkyl$ refers to an alkyl group with a cycloalkyl substituent. The term $-aryl-alkyl$ refers to an aryl group with an alkyl substituent. The terms alkoxycarbonyl $-(C=O)OR$, alkylcarbonyl $(-COR)$ and arylcarbonyl $(-COR)$ refer to a carbonyl group with an alkoxy, alkyl or aryl substituent.

10 When R^5 represents a substituted morpholinyl, piperidinyl, homopiperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropanyl, diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, granatanyl, oxogranatanyl or azacycloheptyl, one or more substituents may be present and are as defined above for R^8 .

All the groups mentioned in the definition of R^1 to R^9 may optionally be branched
15 and/or substituted.

According to a second aspect of the present invention there is provided a compound of formula (II):



20 wherein

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or
25 unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, $-OH$, $-CN$, $-C=CH$, $-C(=O)NH_2$, C_{1-3} alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{1-3} alkyloxy, C_{1-3} alkylcarbonyl, $-CHO$, or $-SO_2Me$;
p is 0, 1 or 2;

Q is $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, $-(\text{optionally substituted } C_{1-3}\text{alkyl})_g-NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ or $-(5\text{- or }6\text{-membered aromatic or heteroaromatic})$

ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur)-L_n-R⁵_m;

g is 0 or 1;

k is 0, 1 or 2;

5 R^a represents H or an optionally substituted C₁₋₆alkyl group, and R^b represents -L_n-R⁵_m, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

10 R^{a2} represents H or an optionally substituted C₁₋₆alkyl group, and R^{b2} represents -L_n-R⁵_m, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

15 R^{a3} represents H or an optionally substituted C₁₋₆alkyl group, and R^{b3} represents -L_n-R⁵_m, -SO₂NR^{a4}R^{b4}, -C(=O)NR^{a5}R^{b5}, -SO₂R^{a6}, -C(=O)OR^{a7}, or R^{a3} and R^{b3} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

20 R^{a4} represents H or an optionally substituted C₁₋₆alkyl group, and R^{b4} represents -L_n-R⁵_m, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C₁₋₆alkyl group, and R^{b5} represents -L_n-R⁵_m, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

25 R^{a6} represents -L_n-R⁵_m;

R^{a7} represents -L_n-R⁵_m;

R^{a8} represents -L_n-R⁵_m;

R^{a9} represents -L_n-R⁵_m;

R^{a10} represents -L_n-R⁵_m;

30 L represents a linker selected from optionally substituted C₂₋₁₀alkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₆₋₁₄aryl, optionally substituted

-C₂₋₄alkyl-C₆₋₁₄aryl, optionally substituted -C₆₋₁₄aryl-C₁₋₄alkyl, optionally substituted C₃₋₁₂cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

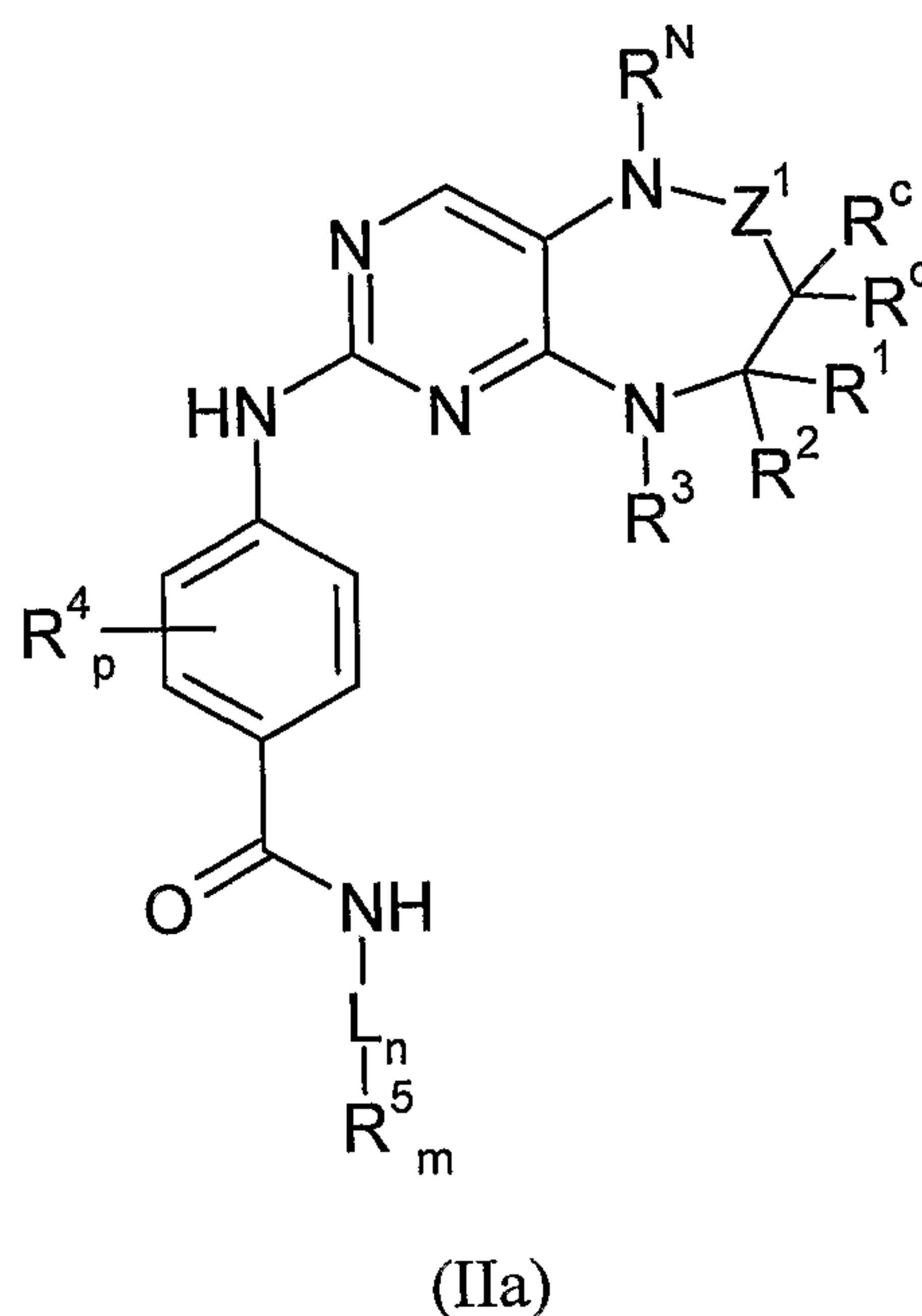
R⁵ represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and -NR⁸R⁹;

R⁶, R⁷ each independently represents hydrogen or an optionally substituted C₁₋₄alkyl group;

R⁸, R⁹ each independently represents hydrogen, optionally substituted C₁₋₆alkyl, optionally substituted -C₁₋₄alkyl-C₃₋₁₀cycloalkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₆₋₁₄aryl, optionally substituted -C₁₋₄alkyl-C₆₋₁₄aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C₁₋₄alkyloxycarbonyl, optionally substituted optionally substituted C₆₋₁₄arylcarbonyl, optionally substituted C₁₋₄alkylcarbonyl, optionally substituted C₆₋₁₄arylmethyloxycarbonyl, optionally substituted C₆₋₁₄arylsulphonyl, optionally substituted C₁₋₄alkylsulphonyl, optionally substituted C₆₋₁₄aryl-C₁₋₄alkylsulphonyl, or R⁸ and R⁹ together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and Z¹ is C=O or CR^fR^g wherein R^f, R^g each independently represents hydrogen, an optionally substituted C₁₋₆alkyl group or an optionally substituted C₃₋₆cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms,

or pharmacologically acceptable salts thereof.

According to a third aspect of the present invention there is provided a compound of formula (IIa):



5 wherein

R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or
 10 unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or
 unsaturated ring optionally comprising 1 to 2 heteroatoms;

15 R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an
 20 optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally

substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, $-OH$, $-CN$, $-C=CH$, $-C(=O)NH_2$, C_{1-3} alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{1-3} alkyloxy, C_{1-3} alkylcarbonyl, $-CHO$, or $-SO_2Me$; p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted

azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

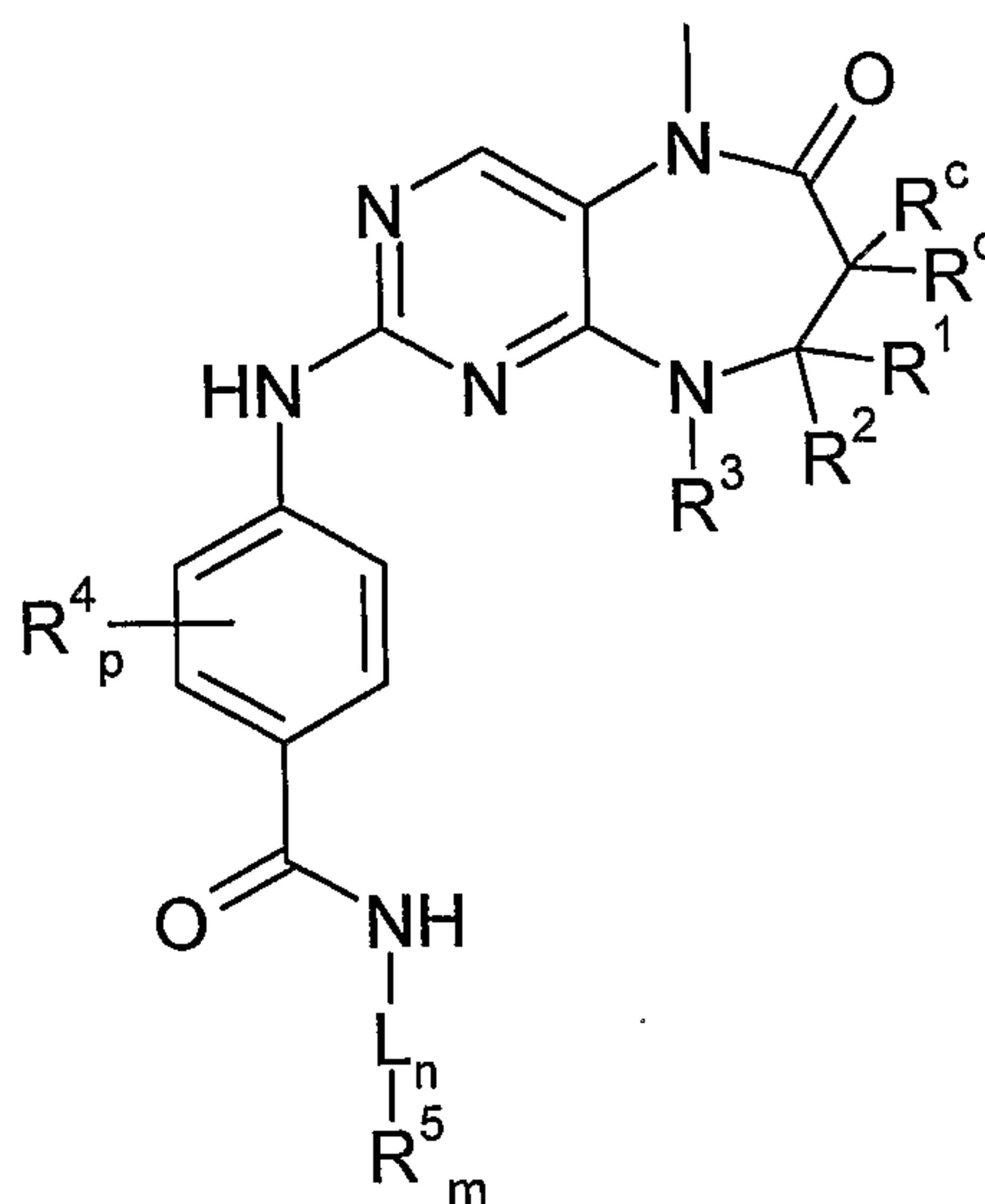
R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group;

5 R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and
15 Z^1 is $C=O$ or CR^fR^g wherein R^f , R^g each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms,
20 or pharmacologically acceptable salts thereof.

In one embodiment of the second aspect of the invention, Z^1 is $C=O$ or CH_2 .

According to a fourth aspect of the present invention there is provided a compound of formula (III):

21



(III)

wherein

R^1 , R^2 each independently represents hydrogen or an optionally substituted C_{1-6} alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

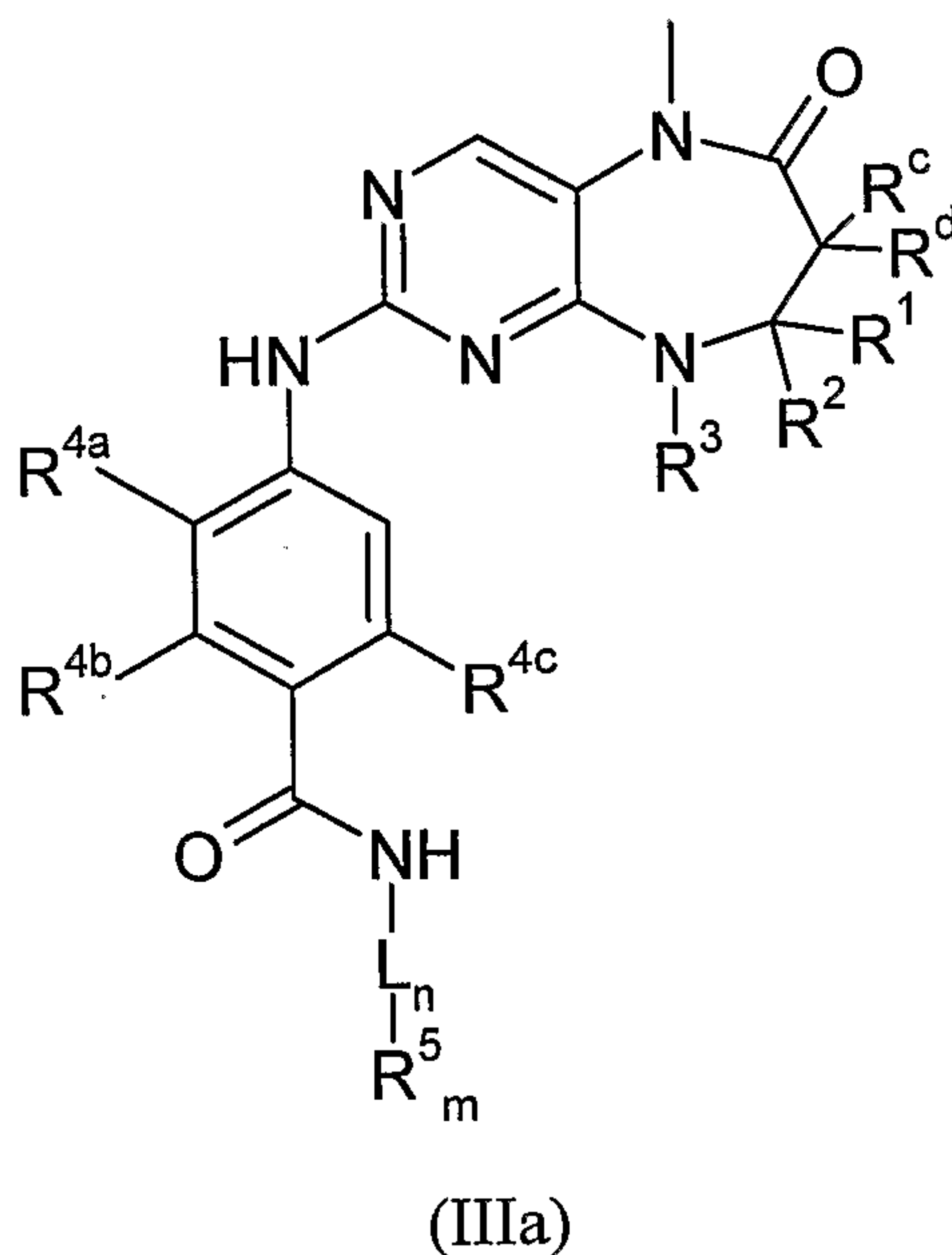
m is 1 or 2;

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group; and

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl,
 optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted
 C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted
 $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl,
 optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl,
 optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted
 C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally
 substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally
 substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom
 to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or
 unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,
 or pharmacologically acceptable salt thereof.

According to a fifth aspect of the present invention there is provided a compound of
 formula (IIIa):



wherein

R^1 , R^2 each independently represents hydrogen or an optionally substituted C_{1-6} alkyl
 group, or R^1 and R^2 together with the carbon atom to which they are attached form a
 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2
 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^{4a} , R^{4b} , R^{4c} each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxy group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is the number of $R^{4a, 4b, 4c}$ groups that are not hydrogen and is selected from 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted

C₃₋₁₂cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

m is 1 or 2;

5 R⁵ represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted
10 sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and -NR⁸R⁹;

R⁶, R⁷ each independently represents hydrogen or an optionally substituted C₁₋₄alkyl group; and

15 R⁸, R⁹ each independently represents hydrogen, optionally substituted C₁₋₆alkyl, optionally substituted -C₁₋₄alkyl-C₃₋₁₀cycloalkyl, optionally substituted C₃₋₁₀cycloalkyl, optionally substituted C₆₋₁₄aryl, optionally substituted -C₁₋₄alkyl-C₆₋₁₄aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C₁₋₄alkyloxycarbonyl,
20 optionally substituted optionally substituted C₆₋₁₄arylcarbonyl, optionally substituted C₁₋₄alkylcarbonyl, optionally substituted C₆₋₁₄arylmethyloxycarbonyl, optionally substituted C₆₋₁₄arylsulphonyl, optionally substituted C₁₋₄alkylsulphonyl, optionally substituted C₆₋₁₄aryl-C₁₋₄alkylsulphonyl, or R⁸ and R⁹ together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or
25 unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,

or pharmacologically acceptable salt thereof.

In one embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R¹ and R² may be identical or different and represent hydrogen or a C₁-C₆alkyl group optionally substituted by one or more substituents selected from C₁₋₃alkyloxy,

30 C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^1 and R^2 may be identical or different and represent hydrogen or a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^1 and R^2 are different wherein one of R^1 or R^2 represents hydrogen and the other represents a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 together represent a 2- to 5-membered alkyl bridge optionally comprising 1 to 2 heteroatoms selected from oxygen or nitrogen and optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 together represent an ethylene or propylene bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^c and R^d may be identical or different and represent hydrogen or a C_1 - C_6 alkyl group optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^c and R^d may be identical or different and represent hydrogen or a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^c and R^d are different wherein one of R^c or R^d represents hydrogen and the other represents a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^c and R^d together represent a 2- to 5-membered alkyl bridge optionally comprising 1 to 2 heteroatoms selected from oxygen or nitrogen and optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^c and R^d together represent an ethylene, propylene or butylene bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, at least one of R^1 , R^2 , R^c , or R^d is hydrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, at least two of R^1 , R^2 , R^c , or R^d are hydrogen.

5 In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and one of R^c or R^d is hydrogen.

10 In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and one of R^c or R^d is hydrogen and the other is methyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and R^c and R^d are methyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and R^c and R^d together represent an ethylene bridge.

15 In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^3 represents hydrogen; a C_1 - C_{12} alkyl, for example ethyl, propyl, butyl, pentyl or hexyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; a C_2 - C_{12} alkenyl, for example C_5 - C_7 alkenyl, optionally substituted by one or more substituents selected from
20 C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; C_2 - C_{12} alkynyl, for example C_5 - C_7 alkynyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; a C_6 - C_{14} aryl, for example phenyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-
25 (C₁₋₃alkyl)amino; a C_3 - C_{12} cycloalkyl, for example cyclopentyl or cyclohexyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; a C_3 - C_{12} cycloalkenyl, for example C_5 - C_7 cycloalkenyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino;
30 C_7 - C_{12} polycycloalkyl optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino;

C₇-C₁₂polycycloalkenyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₅-C₁₂spirocycloalkyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; 5 C₃-C₁₂heterocycloalkyl which contains 1 to 2 heteroatoms selected from oxygen, nitrogen or sulphur, for example pyranyl or piperinyl, pyrrolidinyl, pyrazinyl or morpholinyl, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; and C₃-C₁₂heterocycloalkenyl which contains 1 to 2 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by one or 10 more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R³ represents isopropyl, isobutyl, isopentyl, cyclopentyl, phenyl or cyclohexyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth 15 aspects, R³ represents cyclopentyl, or cyclohexyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R¹ and R³ or R² and R³ together represent a saturated or unsaturated C₃-C₄alkyl bridge optionally comprising 1 heteroatom selected from oxygen or nitrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth 20 aspects, when p is 1 or 2, R⁴ represents a group selected from among -CN; hydroxyl; -NR⁶R⁷; halogen, for example chlorine or fluorine; C₁-C₆alkyl, for example methyl, ethyl or propyl, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₂-C₆alkenyl, for example ethenyl or propenyl, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, 25 C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₂-C₆alkynyl, for example ethynyl, propynyl or butynyl, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₁-C₅alkyloxy, for example methoxy, ethoxy or propargyloxy, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₂-C₅alkenyloxy optionally substituted by one 30 or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂,

C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₂-C₅alkynyloxy optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₁-C₆alkylthio optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₁-C₆alkylsulphoxo optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino and C₁-C₆alkylsulphonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino.

10 In another embodiment, for compounds of the first, second, third and fourth aspects, when p is 1, R⁴ represents methoxy, methyl, ethoxy, chlorine or fluorine.

In another embodiment, for compounds of the first, second, third, and fourth aspects, when p is 2, each R⁴ may be the same or different and selected from methoxy, methyl, ethoxy, ethyl, propargyloxy, chlorine or fluorine.

15 In another embodiment, for compounds of the first, second, third, and fourth aspects, when p is 2 and when each R⁴ is adjacent, both R⁴ together with the aromatic ring atoms to which they are attached form a 4- to 7-member unsaturated ring optionally comprising 1 to 2 heteroatoms.

In another embodiment, for compounds of the fifth aspect, when p is 1, R^{4b} and R^{4c} are 20 hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine.

In another embodiment, for compounds of the fifth aspect, when p is 2, R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine.

In another embodiment, for compounds of the fifth aspect, when p is 2, R^{4c} is 25 hydrogen and R^{4a} and R^{4b} together form a OCH₂O bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, L represents a linker selected from among C₂-C₁₀alkyl, for example ethyl, propyl, butyl or pentyl, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₂-C₁₀alkenyl, 30 optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₆-C₁₄aryl, for example phenyl,

optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; -C₂-C₄alkyl-C₆-C₁₄aryl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; -C₆-C₁₄aryl-C₁-C₄alkyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₃-C₁₂cycloalkyl, for example cyclohexyl, optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; and heteroaryl which contains 1 or 2 nitrogen atoms optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, when n is 1, L represents an optionally substituted C₂₋₁₀alkyl or an optionally substituted C₃₋₁₂cycloalkyl linker.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, when n is 1, L represents cyclohexyl, -C(CH₃)₂-CH₂- or -CH₂-C(CH₃)₂-CH₂-.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, n is 0.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, m is 1.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R⁵ represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted granatanyl, optionally substituted oxogranatanyl -NR⁸R⁹ and optionally substituted azacycloheptyl wherein each morpholinyl, piperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropenyl, diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, -NR⁸R⁹ and azacycloheptyl is optionally substituted by one or more groups as defined for R⁸.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents hydrogen, $-NR^8R^9$ or a piperidinyl, morpholinyl, pyrrolidinyl, sulfoxomorpholiny, piperazinyl, thiomorpholinyl, tropenyl, granatanyl, oxogranatanyl or azacycloheptyl each optionally substituted by one or more groups as defined for R^8 .

5 In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents piperidinyl optionally substituted by one or more groups as defined for R^8 .

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents pyrrolidinyl optionally substituted by one or more groups as defined for
10 R^8 .

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents granatanyl optionally substituted by one or more groups as defined for R^8 .

In another embodiment, for compounds of the first, second, third, fourth and fifth
15 aspects, the groups R^6 and R^7 may be identical or different and represent hydrogen or C_1 - C_4 alkyl, for example methyl or ethyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^8 and R^9 may be identical or different and represent hydrogen; a C_1 - C_6 alkyl, for example methyl, ethyl or propyl, optionally substituted by one or more
20 substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; $-C_1$ - C_4 alkyl- C_3 - C_{10} cycloalkyl, for example $-CH_2$ -cyclopropyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; C_3 - C_{10} cycloalkyl optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂,
25 C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; C_6 - C_{14} aryl, for example phenyl, optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; $-C_1$ - C_4 alkyl- C_6 - C_{14} aryl, for example benzyl optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; pyranyl optionally substituted by
30 one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino; pyridinyl optionally substituted by one or more

substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; pyrimidinyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; pyranlyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₁-C₄alkyloxycarbonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₆-C₁₄arylcabonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₁-C₄alkylcarbonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₆-C₁₄ arylmethyloxycarbonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₆-C₁₄arylsulphonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino; C₁-C₄alkylsulphonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino and C₆-C₁₄aryl-C₁-C₄alkylsulphonyl optionally substituted by one or more substituents selected from C₁₋₃alkyloxy, C₁₋₃alkylthio, C₁₋₃alkyl-S(O)₂, C₁₋₃alkylamino and di-(C₁₋₃alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R⁸ represents methyl, ethyl or propyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R⁹ represents methyl, ethyl or propyl.

In another embodiment, for the compound of formula (I), R^N represents C₁₋₃alkyl.

In another embodiment, for the compound of formula (I), R^N represents methyl or ethyl.

In another embodiment, for the compound of formula (I), Z¹ represents C=O or CR^fR^g.

In another embodiment, for the compound of formula (I), Z¹ represents C=O or CR^fR^g, and Z² represents CR^cR^d.

In another embodiment, for the compound of formula (I), Z¹ represents C=O or CH₂.

In another embodiment, for the compound of formula (I), Q represents $-\text{CH}_2\text{-NR}^{\text{a3}}\text{R}^{\text{b3}}$ or $-\text{C}(=\text{X}^1)\text{-NR}^{\text{a}}\text{R}^{\text{b}}$, wherein X^1 is O.

In another embodiment, for the compounds of formula (I), (II), (IIa), (III) or (IIIa), n is 1 and L is an optionally substituted C_{2-10} alkyl linker.

5 In another embodiment, for the compounds of formula (I), (II), (IIa), (III) or (IIIa), n is 0.

In a further embodiment of the invention there is provided a subset of compounds of formula (III) or (IIIa) wherein R^1 to R^4 , $\text{R}^{4\text{a}}$, $\text{R}^{4\text{b}}$, $\text{R}^{4\text{c}}$, R^{c} , R^{d} , R^6 and R^7 are as hereinbefore defined; and L represents a linker selected from among optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-\text{C}_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-\text{C}_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 1; m denotes 1 or 2; R^5 denotes hydrogen or a group which is bound to L via a nitrogen atom, selected from optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, $-\text{NR}^8\text{R}^9$ and optionally substituted azacycloheptyl; R^8 , R^9 independently represent hydrogen, C_{1-6} alkyl, $-\text{C}_{1-4}$ alkyl- C_{3-10} cycloalkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, $-\text{C}_{1-4}$ alkyl- C_{6-14} aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4} alkyloxycarbonyl, C_{6-14} arylcarbonyl, C_{1-4} alkylcarbonyl, C_{6-14} arylmethyloxycarbonyl, C_{6-14} arylsulphonyl, C_{1-4} alkylsulphonyl or C_{6-14} aryl- C_{1-4} alkylsulphonyl, or pharmacologically acceptable salts thereof.

In a still further embodiment of the invention there is provided another subset of compounds of formula (III) or (IIIa) wherein p, R^1 to R^4 , $\text{R}^{4\text{a}}$, $\text{R}^{4\text{b}}$, $\text{R}^{4\text{c}}$, R^{c} , R^{d} , R^6 and R^7 are as hereinbefore defined; L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-\text{C}_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-\text{C}_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes hydrogen or a group which is bound to L via a carbon atom, selected from among piperidinyl, piperazinyl, pyrrolidinyl, piperazinylcarbonyl, tropenyl, morpholinyl, granatanyl, oxogranatanyl and azacycloheptyl each optionally

substituted by one or more groups as defined for R^8 ; and R^8 independently represent hydrogen, C_{1-6} alkyl, $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, $-C_{1-4}$ alkyl- C_{6-14} aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4} alkyloxycarbonyl, C_{6-14} arylcarbonyl, C_{1-4} alkylcarbonyl, C_{6-14} arylmethyloxycarbonyl, C_{6-14} arylsulphonyl, C_{1-4} alkylsulphonyl or
 5 C_{6-14} aryl- C_{1-4} alkylsulphonyl, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p, R^3 to R^9 , R^c and R^d are as hereinbefore defined; and R^1 , R^2 each independently represents hydrogen, Me, Et, Pr, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 5- membered
 10 cycloalkyl ring, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p and R^1 to R^9 are as hereinbefore defined; and R^c , R^d each independently represents hydrogen, Me, Et, Pr, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 5- membered cycloalkyl ring, or
 15 pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p and R^3 to R^9 are as hereinbefore defined; and at least two of R^1 , R^2 , R^c or R^d are hydrogen.

In an additional embodiment of the invention there is provided an additional subset of
 20 compounds of formula (III) or (IIIa) wherein L, m, n, p and R^3 to R^9 are as hereinbefore defined; R^1 and R^2 are hydrogen, and one of R^c or R^d is hydrogen.

In a further additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein R^1 , R^2 , R^c , R^d , m, n and R^5 to R^8 are as hereinbefore defined; and R^3 represents an optionally substituted C_{1-10} alkyl, optionally
 25 substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl or optionally substituted C_{6-14} aryl group or R^1 and R^3 or R^2 and R^3 together represent a saturated or unsaturated C_{3-4} alkyl bridge optionally comprising 1 or 2 heteroatoms; p is 0 or 1; R^4 represents OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2 , F, Cl, Br, O-propargyl, O-butynyl, CN, SMe, NMe₂, CONH₂, ethynyl, propynyl, butynyl or allyl; and L denotes a linker selected
 30 from among optionally substituted phenyl, phenylmethyl, cyclohexyl and branched C_{1-6} alkyl, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl or optionally substituted C_{6-14} aryl group; p is 0 or 1; R^4 represents OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2 , F, CL, Br, O-propargyl, O-butynyl, CN, SMe, NMe₂, CONH₂, ethynyl, propynyl, butynyl or allyl; L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted - C_{2-4} alkyl- C_{6-14} aryl, optionally substituted - C_{6-14} aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes hydrogen or a group, which is bound to L via a carbon atom, selected from among -NR⁸R⁹, piperidinyl, piperazinyl, pyrrolidinyl, piperazinylcarbonyl, tropenyl, morpholinyl, granatanyl, oxogranatanyl and azacycloheptyl each optionally substituted by one or more groups as defined for R⁸; R⁸, R⁹ each independently represent hydrogen, C_{1-6} alkyl, - C_{1-4} alkyl- C_{3-10} cycloalkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, - C_{1-4} alkyl- C_{6-14} aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4} alkyloxycarbonyl, C_{6-14} arylcarbonyl, C_{1-4} alkylcarbonyl, C_{6-14} arylmethyloxycarbonyl, C_{6-14} arylsulphonyl, C_{1-4} alkylsulphonyl or C_{6-14} aryl- C_{1-4} alkylsulphonyl; R¹, R² are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among -NR⁸R⁹ and piperidinyl each optionally substituted by one or more groups as defined for R⁸; R⁸, R⁹ each independently represent C_{1-6} alkyl; R¹, R² are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; p is 0, 1 or

2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen;
 5 R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; p is 0, 1 or
 10 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together
 15 represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (IIIa) wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5
 20 denotes a group selected from among $-NR^8R^9$ and piperidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b}
 25 is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (IIIa) wherein R^3 represents an optionally substituted C_{1-10} alkyl,
 30 optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5

denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (IIIa) wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

In a further aspect of the invention, there is provided a compound selected from any one of the Examples or pharmacologically acceptable salts thereof.

In a further aspect of the invention, there is provided a compound selected from any one of Examples 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451, 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299,

300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 5 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453 or pharmacologically acceptable salts thereof.

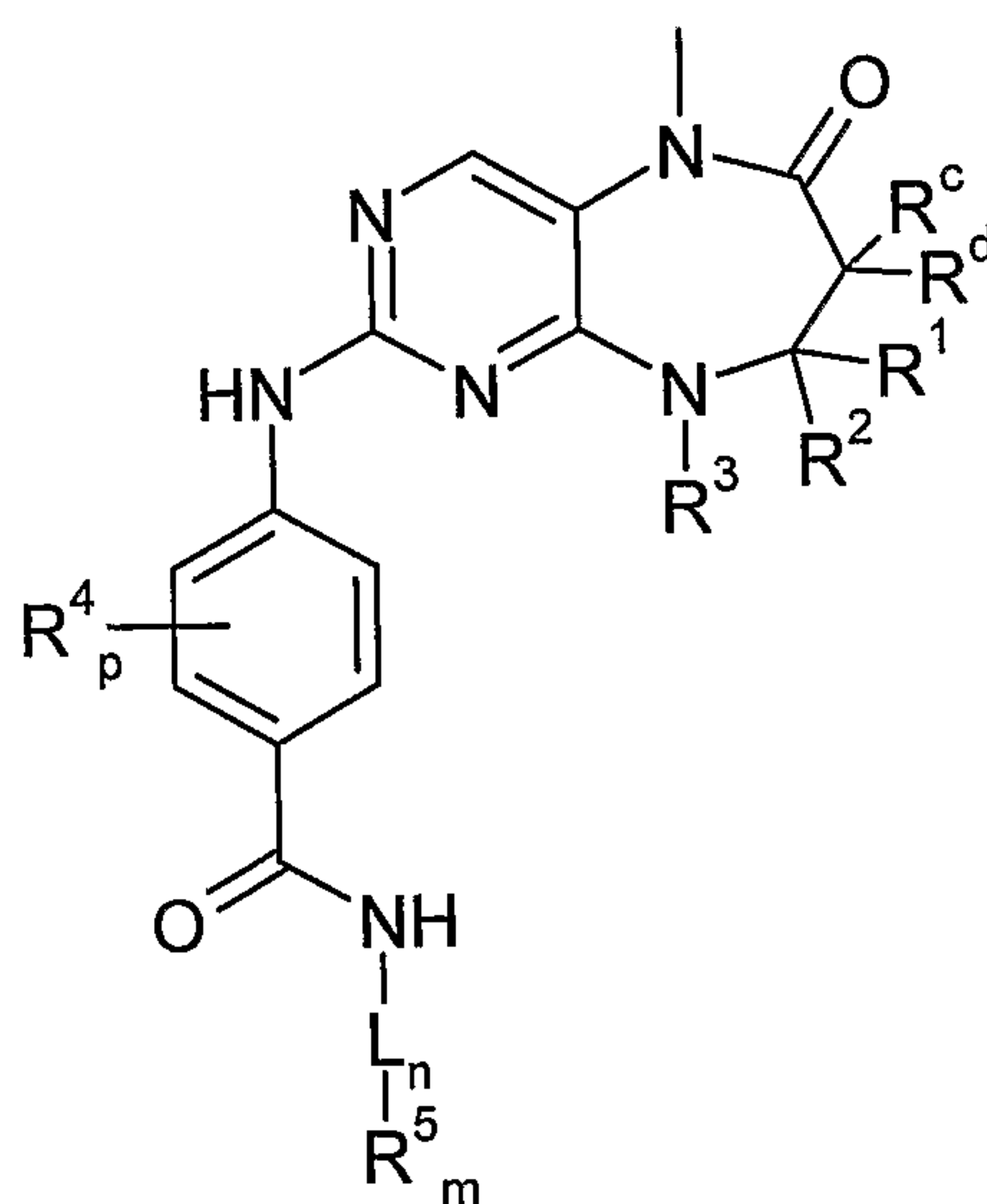
In a further aspect of the invention, there is provided a compound selected from any 10 one of Examples 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 15 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 20 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453, or pharmacologically acceptable salts thereof.

The compounds according to the first, second, third, fourth and fifth aspects of the invention may be present in the form of the individual optical isomers, mixtures of the 25 individual enantiomers, diastereomers or racemates, in the form of the tautomers and also as solvates and/or in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids, such as for example acid addition salts with hydrohalic acids, for example hydrochloric or hydrobromic acid, or organic acids, such as for example oxalic, fumaric, diglycolic or methanesulphonic acid or metal salts such as a magnesium, 30 calcium, sodium or potassium salt

The compounds of formula (I), (II), (IIa), (III) or (IIIa) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or p-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I), (II), (IIa), (III) or (IIIa) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I), (II), (IIa), (III) or (IIIa) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

The invention also relates to a process for preparing a compound of general formula (III),

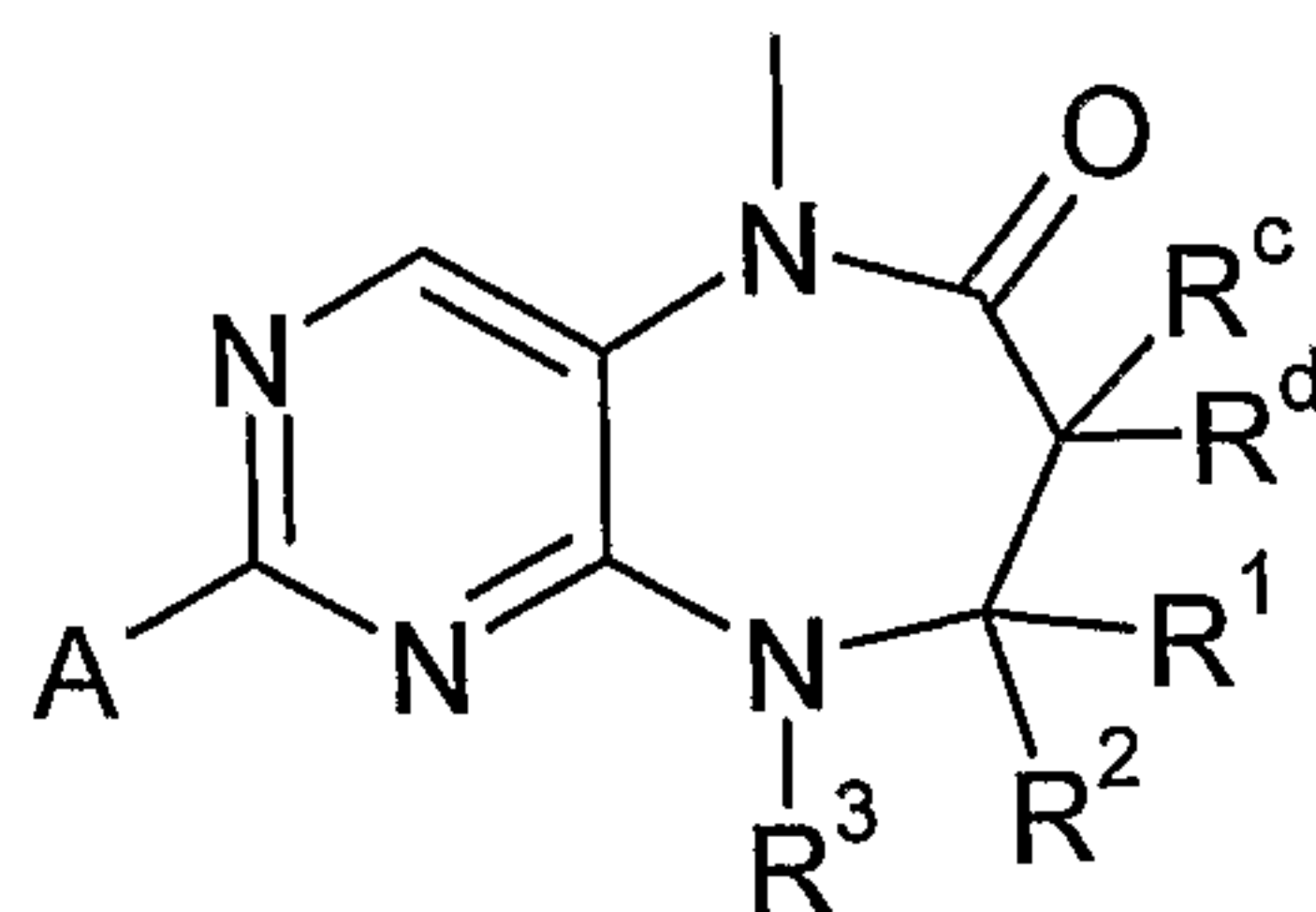


(III)

wherein R^1 - R^5 , R^c , R^d , m , n and L are as hereinbefore defined, comprising either

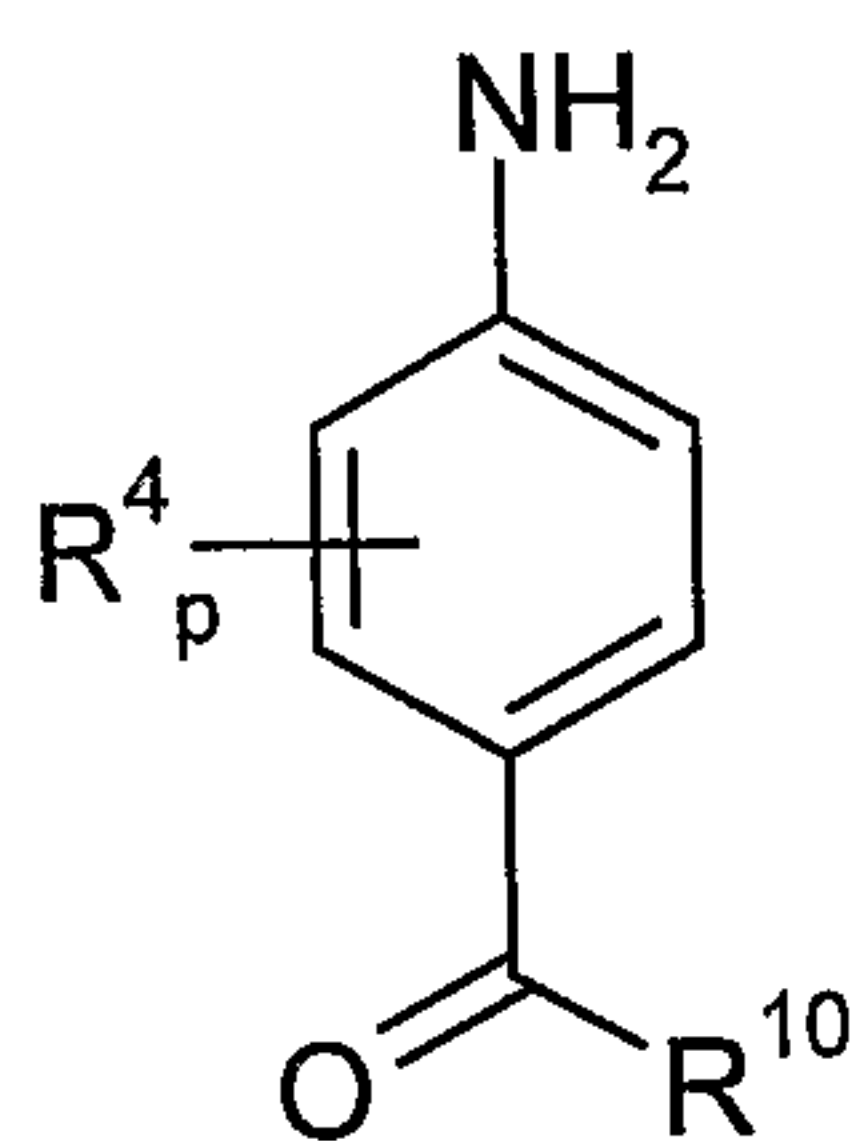
a) reacting a compound of general formula (IV)

40



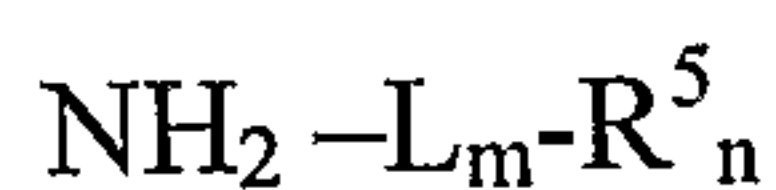
(IV)

wherein R^1 - R^3 are as hereinbefore defined and A is a leaving group,
with an optionally substituted compound of general formula (V):



(V)

wherein R^4 is as hereinbefore defined; and R^{10} denotes OH, $NH-L_m-R_n^5$, OMe, OEt,
and when R^{10} denotes OH, OMe or OEt optionally after previous hydrolysis of the ester group
-COR¹⁰, reacting with an amine of general formula (VI):



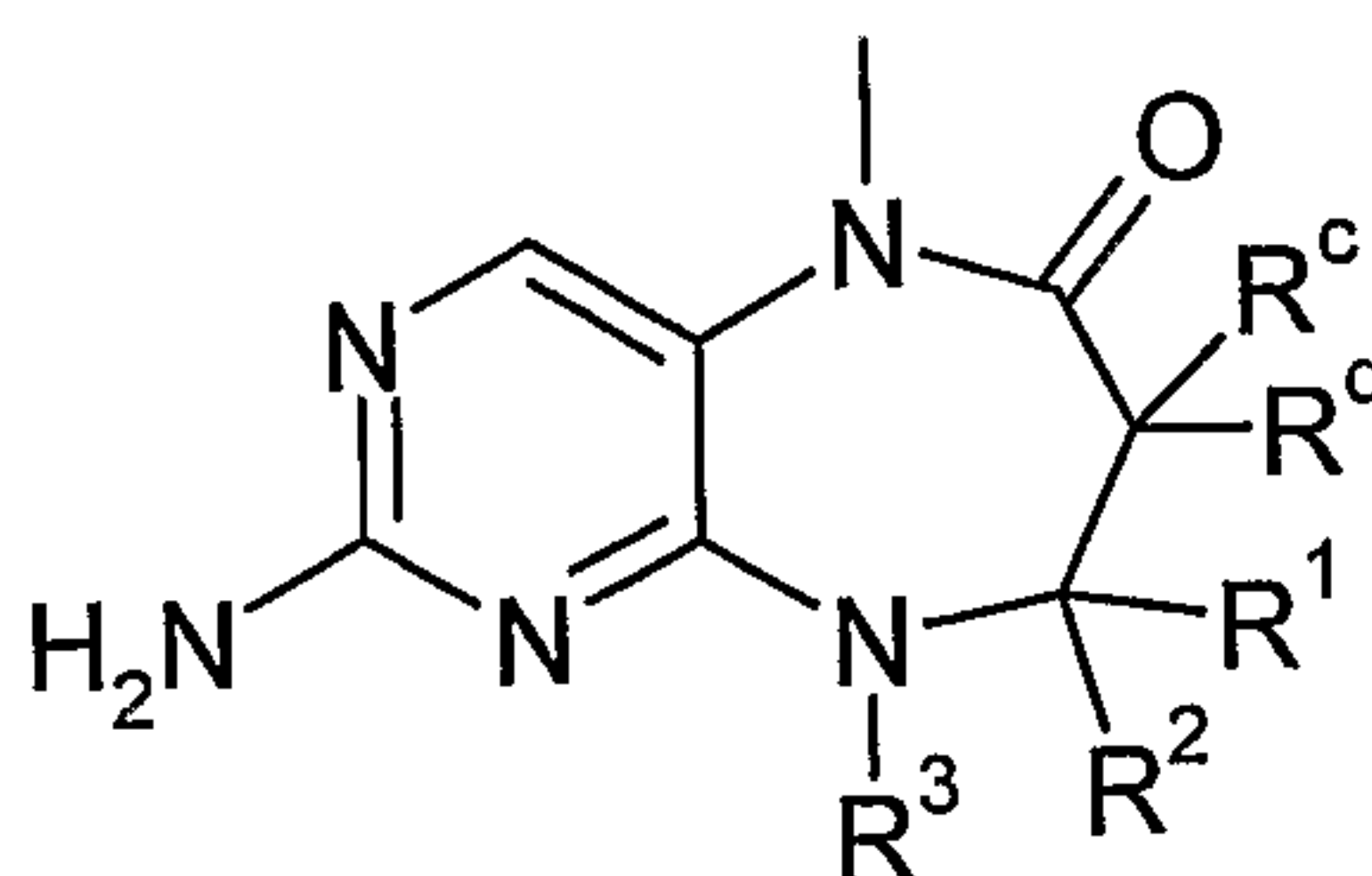
(VI)

wherein R^5 is as hereinbefore defined,

to give a compound of formula (III);

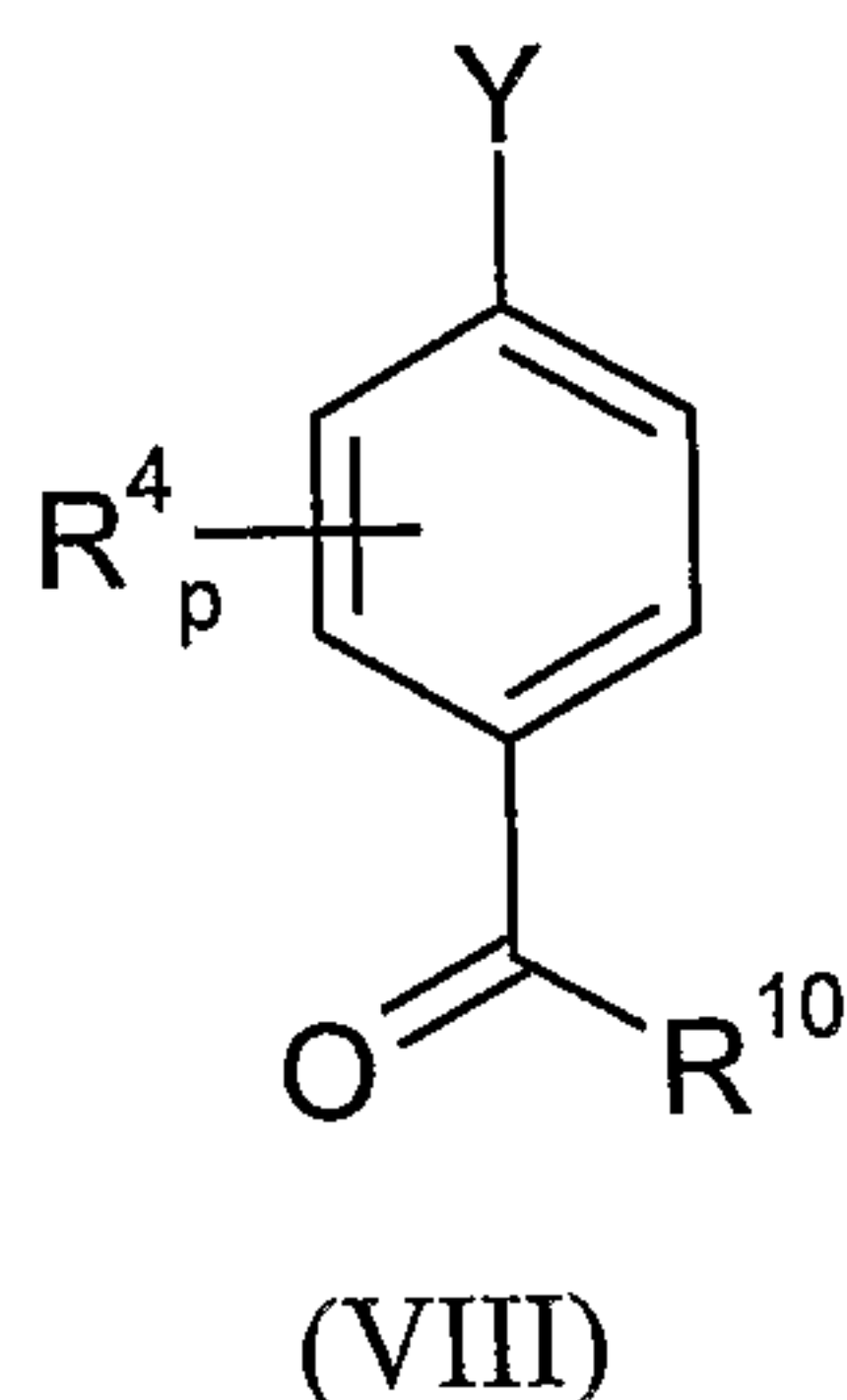
or

b) reacting a compound of general formula (VII)

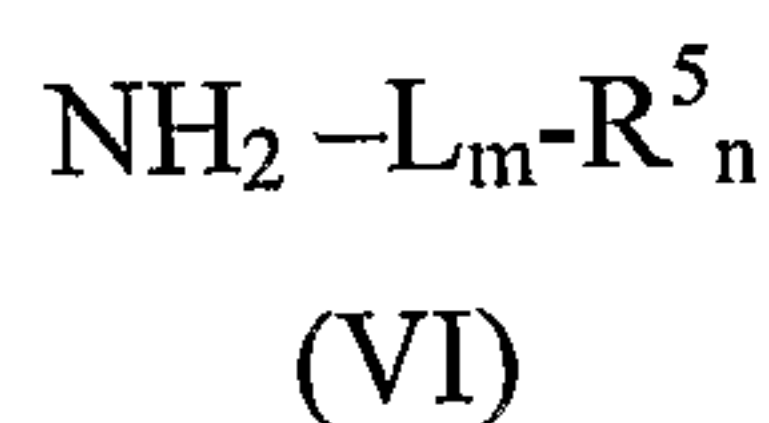


(VII)

wherein R^1 - R^3 are as hereinbefore defined with an optionally substituted compound of general formula (VIII):



wherein Y is a leaving group, p and R^4 are as hereinbefore defined; and R^{10} denotes OH, $NH-L_m-R_n^5$, OMe, OEt, and when R^{10} denotes OH, OMe or OEt optionally after previous hydrolysis of the ester group $-COR^{10}$, reacting with an amine of general formula (VI):



wherein R^5 is as hereinbefore defined,

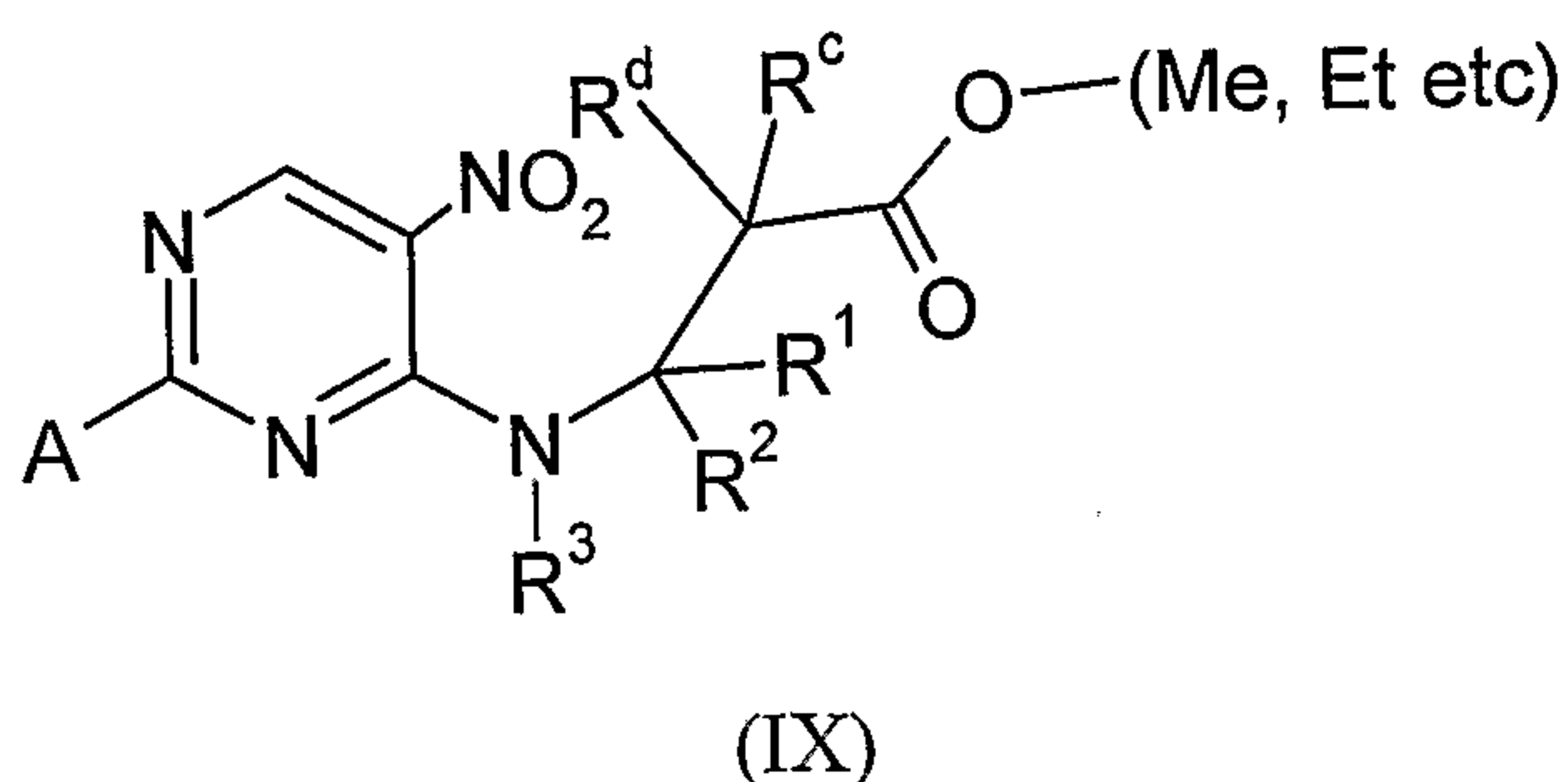
to give a compound of formula (III).

In one embodiment R^{10} is a substituent selected from among OH, NH_2-LR^5 , -O-methyl and -O-ethyl.

The term leaving group includes leaving groups such as for example -O-methyl, -SCN, chlorine, bromine, iodine, methanesulphonyl, trifluoromethanesulphonyl or p-toluenesulphonyl. In one embodiment the leaving group A is chlorine.

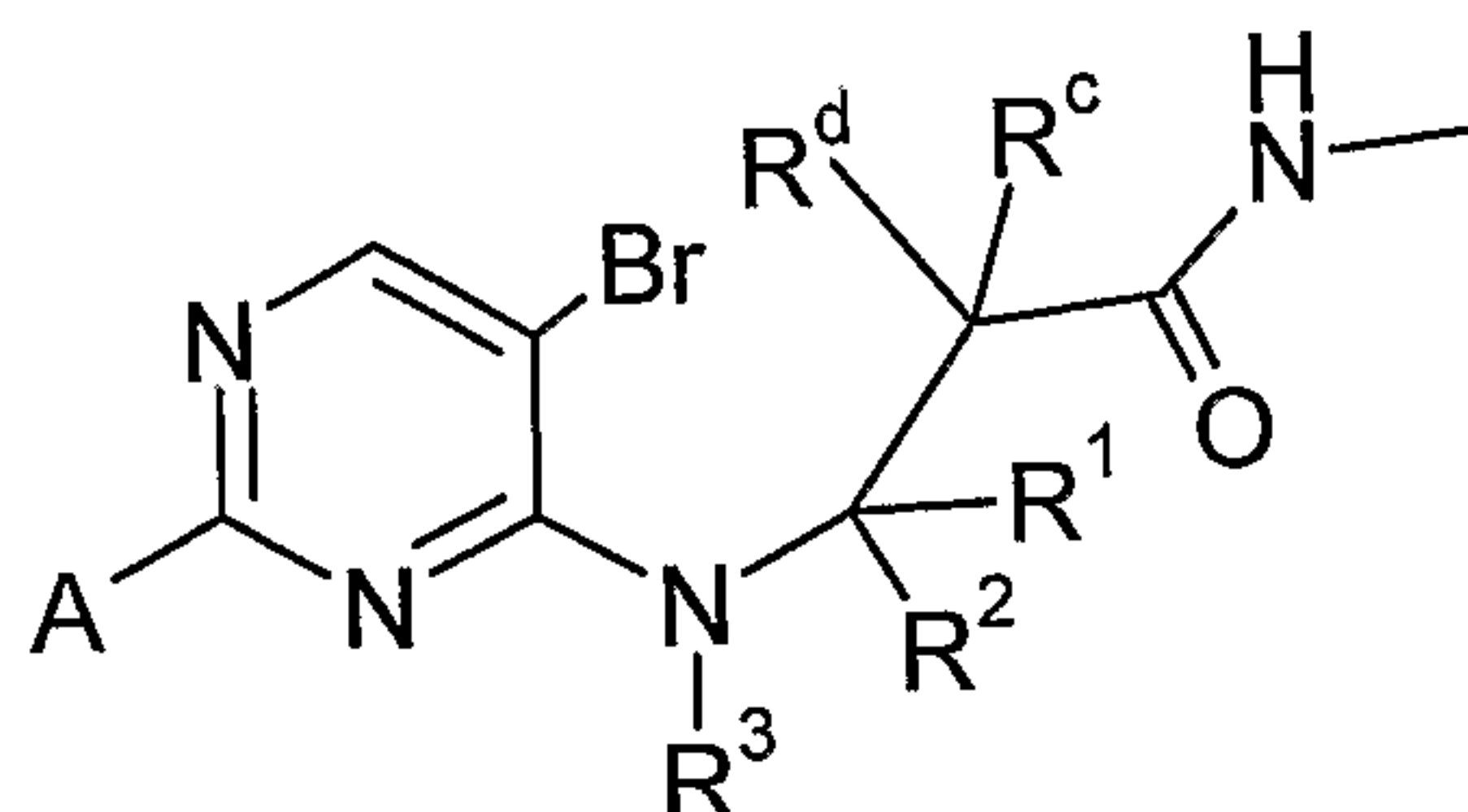
Methods for the preparation of compounds of Formula (V) are described in WO04/076454 and WO03/020722 and are incorporated herein by reference.

Compounds of Formula (IV) where A is chlorine may also be obtained by the reductive cyclisation of a compound of formula (IX)



for example by palladium coupling.

Compounds of Formula (IV) may also be obtained by the cyclisation of a compound of formula (X)

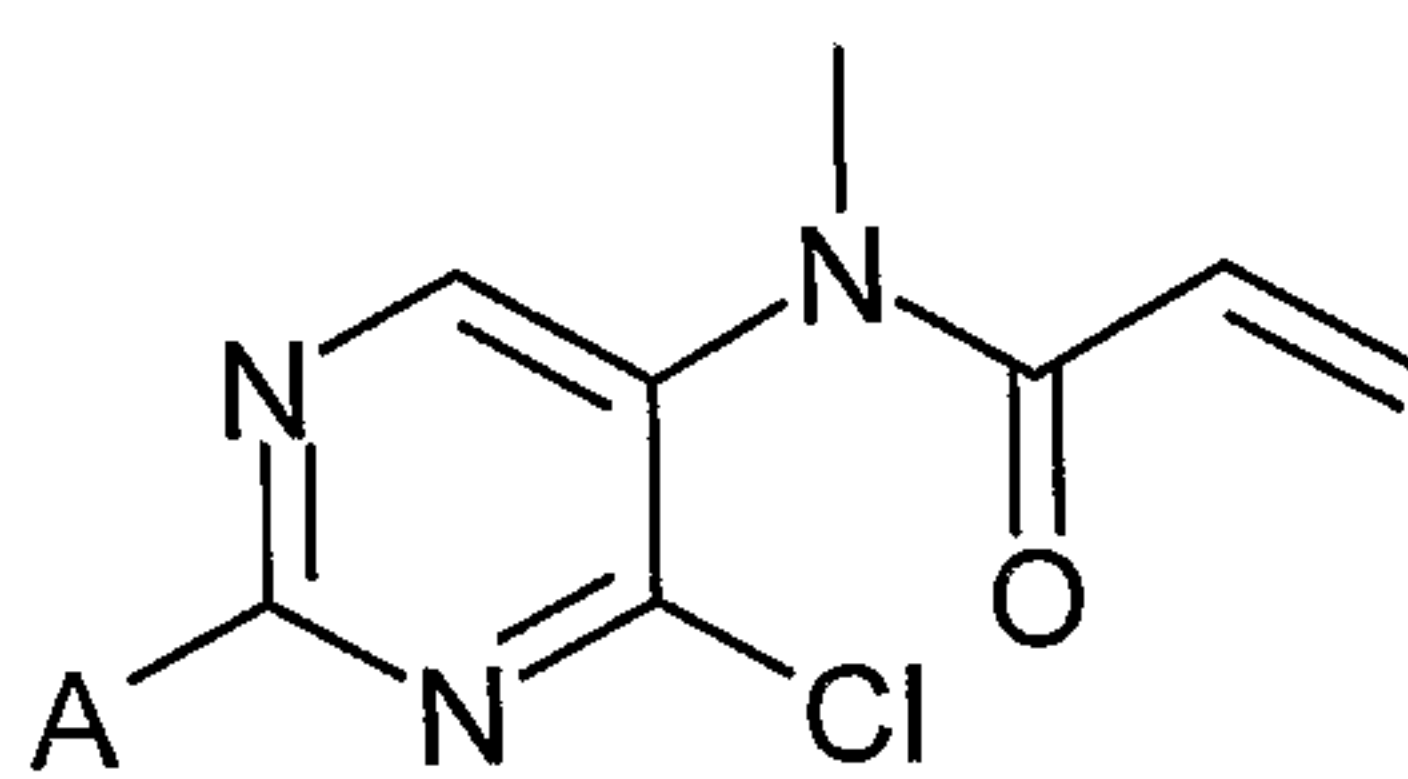


(X)

for example by under catalysis by a suitable palladium coupling compound and in the presence of a suitable ligand and a suitable base.

Furthermore, compounds of formula (IV) may be obtained by reaction of another compound of general formula (IV), wherein R³ is hydrogen, with an alkyl halide, in a polar solvent, such as, for example, N,N-dimethylacetamide, in the presence of a strong base, such as, for example, sodium hydride.

Still furthermore compounds of formula (IV), where R^c, R^d, R¹ & R² are hydrogen, may be obtained by reaction of a compound of formula (XI)

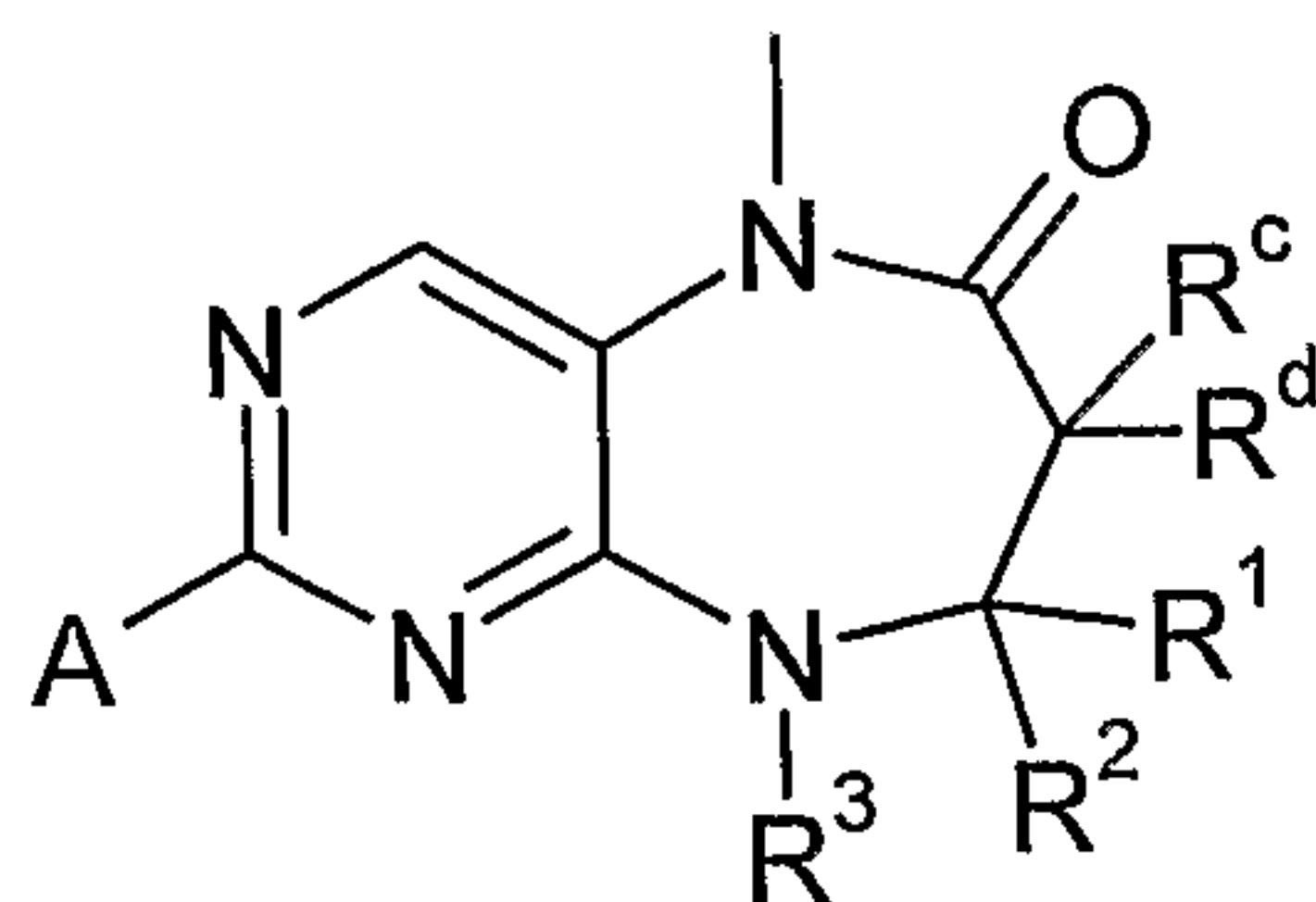


(XI)

with an amine, in the presence of a base, such as triethylamine, and a lewis acid, such as titanium (IV) tetraethoxide.

Compounds of formula (VII) may also be obtained by the reaction of a compound of formula (IV), wherein A is as hereinbefore defined, but typically chloro,

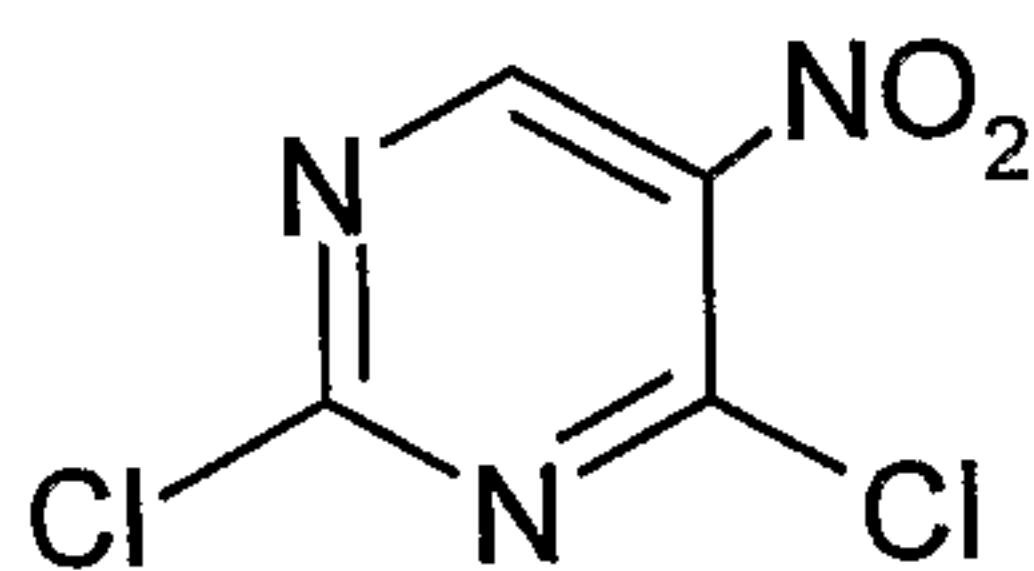
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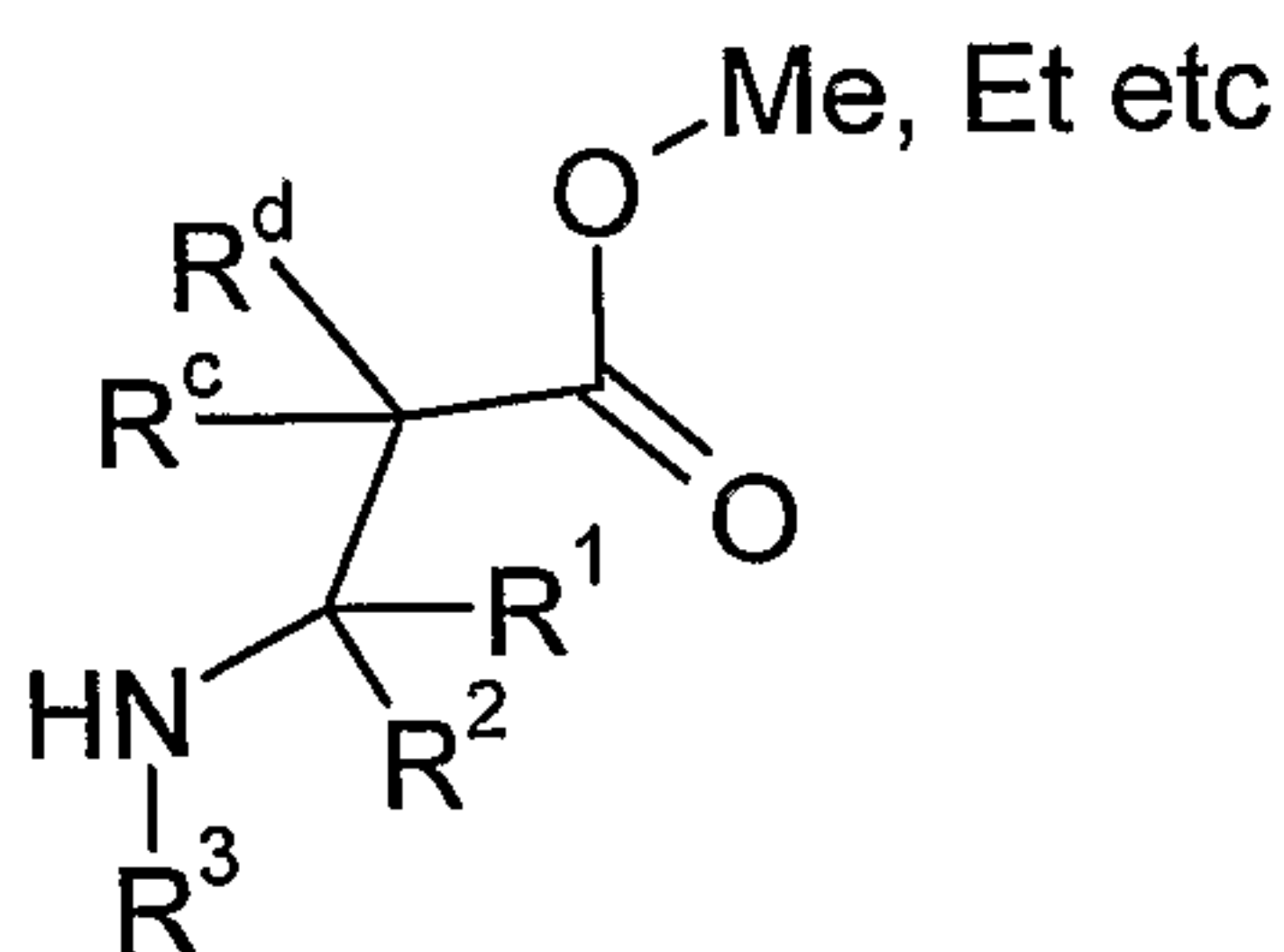
(IV)

with ammonia or a suitably protected equivalent.

Compounds of Formula (IX), wherein A is chlorine, may also be obtained by reaction
 5 of 5-nitro-2,4-dichloropyrimidine



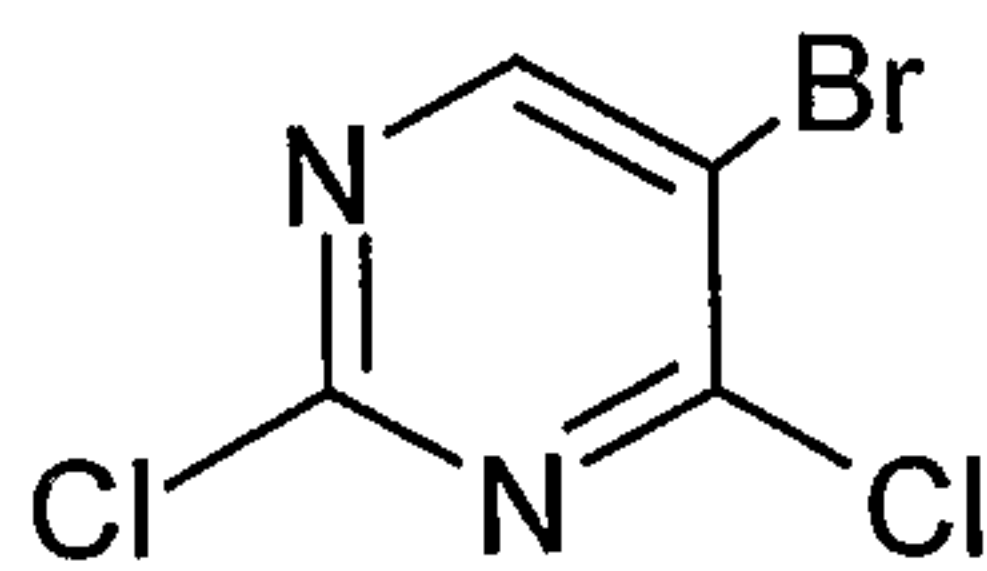
with an amine of Formula (XII)



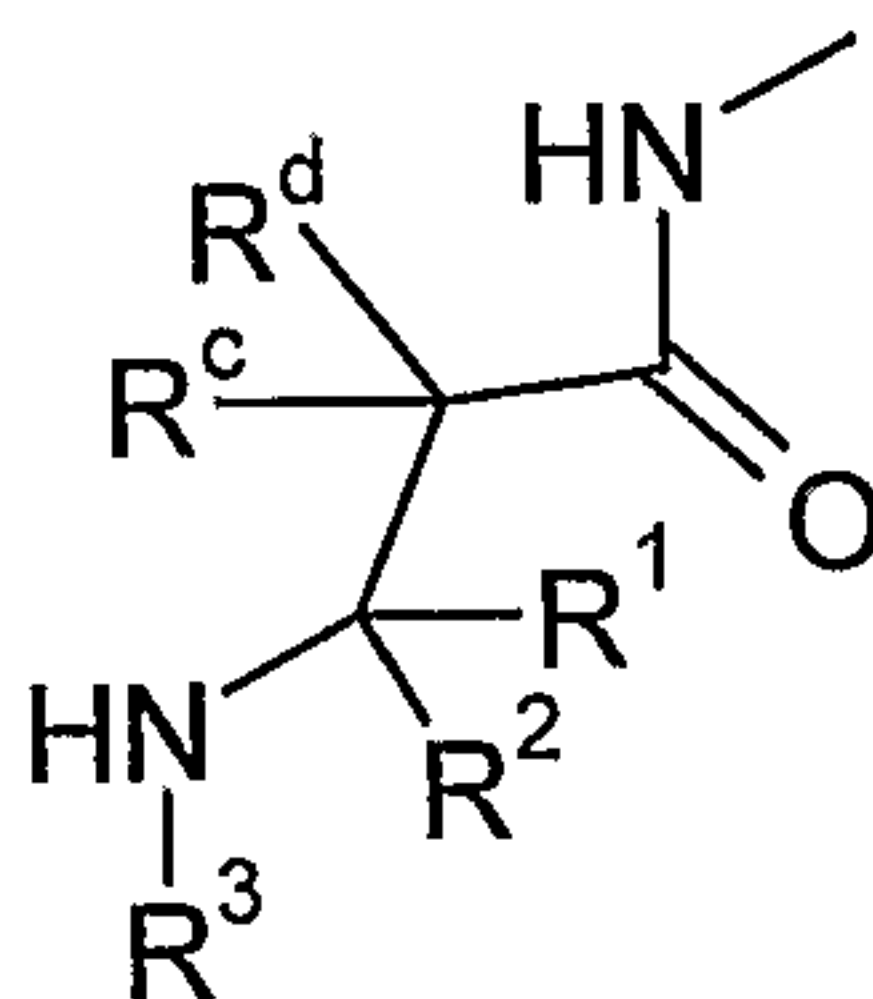
(XII)

10 for example by heating in the presence of a base, such as potassium carbonate, in a polar organic solvent such as acetone.

Compounds of Formula (IX), wherein A is chlorine, may also be obtained by reaction
 of 5-bromo-2,4dichloropyrimide



15 with an amine of Formula (XIII)

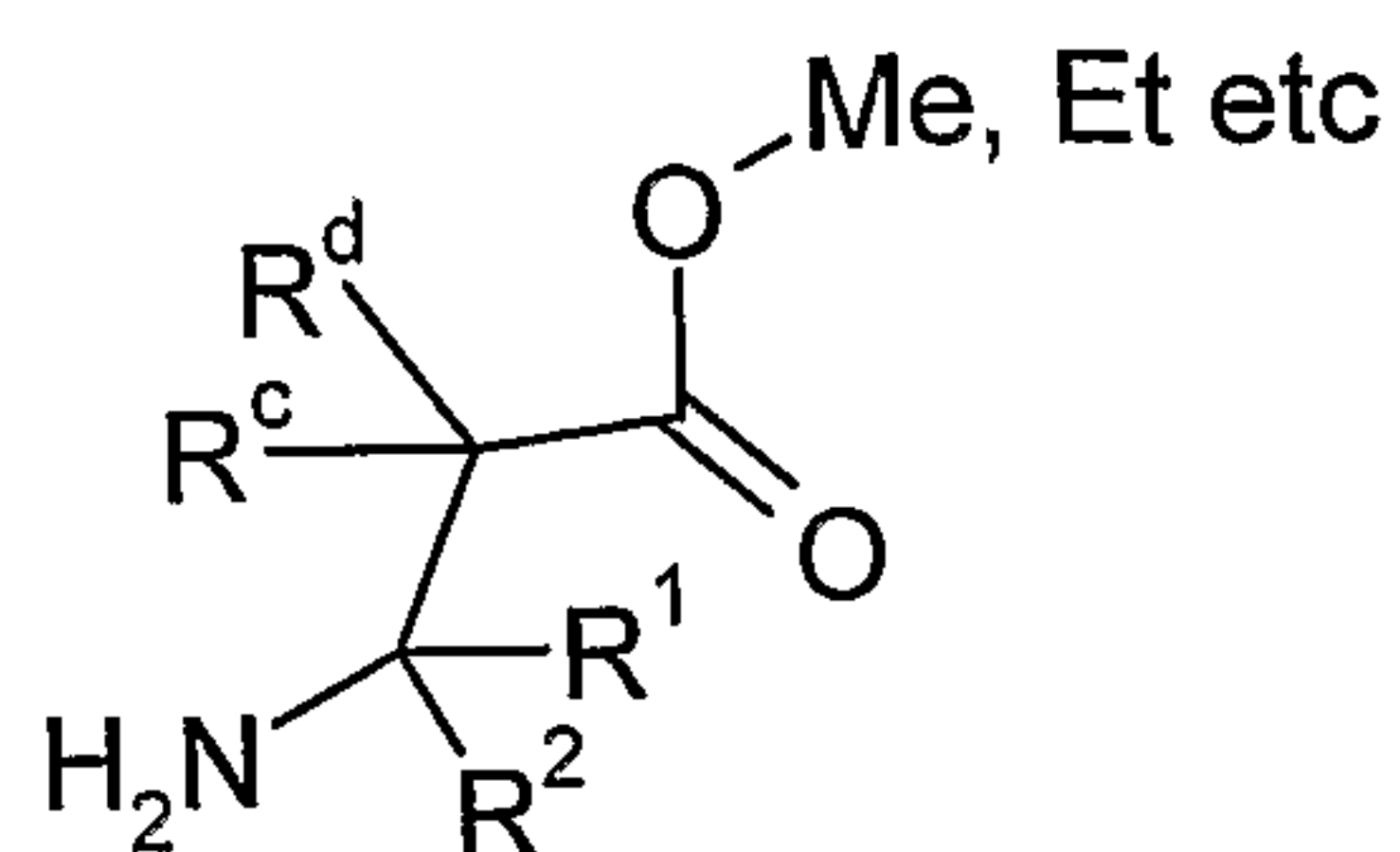


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(XIII)

for example by heating in the presence of a base, such as triethylamine, in a polar organic solvent such as acetonitrile.

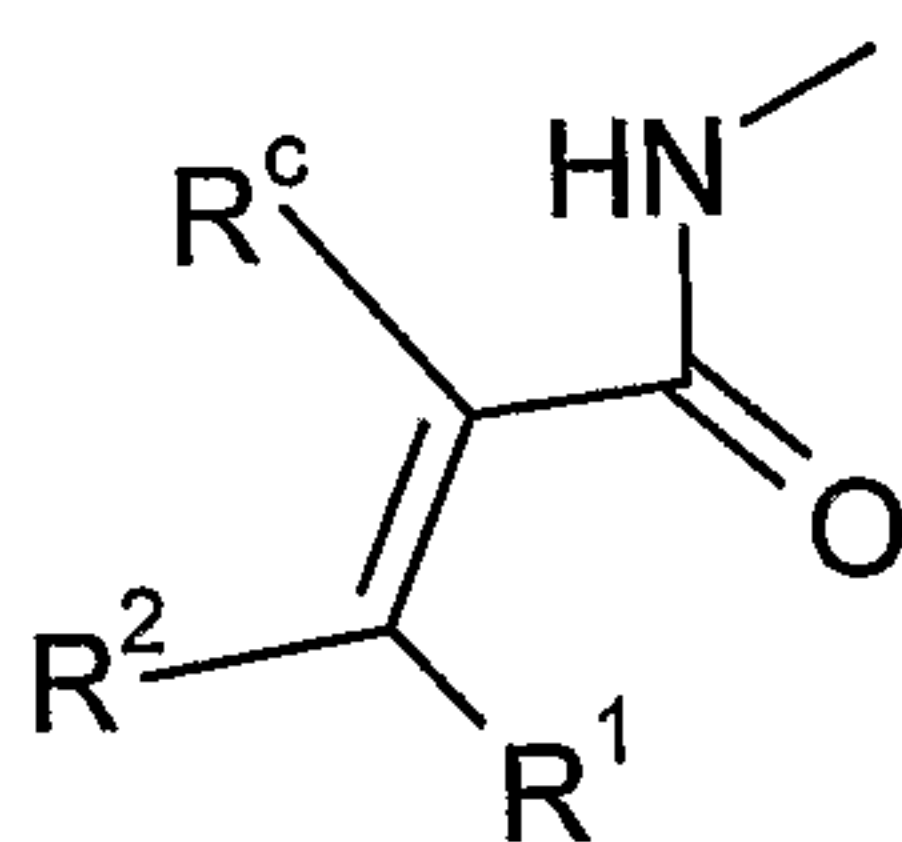
Compounds of Formula (XII), may also be obtained by reaction of esters of an
5 appropriately substituted 3-amino-propanoic acid (XIV)



(XIV)

with a ketone or aldehyde, in the presence of a suitable reducing agent, such as, for example, sodium triacetoxyborohydride..

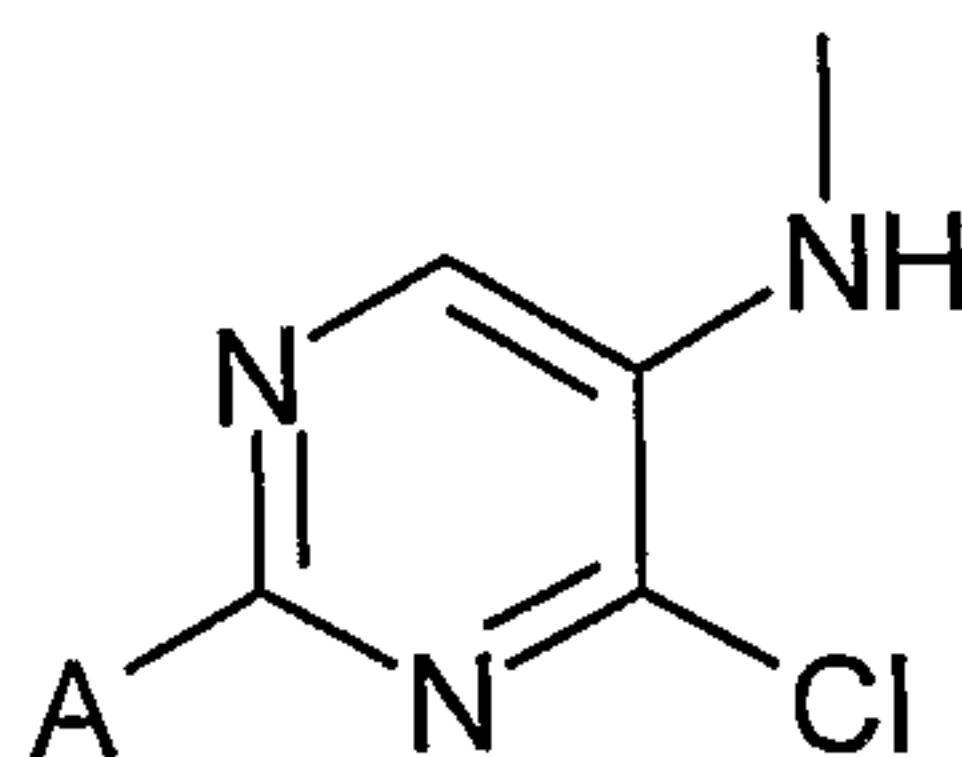
10 Compounds of Formula (XIII), may also be obtained by reaction of amides of propenoic acid (XV)



(XV)

with an amine.

15 Compounds of formula (XI) may also be obtained by the reaction of a compound of formula (XVI),

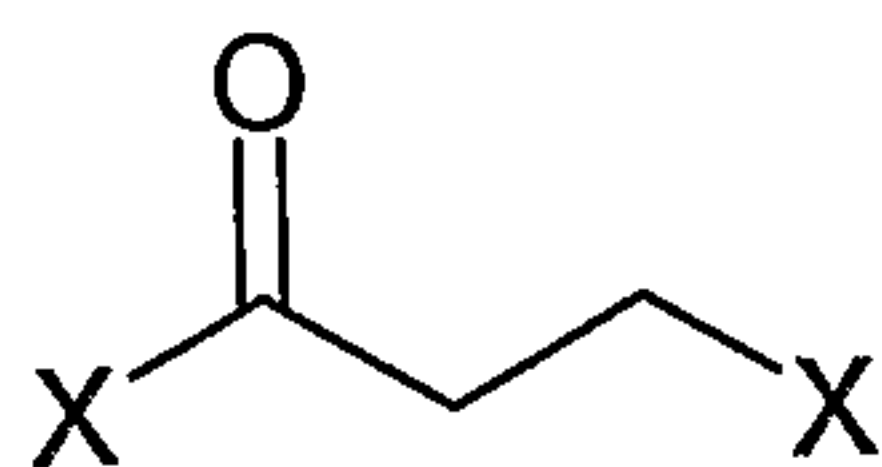


(XVI)

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with a compound of formula (XVII),

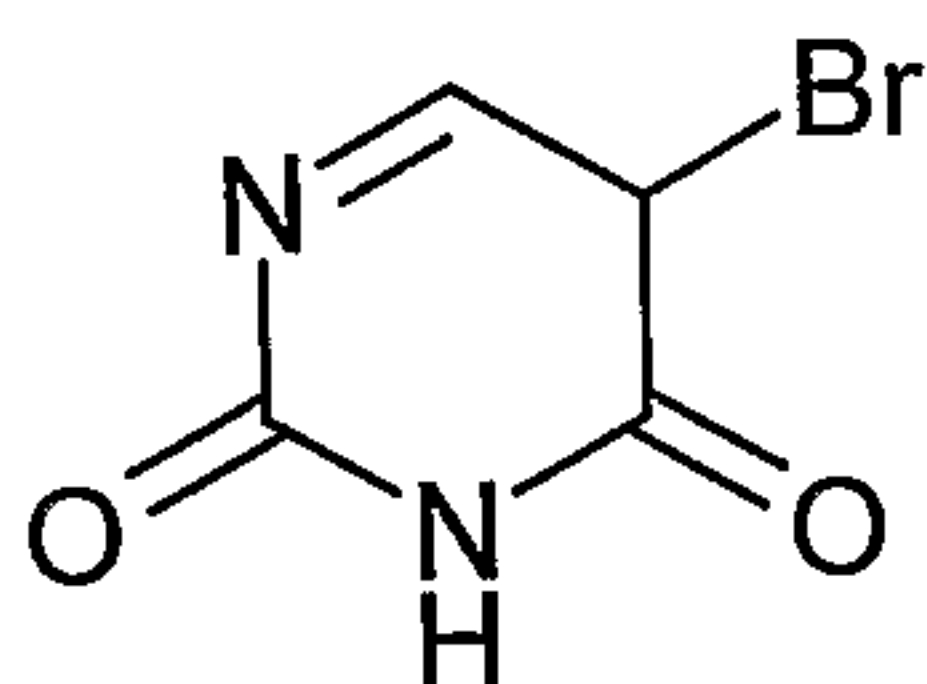
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(XVII)

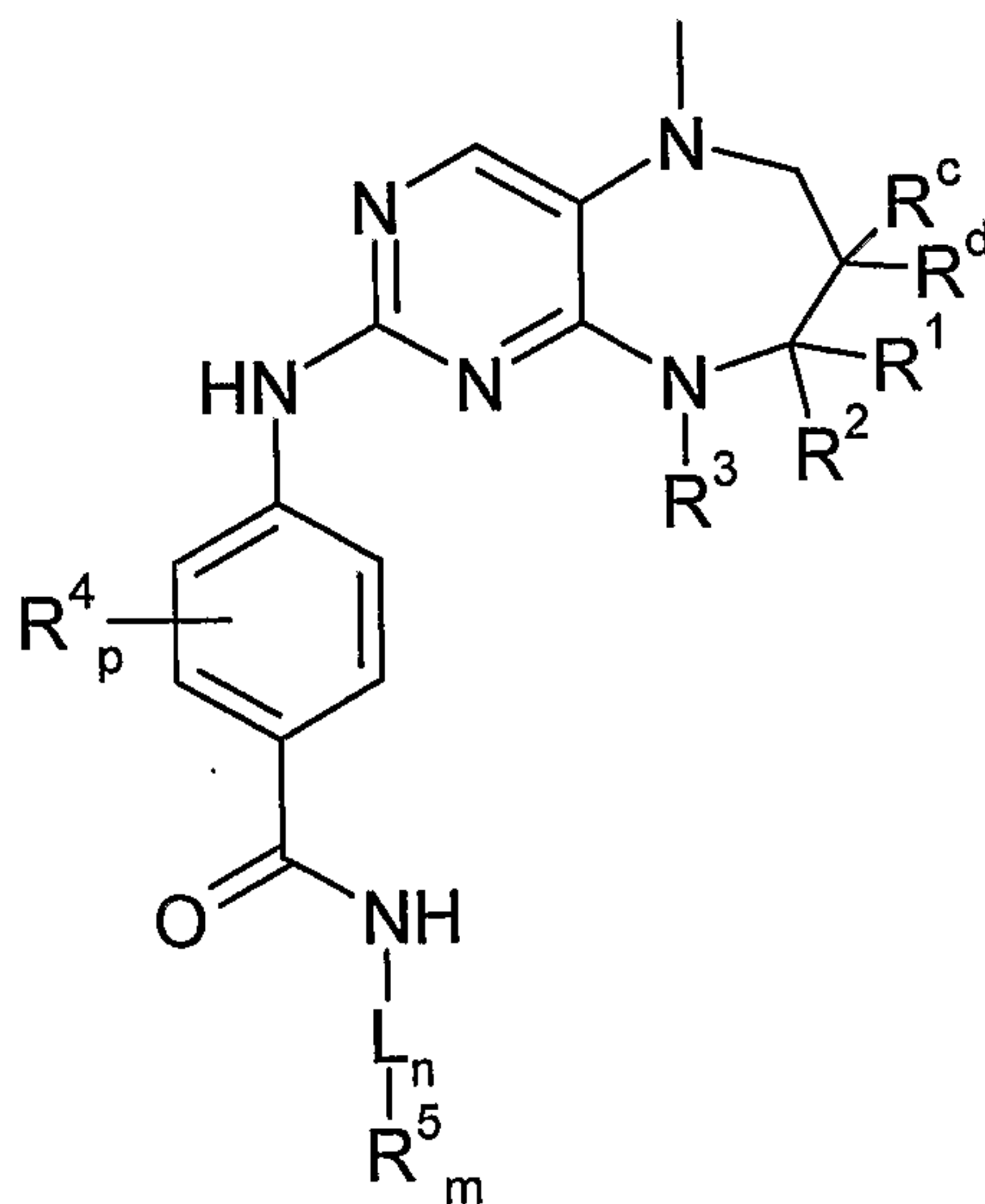
wherein X is a leaving group, typically a halogen, such as chloro, in the presence of a base, such as triethylamine, in an organic solvent, such as dichloromethane.

5 A compound of formula (XVI) may also be obtained by the sequential reaction of 5-bromouracil,



10 with i) methylamine, in a polar solvent, such as ethanol and;
ii) a chlorinating agent, such as phosphorous oxychloride as for instance exemplified in Journal of Medicinal Chemistry (1966), 9(1), 121-6.

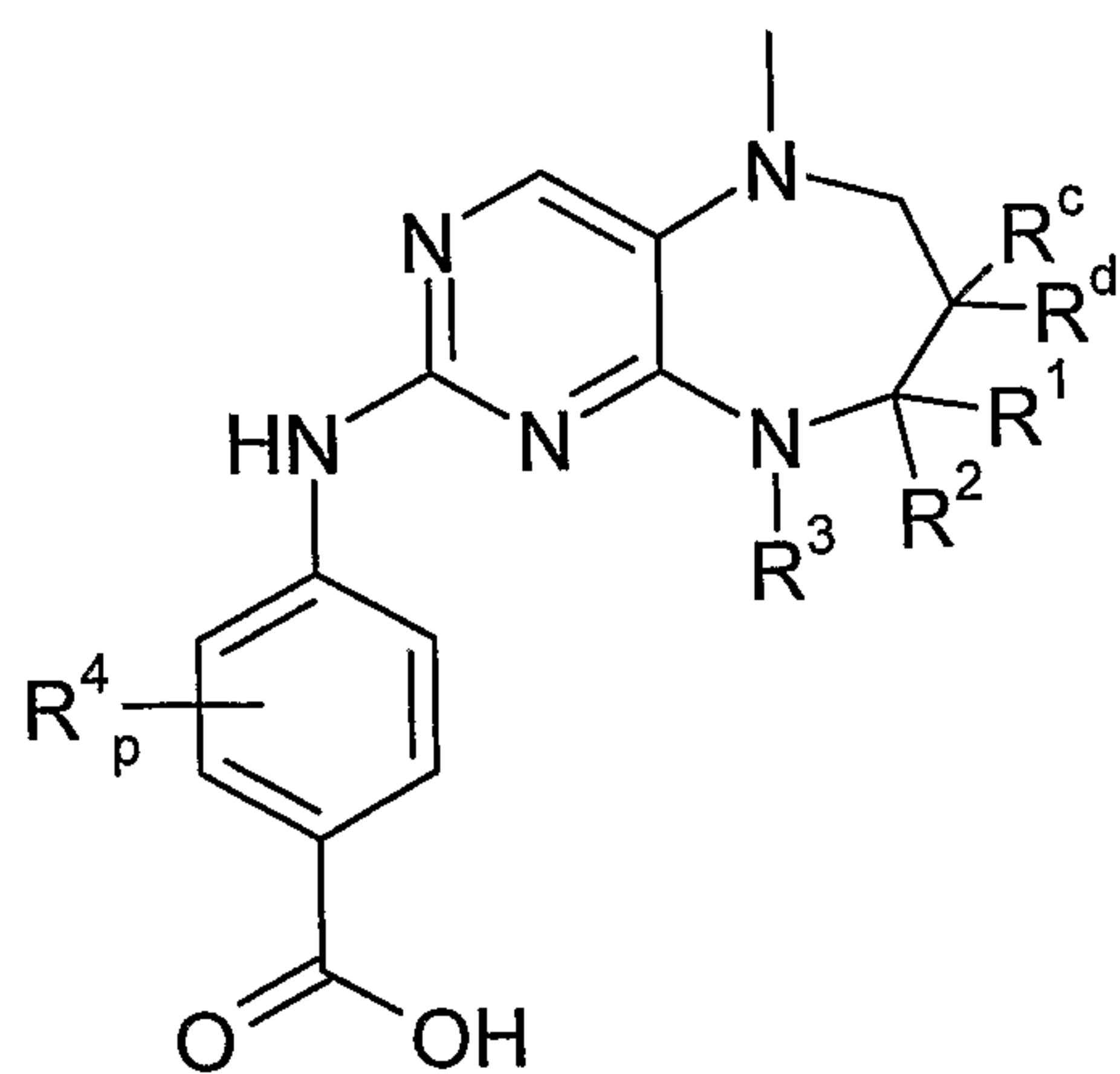
The invention also relates to a process for preparing a compound of general formula (XVIII),



(XVIII)

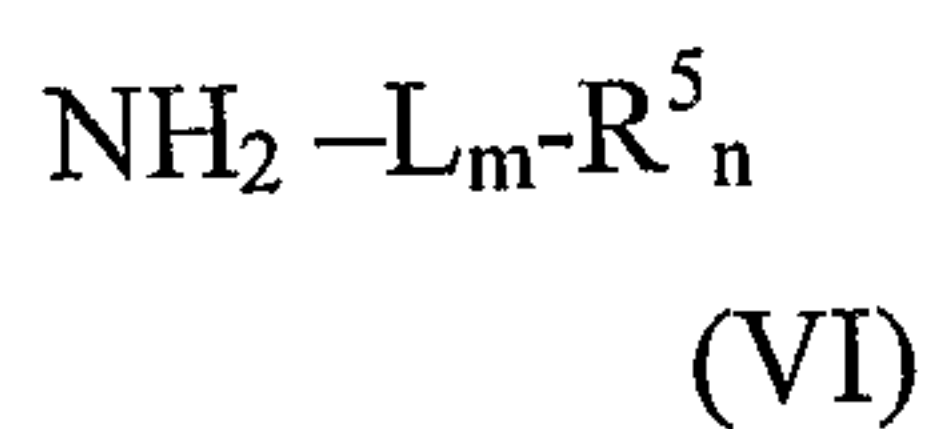
15 wherein R¹-R⁵, R^c, R^d, m, n and L are as hereinbefore defined,
comprising reacting a compound of general formula (XIX)

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(XIX)

with an amine of general formula (VI):

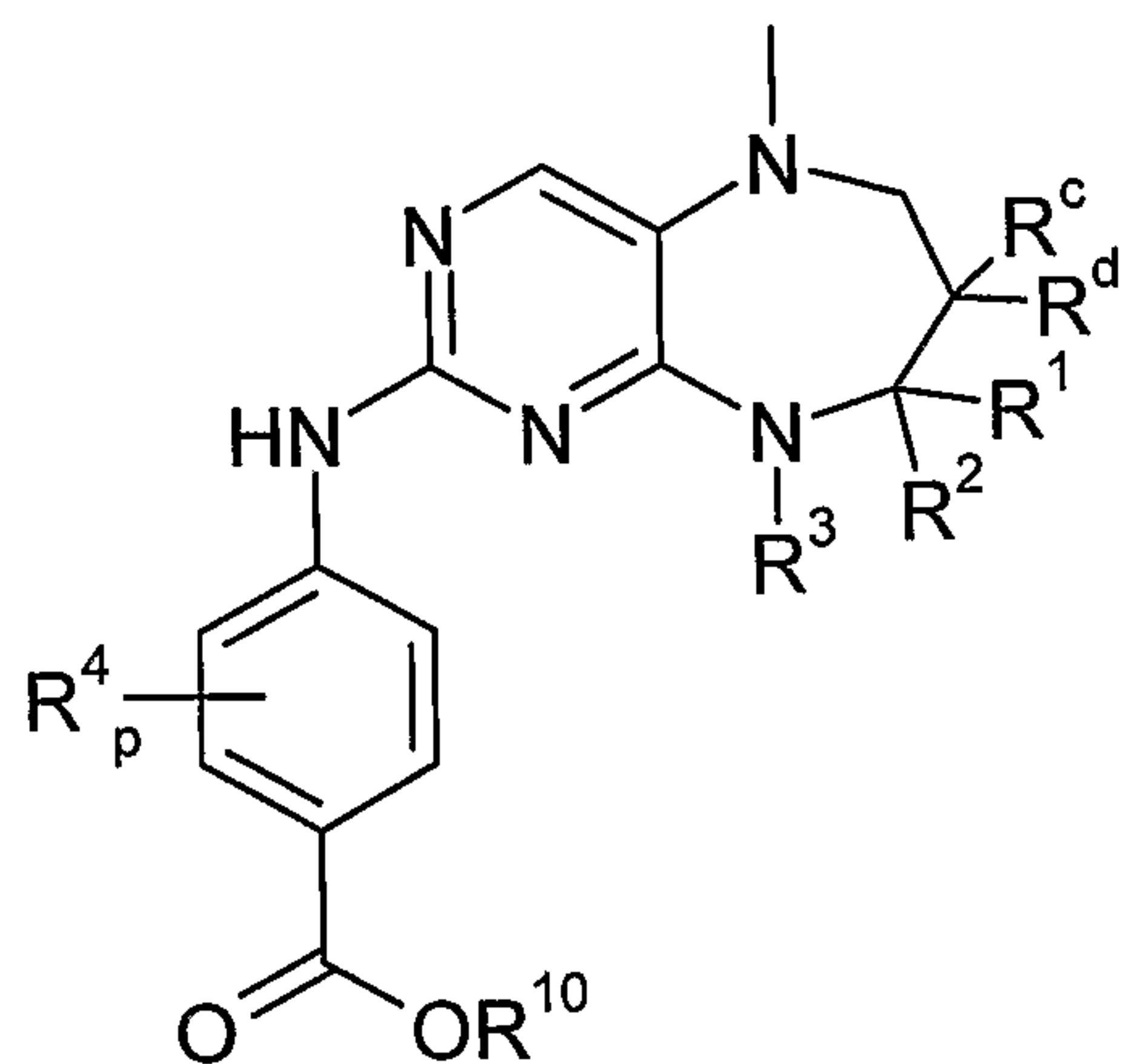


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wherein L and R⁵ are as hereinbefore defined.

Compounds of formula (XIX) may be obtained by hydrolysis of the corresponding esters.

Esters of general formula (XX)

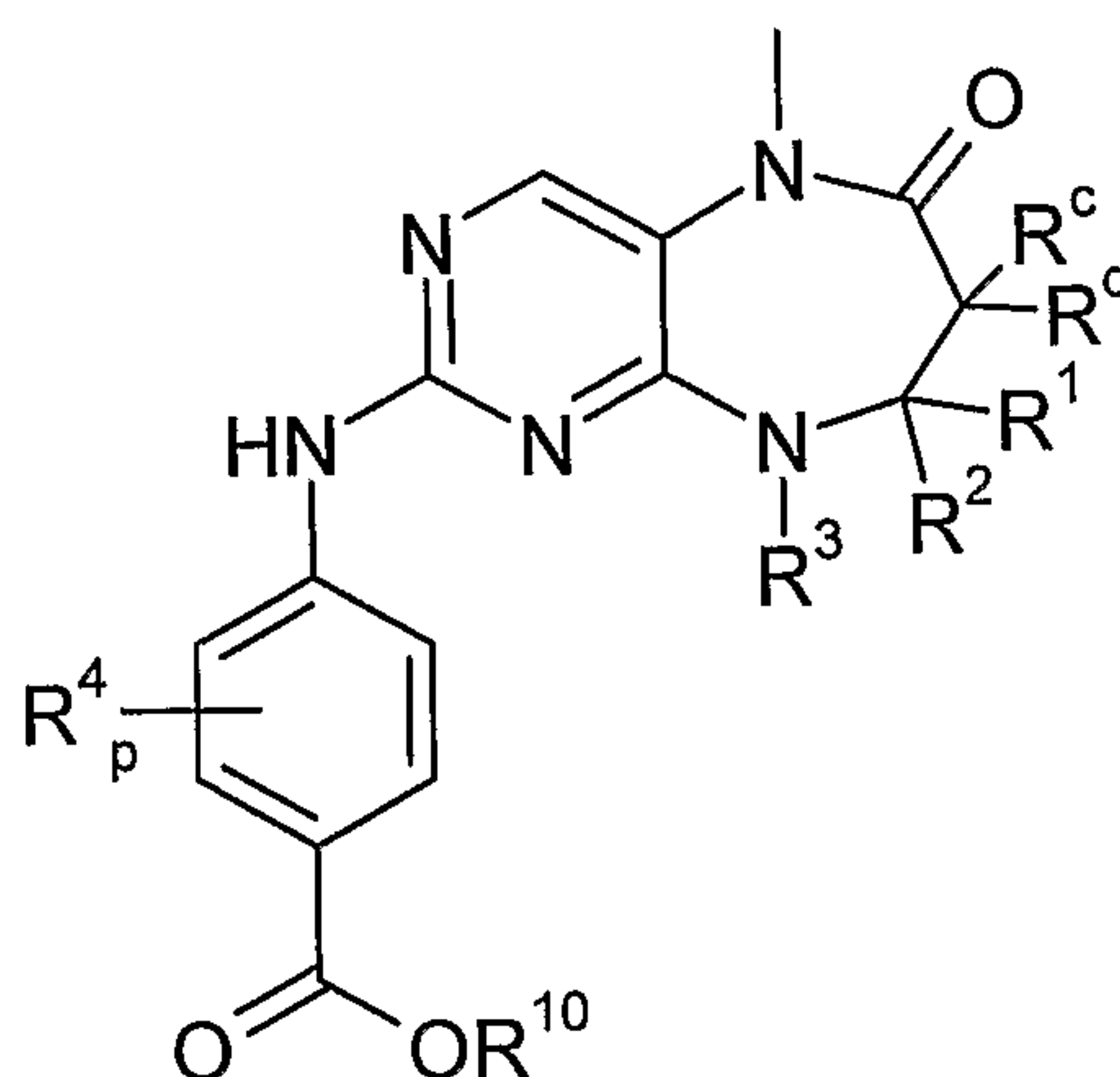


(XX)

10

may be obtained by the reduction of a compound of formula (XXI)

47



(XXI)

which may be prepared as described above.

5 It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I), (II), (IIa), (III) or (IIIa) may involve, at various stages, the addition and removal of one or more protecting groups.

10 The protection and deprotection of functional groups is described in in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley Interscience (1991/1999) and 'Protecting Groups', 3rd edition, P. J. Kocienski, Thieme (2005).

15 The invention further relates to compounds of formula (I), (II), (IIa), (III) or (IIIa) for use as pharmaceutical compositions.

In one embodiment of the invention, compounds of formula (I), (II), (IIa), (III) or (IIIa) are of use as pharmaceutical compositions with an antiproliferative activity.

20 The invention also relates to the use of a compound of formula (I), (II), (IIa), (III) or (IIIa) for preparing a pharmaceutical composition for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

These findings suggest that pharmacological inhibitors of Plk should be of therapeutic value for treatment of proliferative disease including solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In addition Plk inhibitors should

be useful in the treatment of other disorders associated with uncontrolled cellular proliferation.

One aspect of the current invention therefore relates to the use of one or more of the compounds of formula (I), (II), (IIa), (III) or (IIIa) in the treatment of disorders characterised
5 by excessive or anomalous cell proliferation.

Such diseases include for example: viral infections such as HIV and Kaposi's sarcoma; inflammatory and autoimmune diseases such as colitis, rheumatoid arthritis, Alzheimer's disease, glomerulonephritis and wound healing; bacterial, fungal and parasitic infections such as malaria and emphysema; dermatological diseases such as psoriasis; bone diseases;
10 cardiovascular diseases such as restenosis and cardiomyopathy. The compounds in the present invention may be used for the prevention, short- or long-term treatment of the above-mentioned diseases, also in combination with other active substances used for the same indications.

The invention also relates to a method of treating and/or preventing cancer, infections,
15 inflammatory and autoimmune diseases, characterised in that a patient is given an effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa).

The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of general formula (I), (II), (IIa), (III) or (IIIa), or the physiologically acceptable salts thereof, optionally combined with conventional excipients
20 and/or carriers.

The compounds of formula (I), (II) and (III) have activity as pharmaceuticals, in particular as modulators or inhibitors of Plk activity, and may be used in the treatment of proliferative and hyperproliferative diseases/conditions, examples of which include the following cancers:

- 25 (1) carcinoma, including that of the bladder, brain, breast, colon, kidney, liver, lung, ovary, pancreas, prostate, stomach, cervix, colon, thyroid and skin;
- (2) hematopoietic tumours of lymphoid lineage, including acute lymphocytic leukaemia, B cell lymphoma and Burkett's lymphoma;
- (3) hematopoietic tumours of myeloid lineage, including acute and chronic
30 myelogenous leukaemias and promyelocytic leukaemia;

(4) tumours of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and

(5) other tumours, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

5 In one embodiment, the compounds of formula (I), (II) and (III) are useful in the treatment of tumours of the lung, breast and prostate.

Thus, the present invention provides a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined for use in therapy.

10 In a further aspect, the present invention provides the use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

15 The invention also provides a method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

20 The invention still further provides a method of modulating polo-like kinase (Plk) activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

The invention still further provides the use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

The invention still further provides the use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating polo-like kinase (Plk) activity.

The compounds of formula (I), (II) and (III), and pharmaceutically acceptable salts thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I), (II), (IIa), (III) or (IIIa) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable
5 adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99%w (per cent by weight), more preferably from 0.05 to 80%w, still more preferably from 0.10 to 70%w, and even more preferably from 0.10 to 50%w, of active ingredient, all percentages by weight being based on total composition.

10 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical
15 composition of the invention which comprises mixing a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions,
20 heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

The compositions of the invention may be obtained by conventional procedures using
25 conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium
30 carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc;

preservative agents such as ethyl or propyl p-hydroxybenzoate and anti oxidants such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using
5 conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

10 Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or
15 condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters
20 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 (such as ethyl or propyl p- hydroxybenzoate, anti oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening
25 agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and
30 flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together 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
5 excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil in water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally occurring gums such as gum acacia or gum
10 tragacanth, naturally occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

15 Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using
20 one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally acceptable diluent or solvent, for example a solution in 1,3 butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a
25 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. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a
30 conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then
5 conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing
10 finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial
15 Board), Pergamon Press 1990.

The size of the dose for therapeutic purposes of a compound of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

20 In general, a compound of the invention will be administered so that a daily dose in the range, for example, from 0.5 mg to 75 mg active ingredient per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, from 0.5 mg to 30 mg active ingredient per kg body weight will
25 generally be used. Similarly, for administration by inhalation, a dose in the range, for example, from 0.5 mg to 25 mg active ingredient per kg body weight will generally be used. Also, for example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active ingredient.

For further information on Routes of Administration and Dosage Regimes the reader
30 is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The anti cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

5 (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine
10 arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide,
15 amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example
20 megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and N-(2-
25 chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include
30 growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [HerceptinTM], the anti-EGFR antibody panitumumab, the anti erbB1

antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as

5 N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived

10 growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152,

15 PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-

20 (4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-ylloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO

25 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

30 (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy;

(ix) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as cytokine transfected dendritic cells, approaches using cytokine transfected tumour cell lines and approaches using anti idiotypic antibodies; and

(x) other inhibitors of cell cycle such as Eg5, Chk1 or PARP inhibitors.

Examples

The invention will now be further described with reference to the following illustrative examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel;

(iv) SCX-2 cartridges are Ion Exchange SPE columns where the stationary phase is polymeric propylsulfonic acid. These are used to isolate amines.

(v) in general, the course of reactions was followed by TLC or LCMS and reaction times are given for illustration only;

(vi) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vii) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz or 500MHz, in CDCl₃, DMSO-d₆ or DMSO-d₆ + d₄-AcOH unless otherwise indicated;

5 (ix) chemical symbols have their usual meanings; SI units and symbols are used;

(x) solvent ratios are given in volume:volume (v/v) terms; and

(xi) Mass spectra (MS) data was generated on an LCMS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phenomenex Gemini C18 5mm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ mass spectrometer scanning over an appropriate mass range. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is the (M+H)⁺ for positive ion mode and (M-H)⁻ for negative ion mode;

20 (xii) Microwave irradiation of reaction mixtures was performed using Emrys Optimiser instrument;

(xiii) the following abbreviations have been used:

	AcOH	acetic acid
	CDCl ₃	deuteriochloroform
25	DCM	dichloromethane
	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMA	<i>N,N</i> -dimethylacetamide
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
30	DMSO-d ₆	hexadeuterodimethylsulfoxide
	EtOH	ethanol

	EtOAc	ethyl acetate
	HATU	2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium
5	HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium- hexafluoro-phosphate.
	HPLC	high performance liquid chromatography
	MeCN	acetonitrile
	MeOH	methanol
	MeI	methyl iodide
10	MS	mass spectroscopy
	m/z	mass to charge ratio
	NMR	nuclear magnetic resonance
	SCX-2	ion exchange SPE column (polymeric propylsulfonic acid stationery phase)
15	THF	terahydrofuran
	TFA	Trifluoroacetic acid
	XANTPHOS	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

Example 1:

20 **4-[(2-Cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one
(Intermediate 1; 99 mg, 0.34 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide
(WO06/018220; 93 mg, 0.35 mmol) and *p*-toluenesulfonic acid (167 mg, 0.88 mmol) were
25 dissolved in (*R/S*)-4-methyl-2-pentanol (8 mL) and heated at reflux under a blanket of
nitrogen for 24 h. The reaction mixture was cooled and loaded onto an SCX-2 column then
washed with MeOH (15 mL). The crude compound was eluted from the SCX-2 column with
NH₃ (40mL, 7M in MeOH) and the volatiles were removed under reduced pressure.
Purification by column chromatography (SiO₂, eluent gradient: 0-10% NH₃ [7M in MeOH] in
30 DCM), afforded the title compound (159 mg, 89%) as a solid.

¹H NMR (400 MHz, CDCl₃): δ_H 1.26 (t, 5H), 1.56 - 1.83 (m, 9H), 2.04 (s, 3H), 2.20 - 2.29 (m, 3H), 2.64 - 2.71 (m, 2H), 2.85 - 2.95 (m, 2H), 3.29 (s, 3H), 3.68 - 3.71 (m, 2H), 4.12 (q, 1H), 4.90 (quintet, 1H), 5.95 (d, 1H), 7.24 (dd, 1H), 7.42 (s, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.51 (d, 1H); MS m/z 508 [M+H]⁺.

5

Example 2:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

10 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 86 mg, 0.31 mmol), 4-amino-N-(1-methyl-4-piperidyl)benzamide (Intermediate 4; 72 mg, 0.31 mmol) and *p*-toluene sulfonic acid (146 mg, 0.76 mmol) were dissolved in 4-methyl-2-pentanol (5 mL) and refluxed under an atmosphere of nitrogen for 18 hrs. The reaction mixture was loaded onto an SCX-2 column then washed with MeOH (15 mL). The crude compound was eluted from the SCX-2 column with NH₃ (40 mL, 7M in MeOH) and the volatiles were removed under reduced pressure. Purification by column chromatography (SiO₂, eluent gradient: 0-10% NH₃ [7M in MeOH] in DCM) then by preparative HPLC (Sunfire prep RP18, 19 x 100 mm column, eluting with a gradient of 0.1% solution of TFA in H₂O and a 0.1% solution of TFA in MeCN). The product fractions were then loaded onto an SCX-2 column then washed with MeOH (10 mL). The product was
15 eluted from the SCX-2 column with NH₃ (30 mL, 7M in MeOH) and the volatiles removed under reduced pressure to give the title compound (38.5 mg, 26%) as a solid.

¹H NMR (399.9 MHz, DMSO-d₆) δ_H 1.58 - 1.78 (10H, m), 1.92 - 2.04 (4H, m), 2.21 (3H, s), 2.58 - 2.60 (2H, m), 2.79 - 2.83 (2H, m), 3.18 (3H, s), 3.60 - 3.65 (2H, m), 3.71 - 3.79 (1H, m), 4.81 - 4.89 (1H, m), 7.76 (2H, d), 7.82 (2H, d), 7.99 (1H, d), 8.09 (1H, s), 9.44 (1H, s);
25 MS m/z 478 [M+H]⁺.

Example 3:

4-[(4*R/S*)-(2-Cyclopentyl-4,6-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

30 (4*R/S*)-10-Chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 5; 106 mg, 0.36 mmol), 4-amino-N-(1-methyl-4-

piperidyl)benzamide (WO06018220; 95 mg, 0.36 mmol) and *p*-toluene sulphonic acid (170 mg, 0.89 mmol) were dissolved in (*R/S*)-4-methyl-2-pentanol (6 mL) and refluxed under a blanket of nitrogen for 24 hrs. The reaction mixture was cooled to ambient temperature and loaded onto an SCX-2 column and then washed with MeOH (40 mL). The crude compound
5 was eluted from the SCX-2 column with NH₃ (40 mL, 7M in MeOH) and the volatiles removed under reduced pressure. The crude material was then purified by column chromatography (SiO₂, eluent gradient: 0-10% NH₃ [7M in MeOH] in DCM) then by preparative HPLC (Sunfire prep RP18, 19 x 100 mm column, eluting with a gradient composing of a 0.1% solution of TFA in H₂O and a 0.1% solution of TFA in MeCN). The
10 product fractions were loaded onto an SCX-2 column then washed with MeOH (10 mL). The product was eluted from the SCX-2 column with NH₃ (30 mL, 7M in MeOH) and the volatiles removed under reduced pressure to give the title compound (43.9 mg, 23%) as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ_H 1.04 (d, 3H), 1.51 - 1.84 (m, 12H), 1.99 - 2.13 (m, 3H),
15 2.81 - 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quintet, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 522 [M+H]⁺.

Example 4:

**4-[(2-Cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-
20 yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**

To a solution of 4-[(9-cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-
b][1,4]diazepin-2-yl)amino]-3-methoxybenzoic acid (Intermediate 6; 240 mg, 0.60 mmol) and
N-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylene]-N-
methylethylmethanaminium hexafluorophosphate (275 mg, 0.72 mmol) in DMA (10 mL) was
25 added 1-methylpiperidin-4-amine (82 mg, 0.72 mmol) and DIPEA (210 uL, 1.20 mmol), and
the reaction stirred at ambient temperature for 2 hr. The reaction mixture was loaded onto an
SCX-2 column and washed with MeOH (20 mL). The crude product was then eluted from the
SCX-2 column with NH₃ (40 mL, 7M in MeOH) and the volatiles removed under reduced
pressure. Purification by column chromatography (SiO₂, eluent gradient: 5-10% MeOH in
30 DCM) afforded the title compound (160 mg, 54%) as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ_H 1.65 (m, 10H), 1.94 (m, 6H), 2.21 (s, 3H), 2.71 (s, 3H), 2.82 (d, 2H), 3.00 (t, 2H), 3.48 (m, 2H), 3.94 (s, 3H), 4.86 (m, 1H), 7.36 (s, 1H), 7.46 (m, 2H), 7.53 (s, 1H), 8.02 (d, 1H), 8.46 (d, 1H); MS m/z 494 [M+H]⁺.

5 **Example 5:**

4-[(2,6-Dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-Chloro-2,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 9; 185 mg, 0.82 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (215 mg, 0.82 mmol) and *p*-toluenesulphonic acid (389 mg, 2.05 mmol) in (*R/S*)-4-methyl-2-pentanol (6 mL) were heated at 115 °C for 5 h. The reaction mixture was cooled to ambient temperature then passed through a SCX-2 cartridge and washed with MeOH (40 mL). The crude product was eluted off the SCX-2 cartridge with NH₃ (40 mL, 7M in MeOH). Purification by preparative HPLC (Gemini RP C18 30x100mm, gradient mobile phase: 10-80% MeCN/water + 0.5% NH₃) afforded the title compound (180 mg, 48%) as a foam.

¹H NMR (400 MHz, DMSO-d₆) δ_H 1.60 (m, 2H), 1.78 (m, 2H), 1.90 (tr, 2H), 2.19 (s, 3H), 2.62 (tr, 2H), 2.79 (d, 2H), 3.09 (s, 3H), 3.20 (s, 3H), 3.73 (m, 3H), 3.95 (s, 3H), 7.51 (m, 2H), 7.75 (m, 1H), 8.05 (d, 1H), 8.11 (s, 1H), 8.48 (d, 1H); MS m/z 454 [M+H]⁺.

20

The following examples were prepared by an analogous process to that used in the preparation of Example 5 utilising the appropriate pyrimidine derivative (Intermediates 10 – 13) as the electrophile and 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220) as the aniline:

25

Example 6:

3-Methoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

30 **Example 7:**

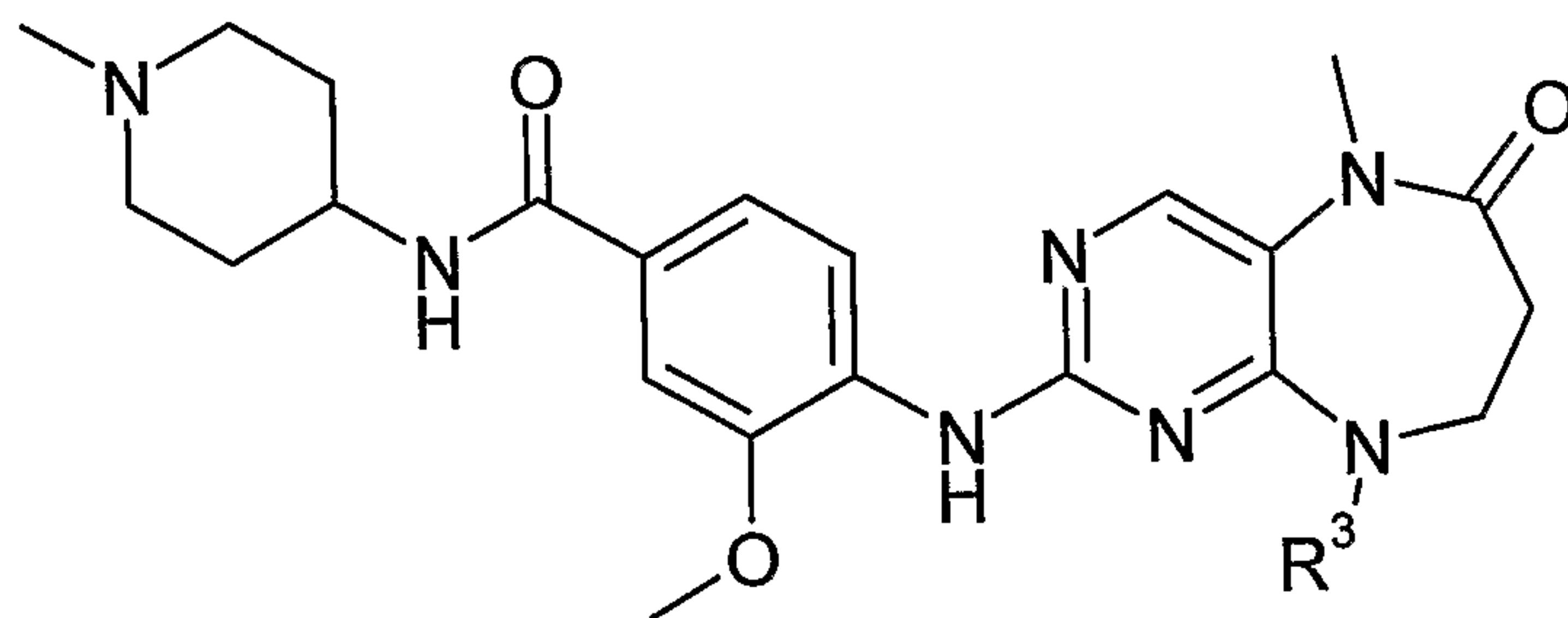
3-Methoxy-4-[[6-methyl-2-(3-methylbutyl)-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

Example 8:

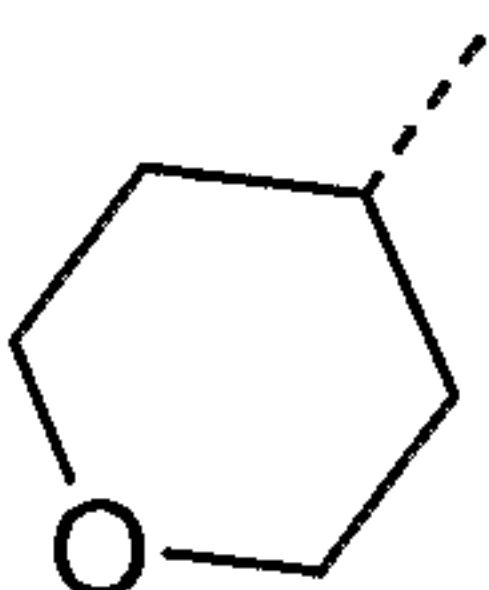
5 **4-[(2-Cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**

Example 9:

10 **3-Methoxy-4-[[6-methyl-2-(oxan-4-yl)-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-N-(1-methyl-4-piperidyl)benzamide**



Example	R ³	¹ H NMR (400 MHz, DMSO-d ₆)	MS m/z [M+H] ⁺
6		1.25 (d, 6H), 1.60 (m, 2H), 1.77 (m, 2H), 1.95 (tr, 2H), 2.19 (s, 3H), 2.60 (tr, 2H), 2.70 (d, 2H), 3.19 (s, 3H), 3.62 (m, 2H), 3.75 (m, 1H), 3.96 (s, 3H), 4.80 (m, 1H), 7.51 (m, 2H), 7.69 (s, 1H), 8.08 (d, 2H), 8.41 (d, 1H)	482
7		0.92 (d, 6H), 1.58 (m, 5H), 1.76 (m, 2H), 1.93 (tr, 2H), 2.19 (s, 3H), 2.61 (tr, 2H), 2.79 (d, 2H), 3.19 (s, 3H), 3.61 (tr, 2H), 3.71 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.70 (s, 1H), 8.06 (d, 2H), 8.35 (d, 1H)	510
8		1.17 (m, 1H), 1.41 (m, 2H), 1.55-1.90 (m, 11H), 1.95 (tr, 2H), 2.19 (s, 3H), 2.59 (tr, 2H), 2.80 (d, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 3.77 (m, 1H), 4.49 (tr, 1H), 7.49	522

Example	R ³	¹ H NMR (400 MHz, DMSO-d ₆)	MS m/z [M+H] ⁺
		(m, 2H), 7.70 (s, 1H), 8.08 (m, 2H), 8.39 (d, 1H)	
9		1.61 (m, 2H), 1.72-2.00 (m, 7H), 2.20 (s, 3H), 2.61 (tr, 2H), 2.80 (d, 2H), 3.19 (s, 3H), 3.50 (tr, 2H), 3.67 (m, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.02 (dd, 2H), 4.62 (tr, 1H), 7.51 (m, 2H), 7.78 (s, 1H), 8.10 (m, 2H), 8.31 (d, 1H)	524

Example 10:

4-[(2-Cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

5 hydrochloride

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 238 mg, 0.85 mmol), 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 250 mg, 0.85 mmol) and *p*-toluenesulfonic acid (405 mg, 2.13 mmol) were dissolved in (*R/S*)-4-methyl-2-pentanol (4 mL) and heated at reflux for 24 h. The reaction mixture was then cooled and loaded onto an SCX-2 column, which was then washed with MeOH (40 mL). The crude product was washed off the SCX-2 column with NH₃ (50 mL, 7M in MeOH). Purification by column chromatography (SiO₂, eluent gradient: 0-10% NH₃ [7M in methanol] in DCM) give a pale yellow oil. HCl (0.43 uL, 2N in Et₂O, 0.85 mmol) was added to a DCM (5 mL) solution of the yellow oil. Concentration under reduced pressure gave the title compound (188 mg, 40%) as a solid.

¹H NMR (400 MHz, CDCl₃): δ_H 1.00 (s, 6H), 1.60 - 1.84 (m, 6H), 2.02 - 2.34 (m, 2H), 2.37 (s, 2H), 2.39 (s, 6H), 2.65 - 2.69 (m, 2H), 3.29 (s, 3H), 3.38 (d, 2H), 3.68 - 3.72 (m, 2H), 3.98 (s, 3H), 4.87 - 4.96 (m, 1H), 7.29 (dd, 1H), 7.51 (d, 1H), 7.67 (s, 1H), 7.95 (s, 1H), 8.51 (d, 1H), 9.14 (t, 1H); MS m/z 524 [M+H]⁺.

Example 11:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-cyclopropyl-4-piperidyl)-3-methoxy-benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 150 mg, 0.36mmol), 1-cyclopropylpiperidin-4-amine (Intermediate 24, 77 mg, 0.55mmol) and HATU (208 mg, 0.55mmol) were stirred in DMF (92ml). DIPEA (191 mL, 1.09mmol) was added and the mixture stirred at room temperature for 3 h. The mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative HPLC to give the title compound as a pale brown solid (127mg, 66%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.29 (2H, s), 0.43 (2H, d), 1.48 – 1.81 (11H, m), 1.94 (2H, m), 2.24 (2H, t), 2.60 (2H, t), 2.96 (2H, d), 3.18 (3H, s), 3.63 (2H, t), 3.78 (1H, m), 3.95 (3H, s), 4.78 - 4.86 (1H, m), 7.46 - 7.51 (2H, m), 7.73 (1H, s), 8.04 (1H, d), 8.09 (1H, s), 8.39 (1H, d); MS m/z 534 [M+H]⁺.

Example 12:

15 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(1-piperidyl)ethyl]benzamide**

A solution of HATU (147 mg, 0.385 mmol) in DMA (1 mL) was added to a mixture of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 144mg, 0.35 mmol), DIPEA (183uL, 1.05 mmol) and 2-(1-piperidyl)ethanamine (Aldrich, 56 mg 0.44 mmol) in DMA (1 mL). The resulting mixture was stirred at room temperature overnight. The mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase HPLC to give the title compound (86mg, 47%)

25

The following examples were prepared by an analogous process to that used in the preparation of Example 12 utilising the acid described in Example 111 and the appropriate amines.

30 **Example 13:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide

5 **Example 14:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

10 **Example 15:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[(1-ethylpyrrolidin-2-yl)methyl]-3-methoxy-benzamide

15

Example 16:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

20 **Example 17:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(5-diethylaminopentan-2-yl)-3-methoxy-benzamide

25

Example 18:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-diethylaminoethyl)-3-methoxy-benzamide

30

Example 19:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

Example 20:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide

Example 21:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-dimethylaminobutyl)-3-methoxy-benzamide

Example 22:

N-(1-azabicyclo[2.2.2]oct-8-yl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 23:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(2-oxoimidazolidin-1-yl)ethyl]benzamide

Example 24:

N-(2-acetamidoethyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 25:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(3-morpholin-4-ylpropyl)benzamide

Example 26:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-imidazol-1-ylpropyl)-3-methoxy-benzamide

5 **Example 27:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-imidazol-1-ylethyl)-3-methoxy-benzamide

10 **Example 28:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-dimethylaminopropan-2-yl)-3-methoxy-benzamide

15

Example 29:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[1-(2-methoxyethyl)-4-piperidyl]benzamide

20

Example 30:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-diethylaminobutyl)-3-methoxy-benzamide

25

Example 31:

30 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-imidazol-1-ylbutyl)-3-methoxy-benzamide

Example 32:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)ethyl]benzamide

5 **Example 33:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(4-pyrrolidin-1-ylbutyl)benzamide

10 **Example 34:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(4-methylpiperazin-1-yl)ethyl]benzamide

15 **Example 35:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-3-methoxy-benzamide

20 **Example 36:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-[(3R)-3-fluoropyrrolidin-1-yl]ethyl]-3-methoxy-benzamide

25 **Example 37:**

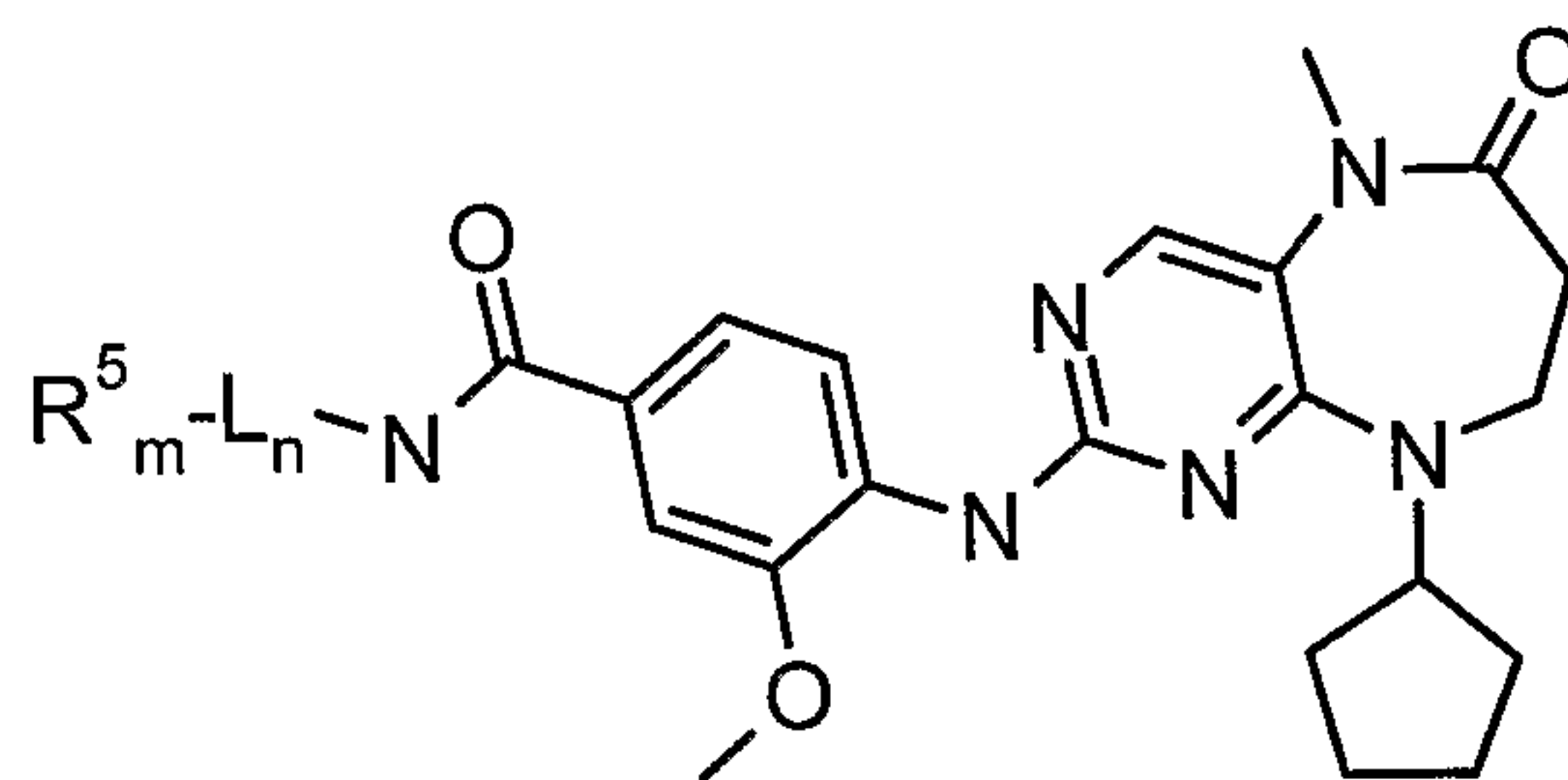
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30 **Example 38:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[3-(pyridin-2-ylamino)propyl]benzamide

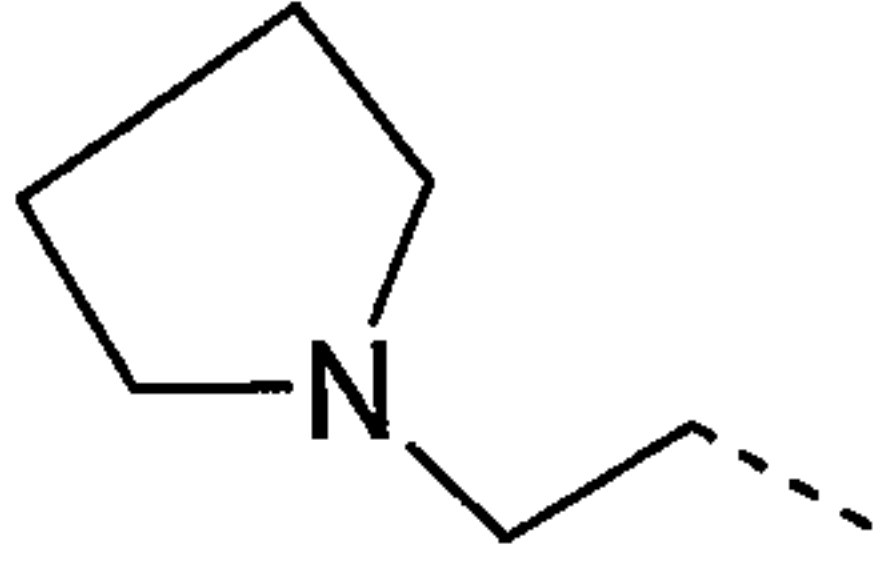
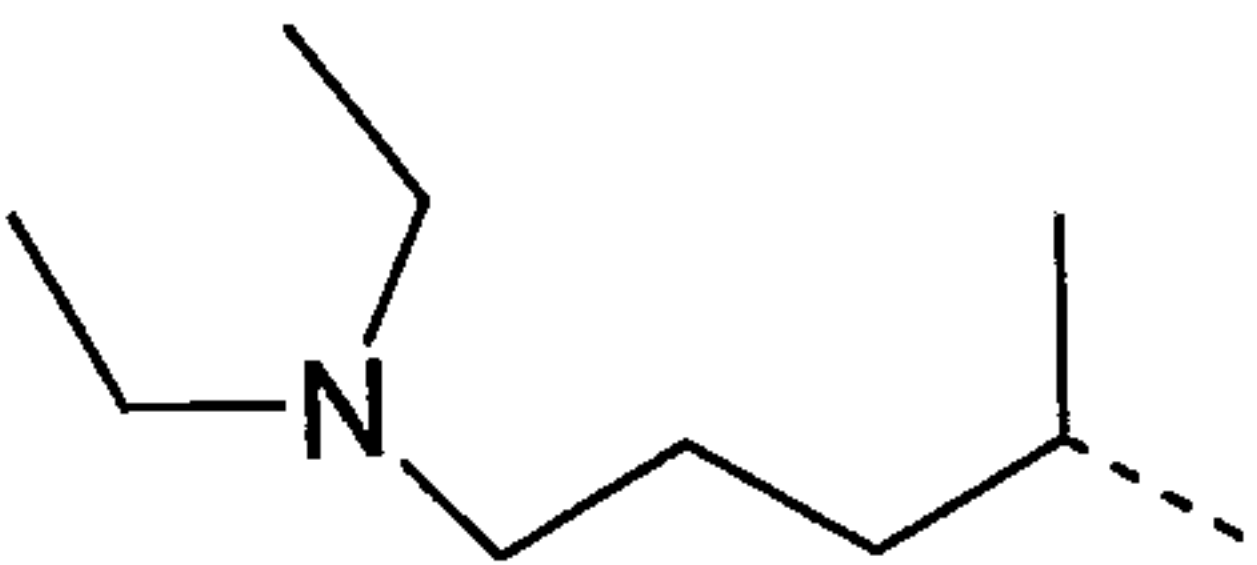
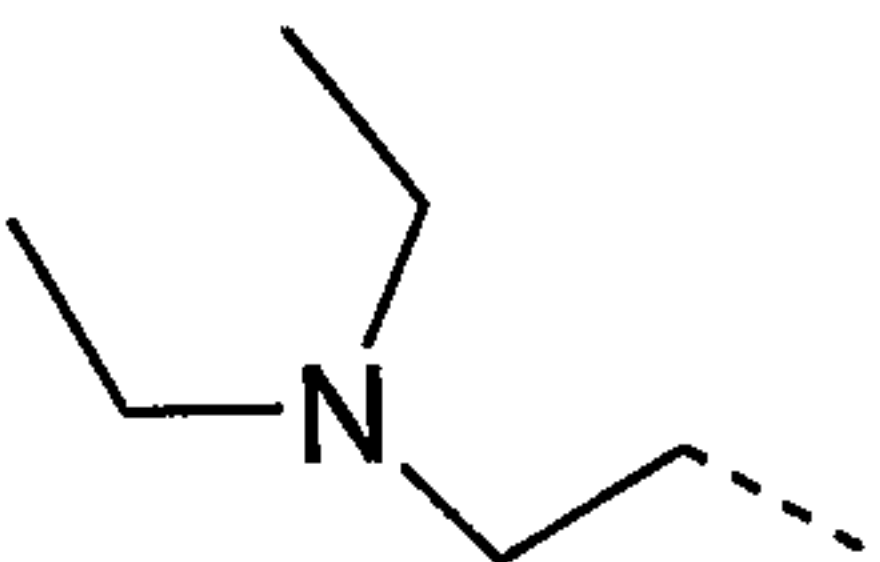
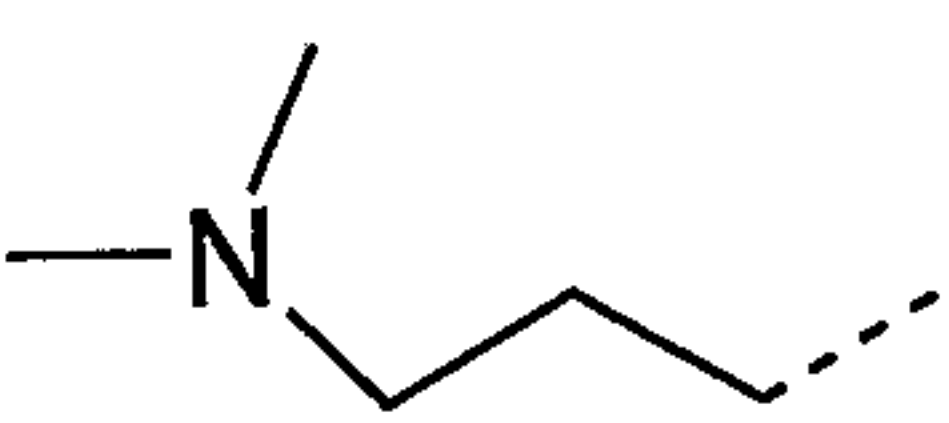
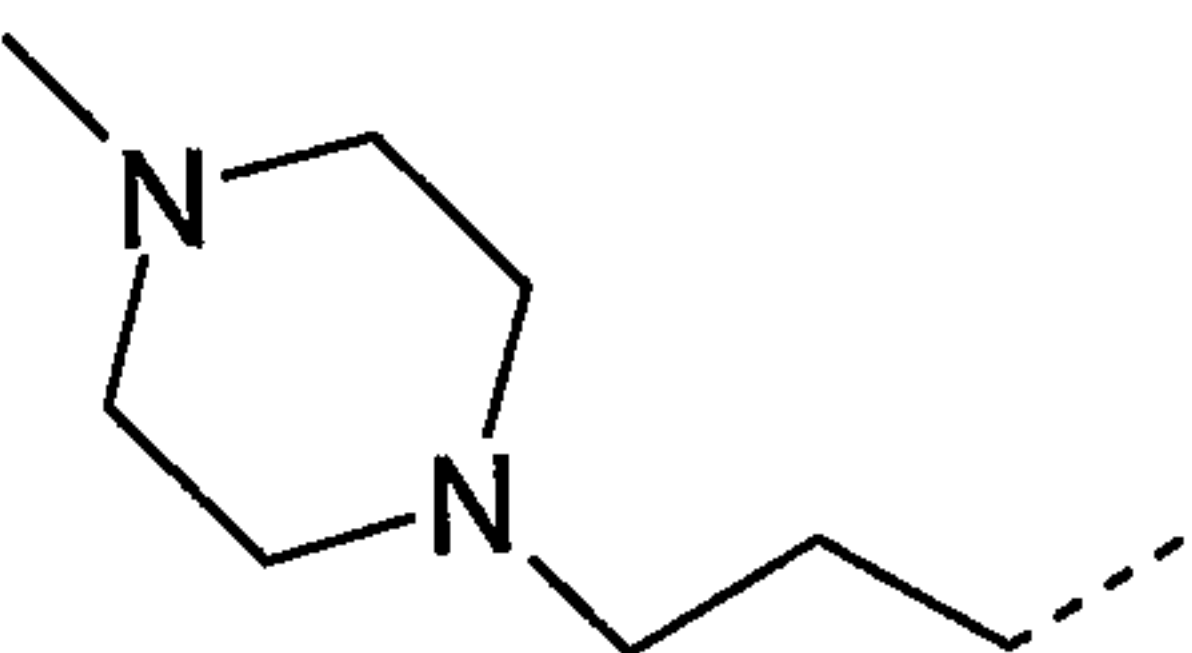
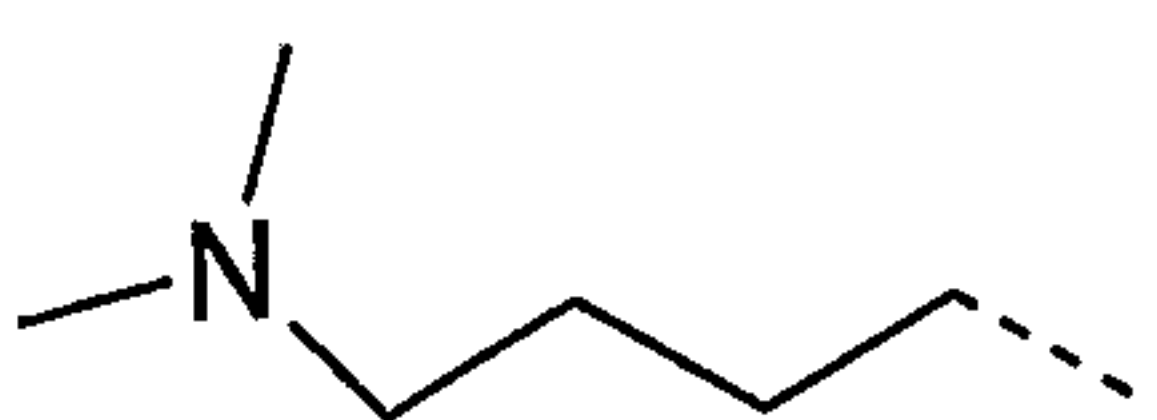
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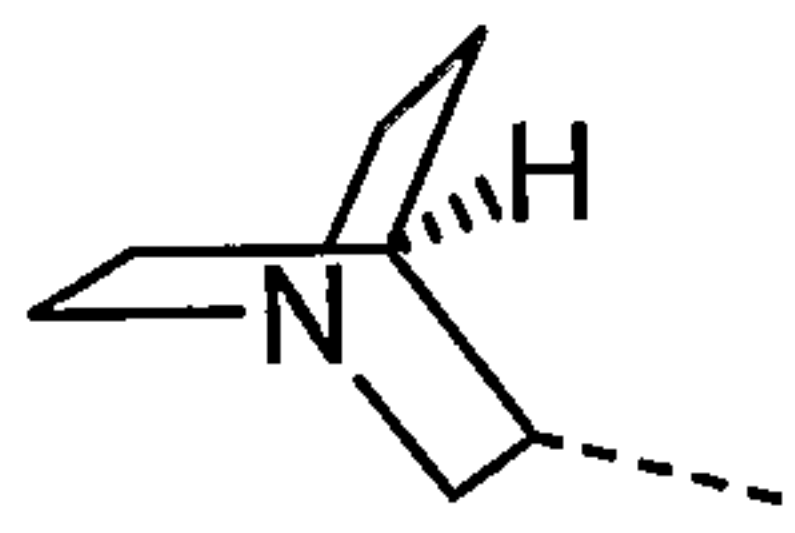
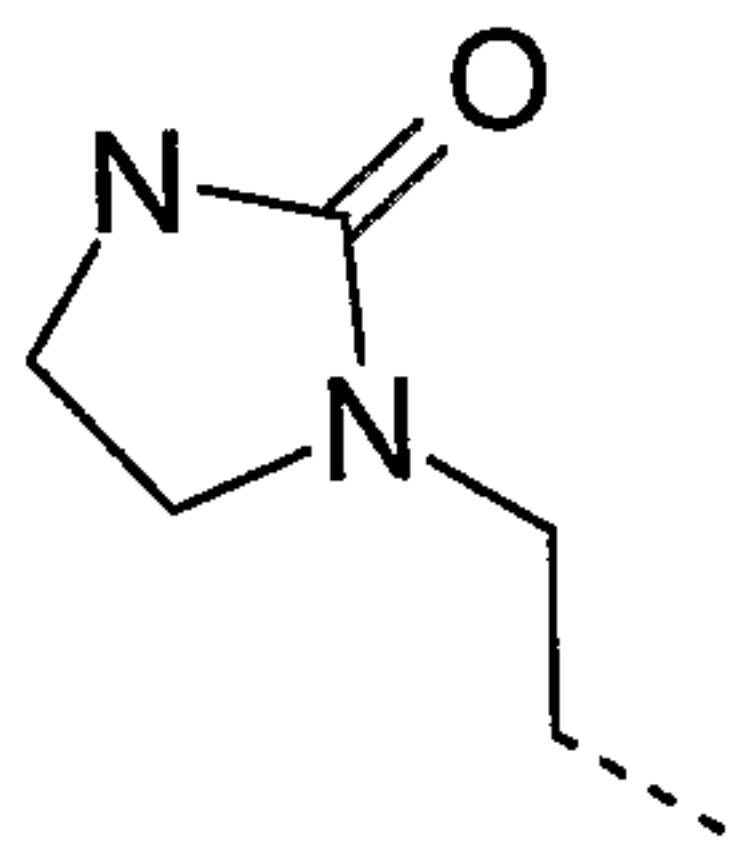
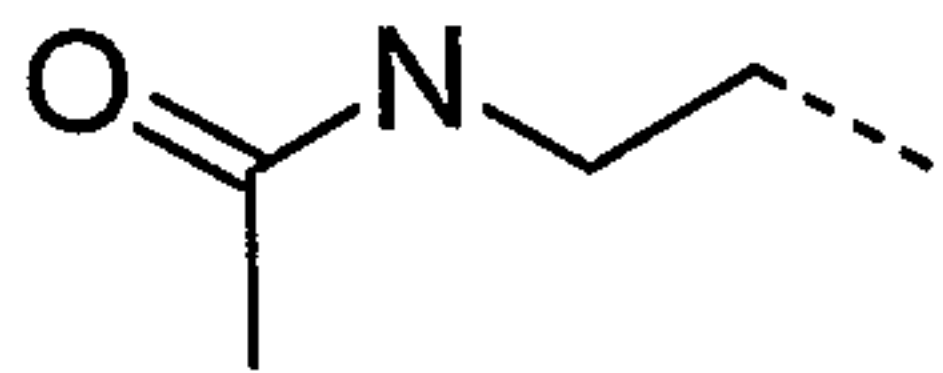
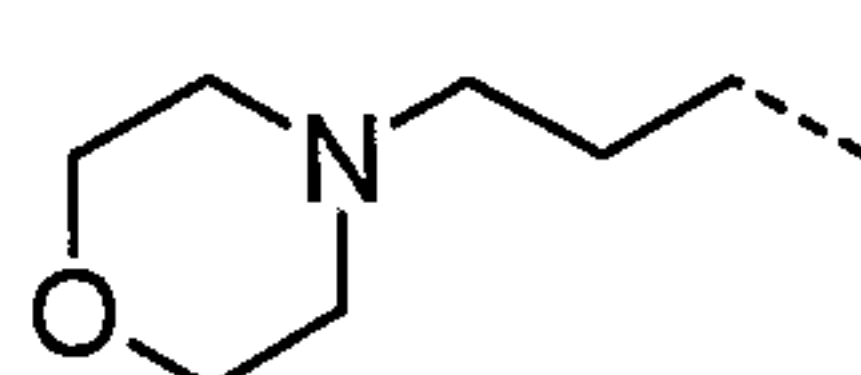
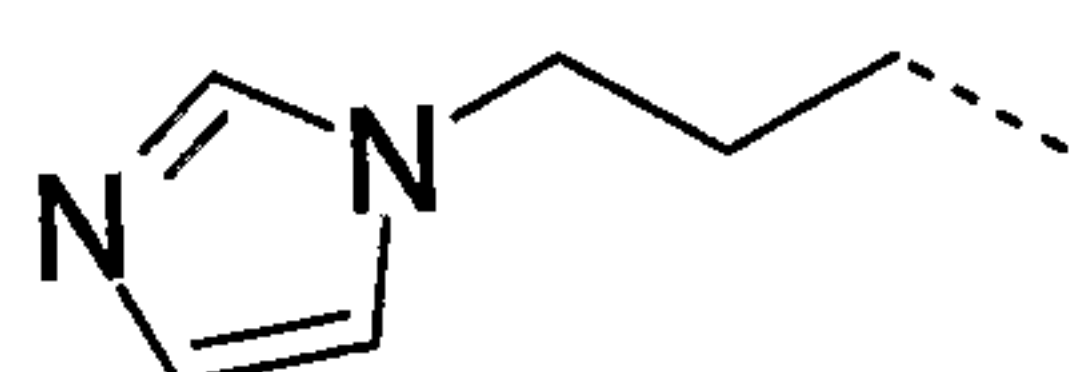
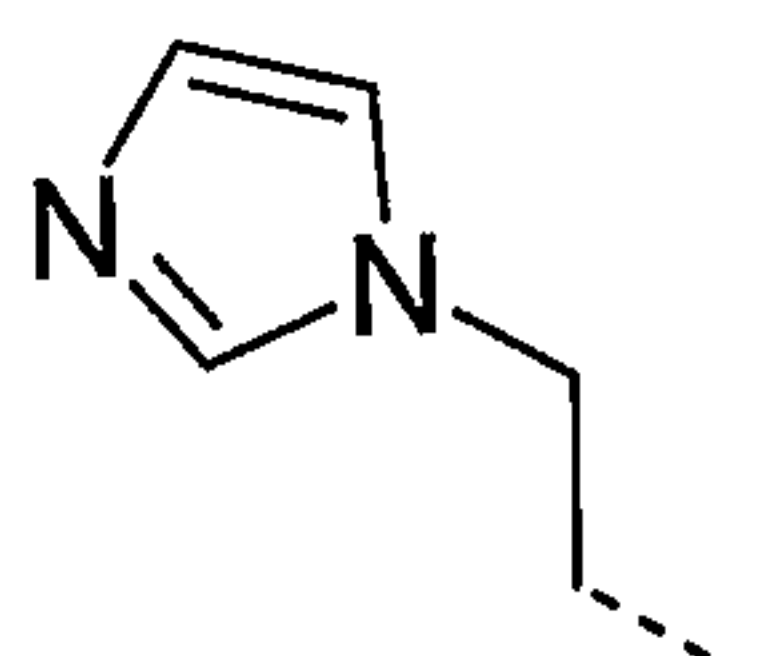
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-3-piperidyl)benzamide

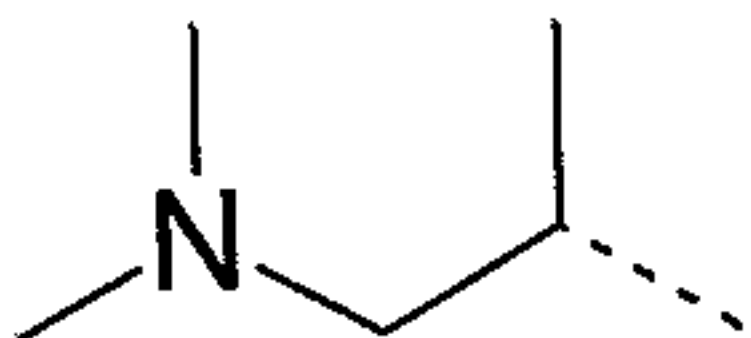
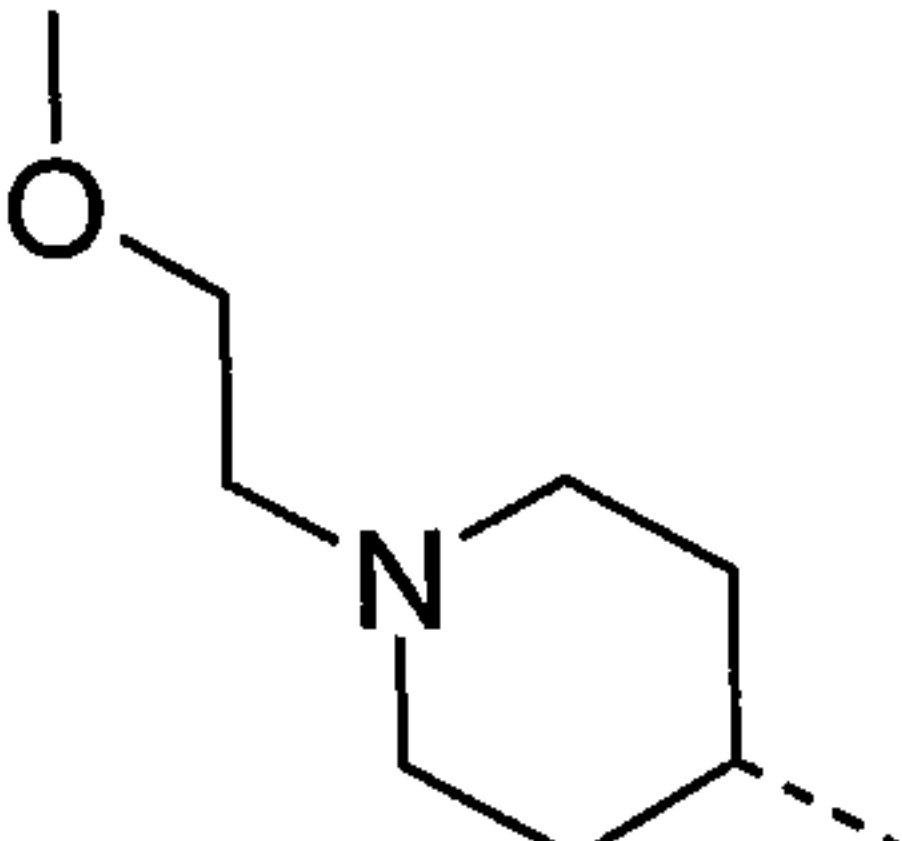
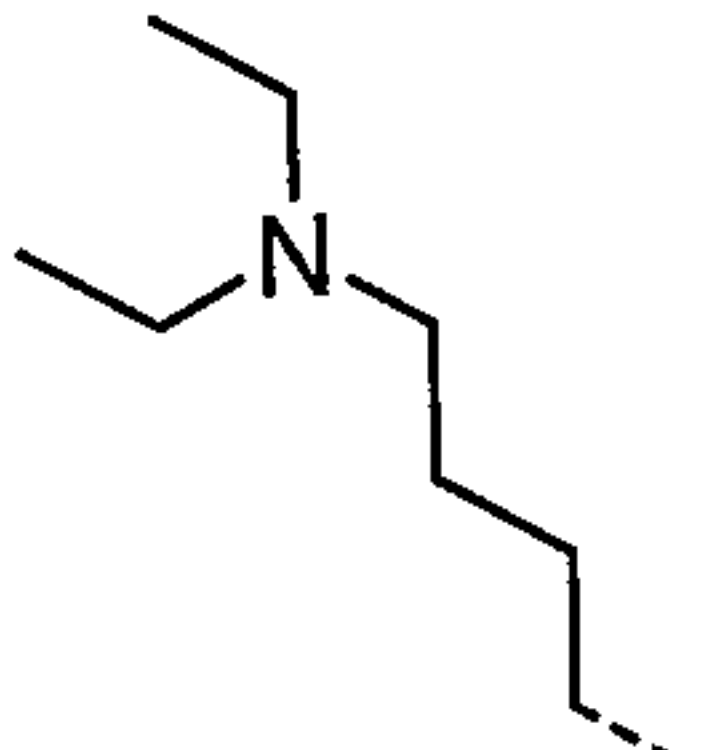
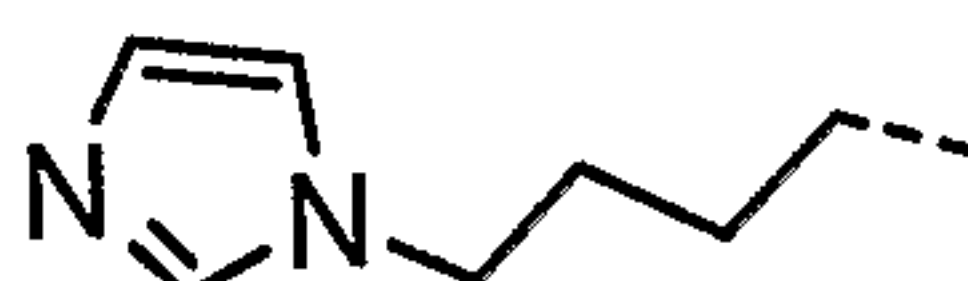
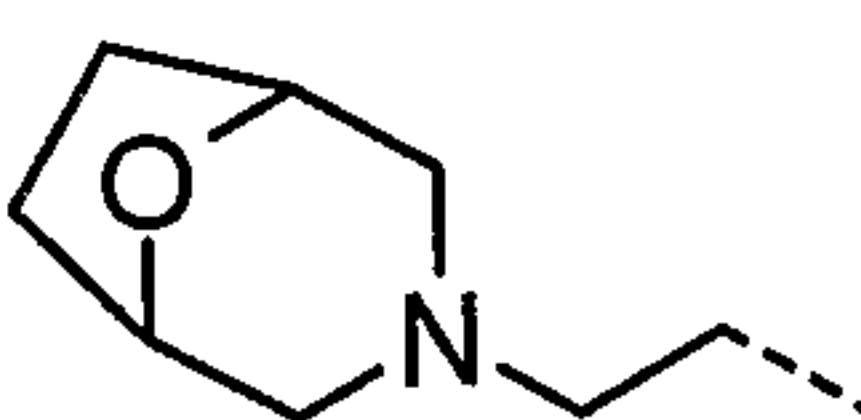
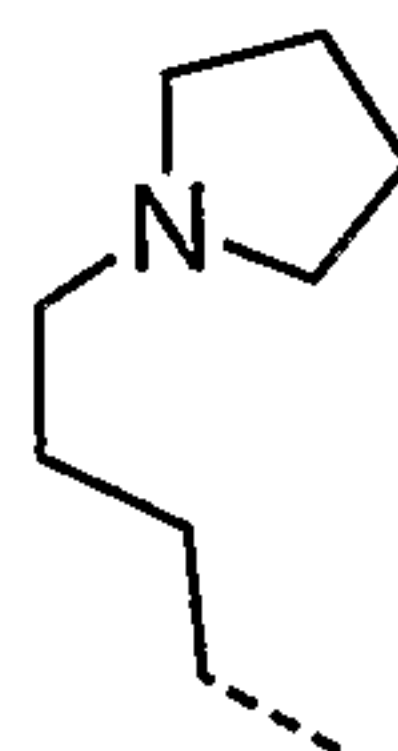


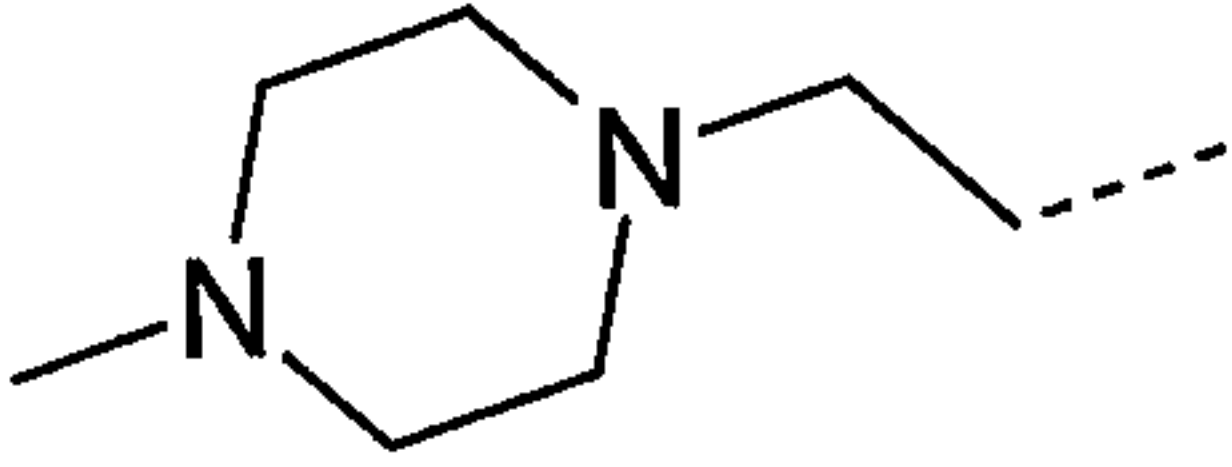
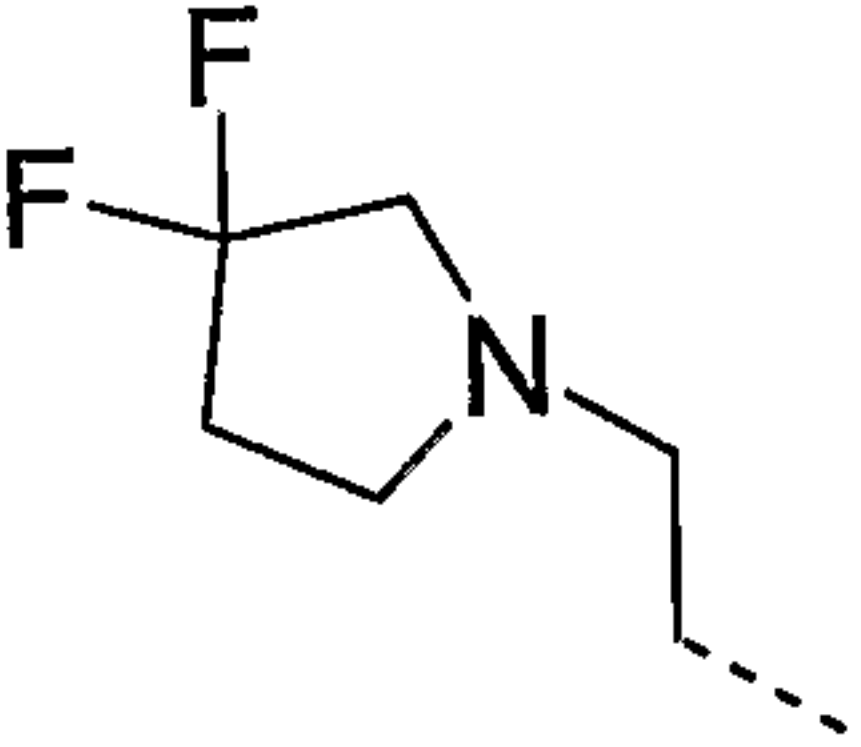
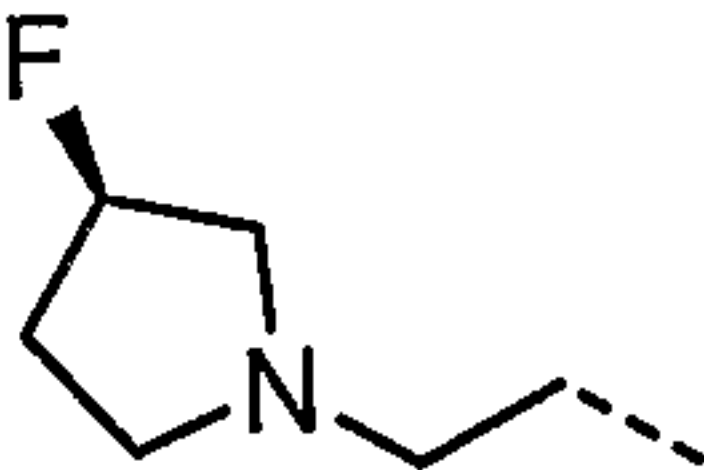
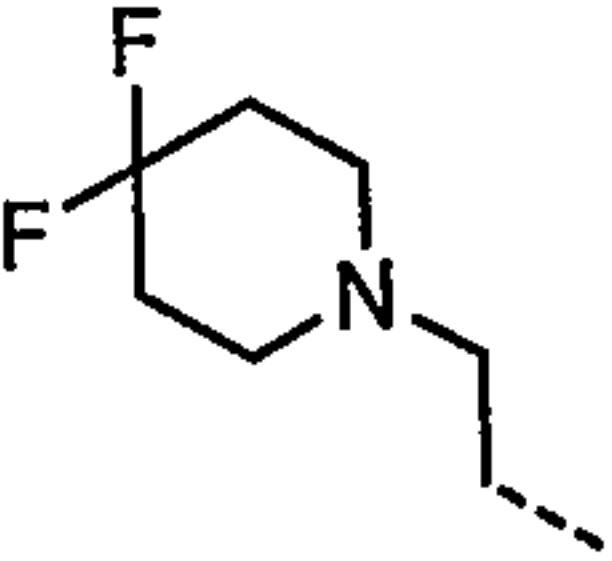
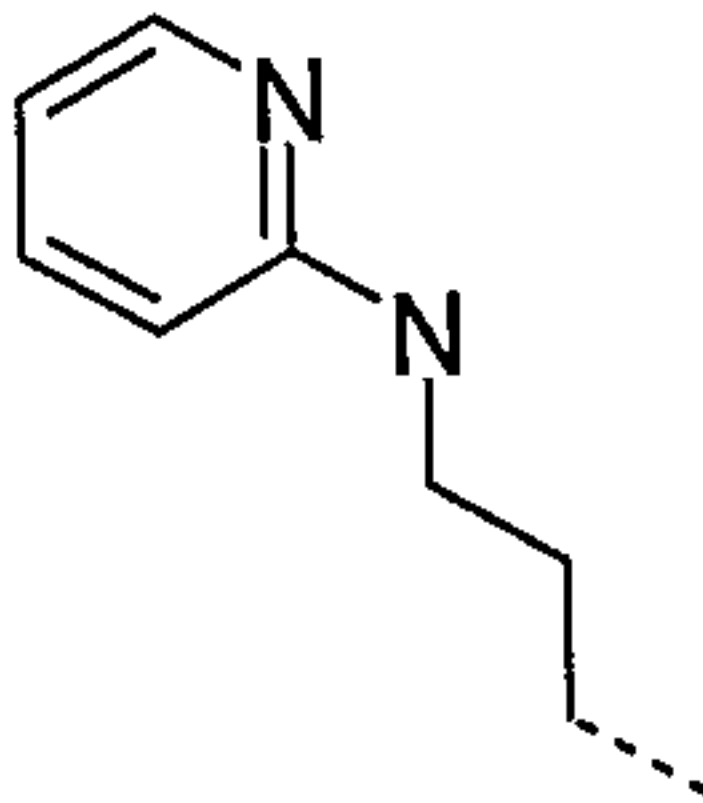
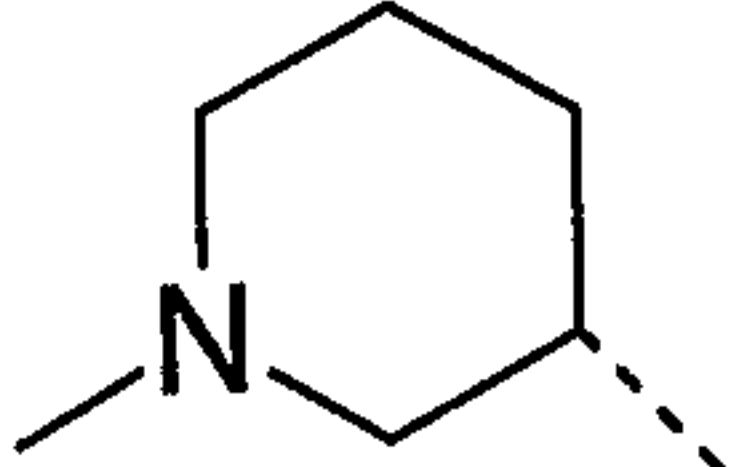
5

Example	$R^5_m-L_n-$	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
13		Aldrich	524	1.88
14		Aldrich	482	2.00
15		Aldrich	522	2.45

Example	$R^5_m-L_n-$	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
16		Aldrich	509	2.35
17		Aldrich	553	2.4
18		Aldrich	511	2.2
19		Aldrich	497	1.99
20		ABCR	552	1.74
21		ABCR	511	2.07

Example	R ⁵ _m -L _n -	Supplier Or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
22		Aldrich	521	1.97
23		Maybridge	524	1.73
24		Aldrich	497	1.7
25		ABCR	539	1.87
26		Aldrich	520	1.87
27		ABCR	506	1.79

Example	R ⁵ _m -L _n -	Supplier Or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
28		Aldrich	497	2.03
29		Chemstep	553	1.96
30		Frinton	539	2.33
31		Asinex	534	1.91
32		US3856783	551	2.07
33		Matrix	537	2.27

Example	R ⁵ _m -L _n -	Supplier Or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
34		Matrix	538	1.74
35		WO2005097750	545	2.2
36		US2005209274	527	2.02
37		Fluorochem	559	2.29
38		US2003069236	546	2.18
39		Fluorochem	509	2.03

The following examples were prepared by an analogous process to that used in the preparation of Example 12 utilising the acid described in Example 111 and the appropriate

BOC- protected amines. Prior to SCX purification the reaction mixture was treated with 4N HCl in dioxane (1 mL) and stirred at room temperature for 24 hr. The reaction mixtures were absorbed onto SCX columns, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative HPLC to give the
5 title compounds

Example 40:

N-(4-aminobutyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

10

Example 41:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(4-piperidyl)benzamide

15

Example 42:

N-(3-aminopropyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

20

Example 43:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-methylaminoethyl)benzamide

25

Example 44:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(3-methylaminopropyl)benzamide

30

Example 45:

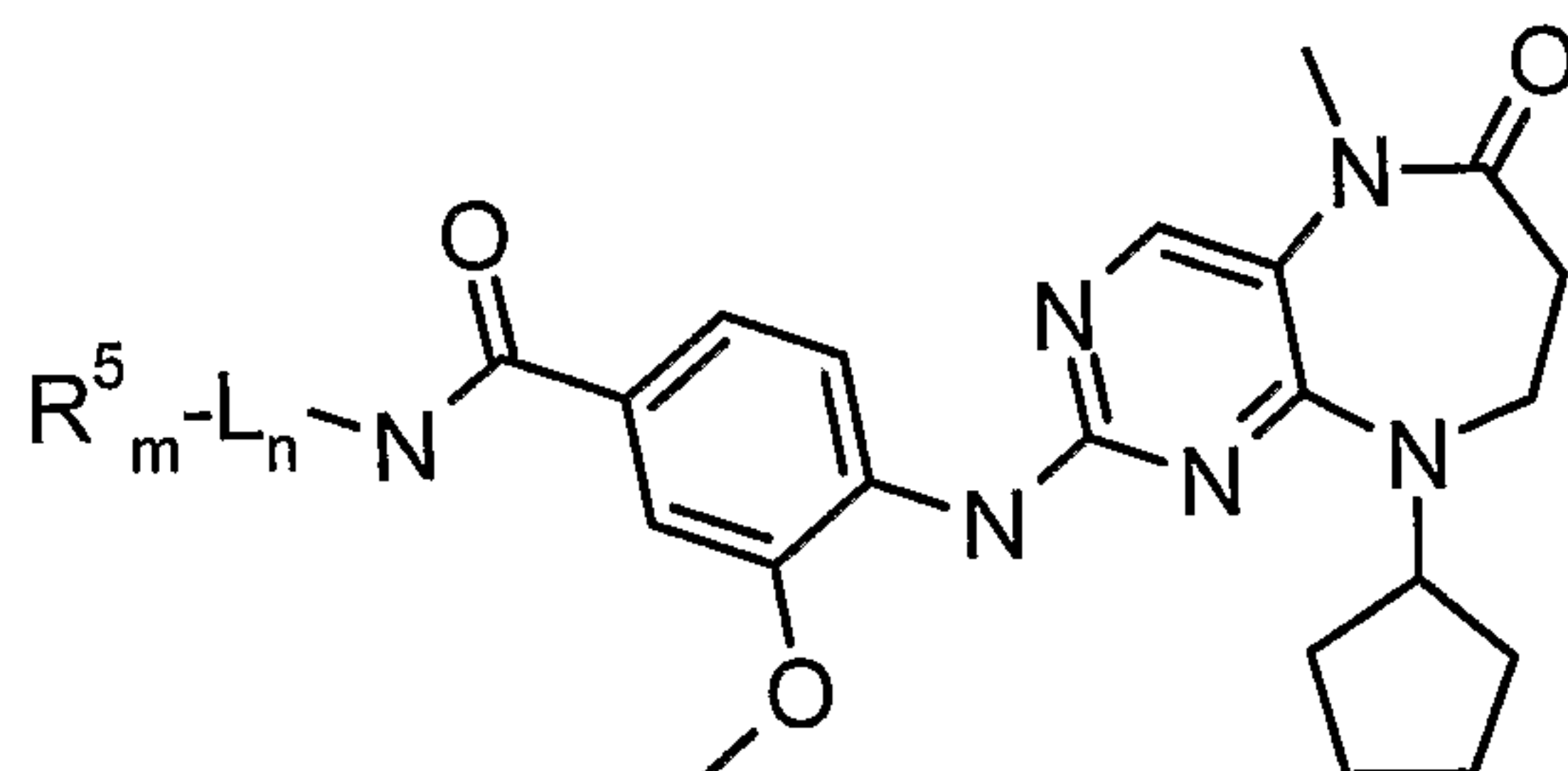
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-pyrrolidin-3-yl-benzamide

5 **Example 46:**

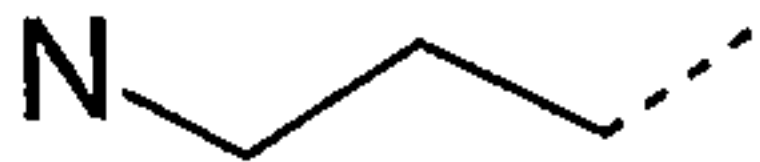
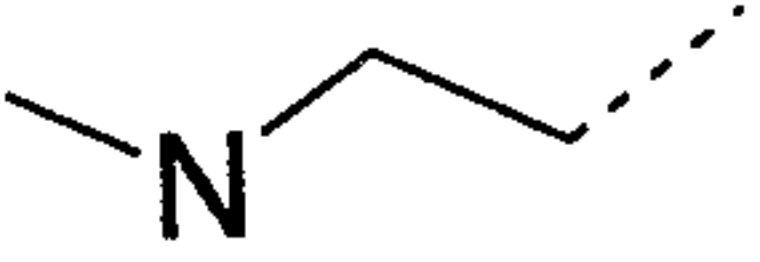
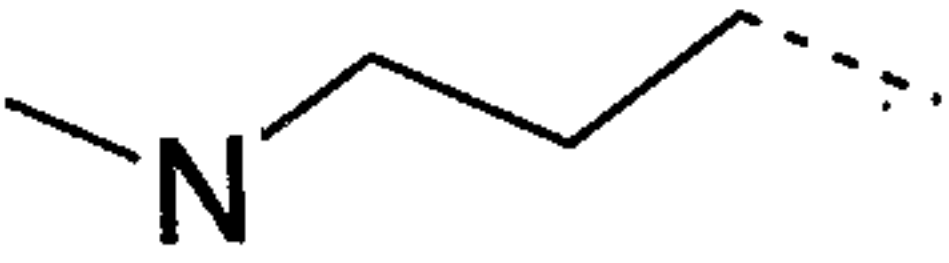
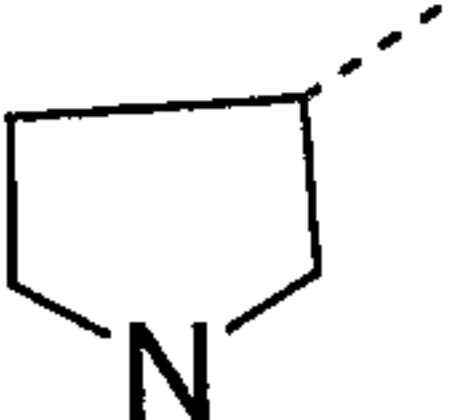
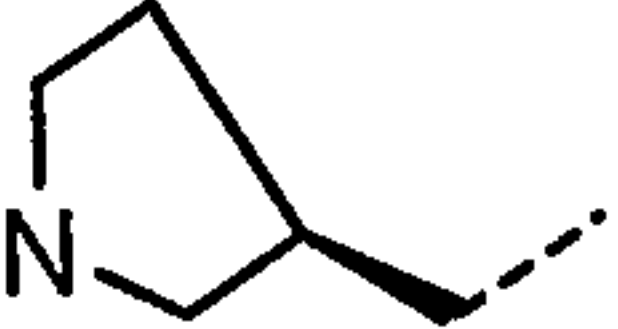
N-(3-amino-2,2-dimethyl-propyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

10 **Example 47:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-ylmethyl]benzamide



Example	R ⁵ _m -L _n -	Supplier or Source of BOC- Protected Amine	MS m/z [M+H] ⁺	Retention time (Minutes)
40		Fluka	482	2.02
41		Aldrich	494	2.02

Example	R ⁵ _m -L _n -	Supplier or Source of BOC- Protected Amine	MS m/z [M+H] ⁺	Retention time (Minutes)
42		Aldrich	468	1.97
43		ABCR	468	1.9
44		ABCR	482	2.26
45		ABCR	480	2.02
46		ABCR	496	2.16
47		ABCR	494	2.47

Example 48:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 211 mg, 0.75 mmol) and 4-amino-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide (Intermediate 27, 211 mg, 0.75 mmol) were combined with p-TSA (357 mg, 1.88 mmol) in 4-methyl-2-pentanol (1 mL) and heated to 150 °C for 18 hr. The cooled reaction mixture was diluted with methanol and water (approx 50 mL) and loaded onto a 50 g SCX-2 cartridge washing with methanol (100 mL) and eluting with 7 N methanolic ammonia (100 mL). The concentrated solution was purified by reversed phase HPLC. The title compound was obtained as a beige solid (178 mg, 45%).

¹H NMR (399.902 MHz, DMSO-d₆) δ 1.50 - 1.81 (m, 10H), 1.90 - 2.00 (m, 4H), 2.16 (s, 3H), 2.58 - 2.61 (m, 2H), 2.72 (br d, 2H), 3.17 (s, 3H), 3.63 - 3.65 (m, 2H), 3.68 - 3.75 (m, 1H), 3.92 (s, 3H), 4.83 (quintet, 1H), 7.19 (d, 1H), 7.79 - 7.82 (m, 2H), 8.11 (s, 1H), 8.33 (d, 1H); MS m/z 526 [M+H]⁺.

Example 49:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-propan-2-yl-4-piperidyl)benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 100mg, 0.24 mmol), N-Isopropyl-4-aminopiperidine (ABCR, 42 mg, 0.29 mmol), HATU (111 mg, 0.29mmol) and DIPEA (127 uL, 0.73 mmol) and DMF (3 mL) were combined and stirred at room temperature for 3 hours. The solvent was evaporated and the residue partitioned between DCM (10 mL) and water (10 mL). The organic phase was added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH and solvents evaporated. The residue was taken up in DCM and purified on silica, eluting with a gradient of 0 – 5% MeOH / DCM followed by 5% then 10% and finally 15% MeOH / DCM. Fractions containing product were combined and evaporated to give the tile compound as a white solid (45 mg, 35%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.99 (d, 6H), 1.55 - 1.73 (m, 8H), 2.00 (m, 4H), 2.27 (m, 2H), 2.60 (m, 2H), 2.69 (m, 1H), 2.81 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.92 (m, 4H), 4.83

(m, 1H), 5.82 (d, 1H), 7.14 (m, 1H), 7.35 (d, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 50:

5 **tert-butyl 4-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]piperidine-1-carboxylate**
4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 113 mg, 0.27 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (ABCR, 50mg, 0.25 mmol), HATU (114 mg, 0.3 mmol) and
10 DIPEA (130 μ L, 0.75 mmol) and DMF (3 mL) were combined and stirred at room temperature for 3 hours. Solvent was evaporated and the residue partitioned between DCM (25 mL) and sat. aq. Bicarb. (25 mL) and gravity filtered through a PTFE cup. The organic phase was added to a silica column and eluted with a shallow gradient of 0 – 10% MeOH / DCM. Fractions containing product were combined and evaporated to a yellow gum to which
15 ether was added and re-evaporated to give the title compound as an orange solid. (89mg, 55%).

¹H NMR (400.132 MHz, CDCl₃) δ 1.37 (m, 11H), 1.53 - 1.71 (m, 6H), 1.97 (m, 4H), 2.60 (m, 2H), 2.86 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.05 (m, 3H), 4.83 (m, 1H), 5.83 (d, 1H), 7.15 (m, 1H), 7.35 (m, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 594
20 $[M+H]^+$.

Example 51:

Benzyl (1S,5R)-6-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]-3-
25 **azabicyclo[3.1.0]hexane-3-carboxylate**
4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 113 mg, 0.27 mmol), benzyl (1S,5R)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (Intermediate 30; 50 mg, 0.25 mmol), HATU (114 mg, 0.3 mmol) and DIPEA (130 μ L, 0.75 mmol) and DMF (3 mL) were
30 combined and stirred at room temperature for 3 hours. Solvent was evaporated and the residue partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), gravity filtered through

a PTFE cup and solvents evaporated. The residue was taken up in DCM and purified on silica eluting with a gradient of 0 – 5% MeOH / DCM. Fractions containing product were combined and evaporated. The resultant material was purified by reversed phase HPLC.

¹H NMR (400.132 MHz, CDCl₃) δ1.64 (m, 8H), 1.97 (m, 2H), 2.58 (m, 3H), 3.22 (s, 3H),
 5 3.46 (m, 2H), 3.62 (m, 2H), 3.78 (m, 2H), 3.90 (s, 3H), 4.82 (m, 1H), 5.05 (s, 2H), 6.08 (s, 1H), 7.12 (m, 1H), 7.26 (m, 5H), 7.34 (d, 1H), 7.61 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 626 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the
 10 preparation of Example 51 utilising the acid described in Example 111 and the appropriate amines.

Example 52:

15 **tert-butyl (3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxybenzoyl]amino]pyrrolidine-1-carboxylate**

Amine available from Chempacific

20 ¹H NMR (400.132 MHz, CDCl₃) δ1.41 (s, 9H), 1.63 (m, 3H), 1.94 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 3.26 (m, 4H), 3.43 (m, 2H), 3.65 (m, 3H), 3.91 (s, 3H), 4.59 (m, 1H), 4.84 (m, 1H), 6.01 (d, 1H), 7.15 (m, 5H), 7.35 (d, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 8.45 (d, 1H); MS m/z 580 [M+H]⁺.

25 **Example 53:**

tert-butyl (3S)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxybenzoyl]amino]pyrrolidine-1-carboxylate

Amine available from Chempacific

30 ¹H NMR (400.132 MHz, CDCl₃) δ1.41 (s, 9H), 1.64 (m, 6H), 1.93 (m, 3H), 2.19 (m, 1H), 2.60 (m, 2H), 3.26 (m, 4H), 3.43 (m, 2H), 3.65 (m, 3H), 3.91 (s, 3H), 4.59 (m, 1H), 4.84 (m,

1H), 6.02 (d, 1H), 7.15 (m, 1H), 7.35 (d, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 8.45 (d, 1H); MS m/z 580 [M+H]⁺.

Example 54:

5 **Benzyl 4-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]piperidine-1-carboxylate**
4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 350 mg, 0.85 mmol), Benzyl 4-aminopiperidine-1-carboxylate (ABCR, 219 mg, 0.94 mmol), HATU (388 mg, 1.02 mmol)
10 and DIPEA (445 μ L, 2.55 mmol) and DMF (5 mL) were combined and stirred at room temperature for 3 hours. Solvent was evaporated and the residues partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), gravity filtered through a PTFE cup and solvents evaporated. The residue was taken up in DCM and purified on silica eluting with a gradient of 0 – 5% MeOH / DCM. Fractions containing product were combined and evaporated. To
15 give the title compound as an orange solid.

¹H NMR (400.132 MHz, CDCl₃) δ 1.38 (m, 2H), 1.62 (m, 6H), 1.97 (m, 4H), 2.60 (m, 2H), 2.94 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.11 (m, 3H), 4.83 (m, 1H), 5.07 (s, 2H), 5.82 (d, 1H), 7.14 (m, 1H), 7.27 (m, 5H), 7.34 (d, 1H), 7.61 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 628 [M+H]⁺.

Example 55:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-yl]benzamide
tert-butyl (3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-
25 8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]pyrrolidine-1-carboxylate (630 mg, 1 mmol) was dissolved in DCN (10 mL), TFA (10 mL) added and stirred at room temperature for 2 hr. The reaction mixture was added to a 10 g SCX-2 column pre wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) then the crude product eluted with 2M ammonia in MeOH and solvents evaporated. The residue was taken up in DCM and
30 purified on silica eluting with a gradient of 0 – 10% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated

to a gum, ether was added and re-evaporated to give the title compound as a solid. (300 mg, 74%)

¹H NMR (400.132 MHz, CDCl₃) δ1.62 (m, 8H), 1.98 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 2.89 (m, 2H), 3.06 (m, 1H), 3.17 (m, 1H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.53 (m, 1H), 4.83 (m, 1H), 6.24 (d, 1H), 7.19 (m, 1H), 7.37 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 480 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 56 utilising the BOC-protected material described in Example 54.

Example 56:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3S)-pyrrolidin-3-yl]benzamide

¹H NMR (400.132 MHz, CDCl₃) δ1.62 (m, 8H), 1.98 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 2.85 (m, 1H), 2.91 (m, 1H), 3.06 (m, 1H), 3.17 (m, 1H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.53 (m, 1H), 4.83 (m, 1H), 6.24 (d, 1H), 7.19 (m, 1H), 7.37 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 480 [M+H]⁺.

Example 57:

N-[(1S,5R)-3-azabicyclo[3.1.0]hex-6-yl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Benzyl (1S,5R)-6-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate (Example 51, 357mg, 0.57 mmol) was dissolved in MeOH (30 mL) and passed through the H-cube at 50 °C on full hydrogen mode at 1 mL per minute. The solution added to a 10 g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH. The basic fractions were evaporated and the residue dissolved in DCM and purified on silica eluting with a gradient of 0 – 10% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to a gum to which ether was added and re-evaporated to give the title compound as a cream solid. (172 mg, 42%).

¹H NMR (400.132 MHz, CDCl₃) δ1.64 (m, 8H), 1.97 (m, 2H), 2.60 (m, 3H), 2.91 (m, 2H), 3.17 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.82 (m, 1H), 6.02 (s, 1H), 7.13 (m, 1H), 7.35 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 492 [M+H]⁺.

5

Example 58:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-diethylaminocyclohexyl)-3-methoxy-benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 100 mg, 0.24 mmol), N,N-diethylcyclohexane-1,4-diamine (ABChem, 46 mg, 0.28 mmol), HATU (111 mg, 0.29 mmol) and DIPEA (127 μL, 0.73 mmol) and DMF (3 mL) were combined and stirred at room temperature for overnight. Solvent was evaporated and the residues partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), gravity filtered through a PTFE cup, solvent evaporated and the residue purified by reverse phase HPLC to give the title compound as a cream solid (114 mg, 83%)

MS m/z 564 [M+H]⁺. Retention Time 2.20 minutes

The following examples were prepared by an analogous process to that used in the preparation of Example 58 utilising the appropriate amines

Example 59:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

25 Amine available from Chontech

¹H NMR (399.902 MHz, CDCl₃) δ1.03 (m, 2H), 1.30 (m, 2H), 1.54 (m, 2H), 1.60 - 1.80 (m, 6H), 1.98 (m, 2H), 2.05 (m, 2H), 2.53 (m, 5H), 2.67 (m, 2H), 3.09 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 4.90 (m, 1H), 5.78 (d, 1H), 7.23 (m, 1H), 7.44 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.49 (d, 1H); MS m/z 548 [M+H]⁺.

30

Example 60:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide

Amine available from ABCChem

MS m/z 536 [M+H]⁺. Retention Time 1.92 minutes

5

Example 61:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

10 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(4-piperidyl)benzamide (Example 41; 80 mg, 0.16 mmol), Ethyl Bromide (ABCR, 13 uL, 0.18 mmol), Triethylamine (0.45 uL, 0.32 mmol) and DMF (3 mL) were combined and heated by microwave irradiation at 75 °C for 1 hr and then at 80 °C for 30 minutes. The reaction mixture was purified by reverse phase HPLC to give the title
15 compound as a white solid (56 mg, 66%)

¹H NMR (399.902 MHz, CDCl₃) δ 1.10 (t, 3H), 1.53 - 1.80 (m, 8H), 2.09 (m, 6H), 2.44 (m, 2H), 2.67 (m, 2H), 2.92 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 4.00 (m, 4H), 4.90 (m, 1H), 5.90 (d, 1H), 7.22 (m, 1H), 7.42 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 522 [M+H]⁺.

20

Example 62:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

To 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-yl]benzamide (Example 55, 140 mg, 0.29 mmol)
25 dissolved in THF (2 mL) was added acetic acid (17 uL, 0.29 mmol) followed by aqueous formaldehyde (1 mL). The reaction mixture was stirred at room temperature for 30 mins and sodium triacetoxyborohydride (100 mg, 0.47 mmol) added and the reaction mixture stirred for a further 2 hrs. The solvent was evaporated and the residue neutralised with sat. aq.
30 sodium bicarbonate and extracted with DCM (2 x 5 mL), gravity filtered through a PTFE cup and solvent evaporated. The resultant material was purified by reverse phase HPLC to give the title compound as a white solid (97 mg, 67%)

¹H NMR (399.902 MHz, CDCl₃) δ1.60 - 1.80 (m, 7H), 2.05 (m, 2H), 2.22 (m, 1H), 2.38 (s, 3H), 2.44 (m, 1H), 2.55 (m, 1H), 2.67 (m, 2H), 2.77 (m, 1H), 2.96 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.69 (m, 1H), 4.91 (m, 1H), 6.45 (d, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 494 [M+H]⁺.

5 The following example was prepared by an analogous process to that used in the preparation of Example 62 utilising the pyrrolidine analogue from Example 56

Example 63:

10 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3S)-1-methylpyrrolidin-3-yl]benzamide**

¹H NMR (399.902 MHz, CDCl₃) δ1.60 - 1.80 (m, 7H), 2.05 (m, 2H), 2.22 (m, 1H), 2.38 (s, 3H), 2.44 (m, 1H), 2.55 (m, 1H), 2.67 (m, 2H), 2.77 (m, 1H), 2.96 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.68 (m, 1H), 4.91 (m, 1H), 6.45 (d, 1H), 7.27 (m, 1H), 7.43 (m, 1H),
15 7.67 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 494 [M+H]⁺.

Example 64:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1S,5R)-3-methyl-3-azabicyclo[3.1.0]hex-6-yl]benzamide

20 To N-[(1S,5R)-3-azabicyclo[3.1.0]hex-6-yl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide (Example 57, 114 mg, 0.23 mmol) dissolved in THF (2 mL) was added acetic acid (13 uL, 0.23 mmol) (material came out of solution), followed by aqueous formaldehyde (0.5 mL, material all dissolved again). The reaction mixture was stirred at room temperature for 30 mins and
25 sodium triacetoxyborohydride (100 mg, 0.47 mmol) added and the reaction mixture stirred for a further 2 hrs. The solvent was evaporated and the residue neutralised with sat. aq. sodium bicarbonate and extracted with DCM (15 mL), filtered through a PTFE cup and evaporated. The resultant material was purified by reverse phase HPLC.

¹H NMR (399.902 MHz, CDCl₃) δ1.56 - 1.80 (m, 8H), 2.04 (m, 2H), 2.30 (s, 3H), 2.39 (m, 2H), 2.66 (m, 2H), 3.12 (m, 1H), 3.17 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 3.96 (s, 3H), 4.89
30

(m, 1H), 6.06 (s, 1H), 7.18 (m, 1H), 7.43 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.48 (d, 1H); MS m/z 506 [M+H]⁺.

Example 65:

5 **Methyl (1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylate**

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 1.1 g, 2.7 mmol), methyl (1S,3R)-3-aminocyclopentane-1-carboxylate (Intermediate 31; 528 mg, 2.94 mmol), HATU (1.22 g, 3.22 mmol) and DIPEA (1.86 mL, 10.68 mmol) and DMF (10 mL) were combined and stirred at room temperature overnight. Solvent was evaporated and the residue partitioned between saturated sodium carbonate and DCM then gravity filtered through a PTFE cup. The organic phase was passed through a silica pad eluting with EtOAc. Fractions containing
15 product were combined and evaporated to give a brown gum which was dissolved in MeOH and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and product eluted with 2M ammonia in MeOH. Solvent was evaporated to a yellow gum, ether was added then re-evaporated to give the title compound as a yellow foam (1.21 g, 84%)

20 ¹H NMR (399.902 MHz, CDCl₃) δ 1.62 (m, 2H), 1.75 (m, 4H), 1.95 (m, 4H), 2.02 - 2.22 (m, 4H), 2.67 (m, 2H), 3.02 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.72 (s, 3H), 3.99 (s, 3H), 4.60 (m, 1H), 4.91 (m, 1H), 7.25 (m, 1H), 7.38 (m, 1H), 7.49 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.53 (d, 1H); MS m/z 537 [M+H]⁺.

25 **Example 66:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-(dipropan-2-ylamino)ethyl]-3-methoxy-benzamide

A solution of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 100 mg, 0.24 mmol), DIPEA (0.127 mL, 0.73 mmol) and HATU (120 mg, 0.32 mmol) in DMF (2 mL) was stirred at
30 ambient temperature for 10 mins. The pale brown solution was add to N,N-dipropan-2-

ylethane-1,2-diamine (ABCR, 43 mg, 0.3 mmol) and the resulting solution stirred at ambient temperature for 18 hours. The reaction solution was purified by reverse phase HPLC to give the title compound as a white solid (43 mg, 33%); MS m/z 538 [M+H]⁺. Retention Time 2.49 mins.

5

The following examples were prepared by an analogous process to that used in the preparation of Example 66, utilising the appropriate amines. NMR data was obtained on a selection of compounds as indicated.

10 **Example 67:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-pyridin-4-yl-benzamide

Example 68:15 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(3-pyrrolidin-1-ylpropyl)benzamide****Example 69:**20 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[3-(1-piperidyl)propyl]benzamide****Example 70:**25 **N-[3-(azepan-1-yl)propyl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide****Example 71:****4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1S,5R)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]benzamide**

30

Example 72:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1,2,2,6,6-pentamethyl-4-piperidyl)benzamide

5 **Example 73:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[1-(1-piperidyl)propan-2-yl]benzamide

Example 74:

10 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-pyridin-3-yl-benzamide

Example 75:

15 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-methyl-2-(1-piperidyl)propyl]benzamide

Example 76:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(pyridin-3-ylmethyl)benzamide

20

Example 77:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(4-methoxyphenyl)benzamide

25 **Example 78:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-diethylaminopropyl)-3-methoxy-benzamide

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.95 (t, 6H), 1.66 (m, 8H), 1.94 (m, 2H), 2.45 (m, 6H), 2.59 (m, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.94 (s, 3H), 4.81 (m, 1H), 7.45 (d, 2H), 7.48 (s, 1H), 7.73 (s, 1H), 8.08 (s, 1H), 8.38 (s, 1H), 8.38 (d, 2H)

30

Example 79:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(1-methylpyrrolidin-2-yl)ethyl]benzamide

5

Example 80:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(pyridin-4-ylmethyl)benzamide

10 **Example 81:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-methyl-1-pyrrolidin-1-yl-propan-2-yl)benzamide

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.37 (s, 6H), 1.67 (m, 10H), 1.94 (m, 2H), 2.60 (m, 6H), 2.78 (s, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.94 (s, 3H), 4.80 (m, 1H), 7.37 (d, 1H), 7.42 (s, 15 1H), 7.48 (s, 1H), 7.72 (s, 1H), 8.08 (s, 1H), 8.36 (d, 1H)

Example 82:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[[[(2S)-1-(cyclopropylmethyl)pyrrolidin-2-yl]methyl]-3-methoxy-benzamide

20 ¹H NMR (400.132 MHz, DMSO-d₆) δ 0.01 (m, 2H), 0.34 (m, 2H), 0.80 (m, 1H), 1.59 (m, 10H), 1.84 (m, 2H), 1.96 (m, 1H), 2.12 (m, 1H), 2.50 (m, 3H), 2.64 (m, 1H), 3.01 (m, 2H), 3.08 (s, 3H), 3.32 (m, 1H), 3.53 (m, 2H), 3.84 (s, 3H), 4.71 (m, 1H), 7.36 (d, 1H), 7.39 (s, 1H), 7.63 (s, 1H), 7.98 (s, 1H), 8.12 (t, 1H), 8.28 (d, 1H)

25 **Example 83:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.29 (s, 2H), 0.51 (s, 2H), 1.66 (m, 10H), 1.94 (m, 2H), 2.43 (s, 2H), 2.51 (m, 4H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (d, 2H), 3.63 (m, 2H), 3.95 30 (s, 3H), 4.82 (m, 1H), 7.38 (d, 1H), 7.47 (s, 1H), 7.74 (s, 1H), 8.09 (s, 1H), 8.38 (d, 1H), 8.49 (t, 1H).

Example 84:

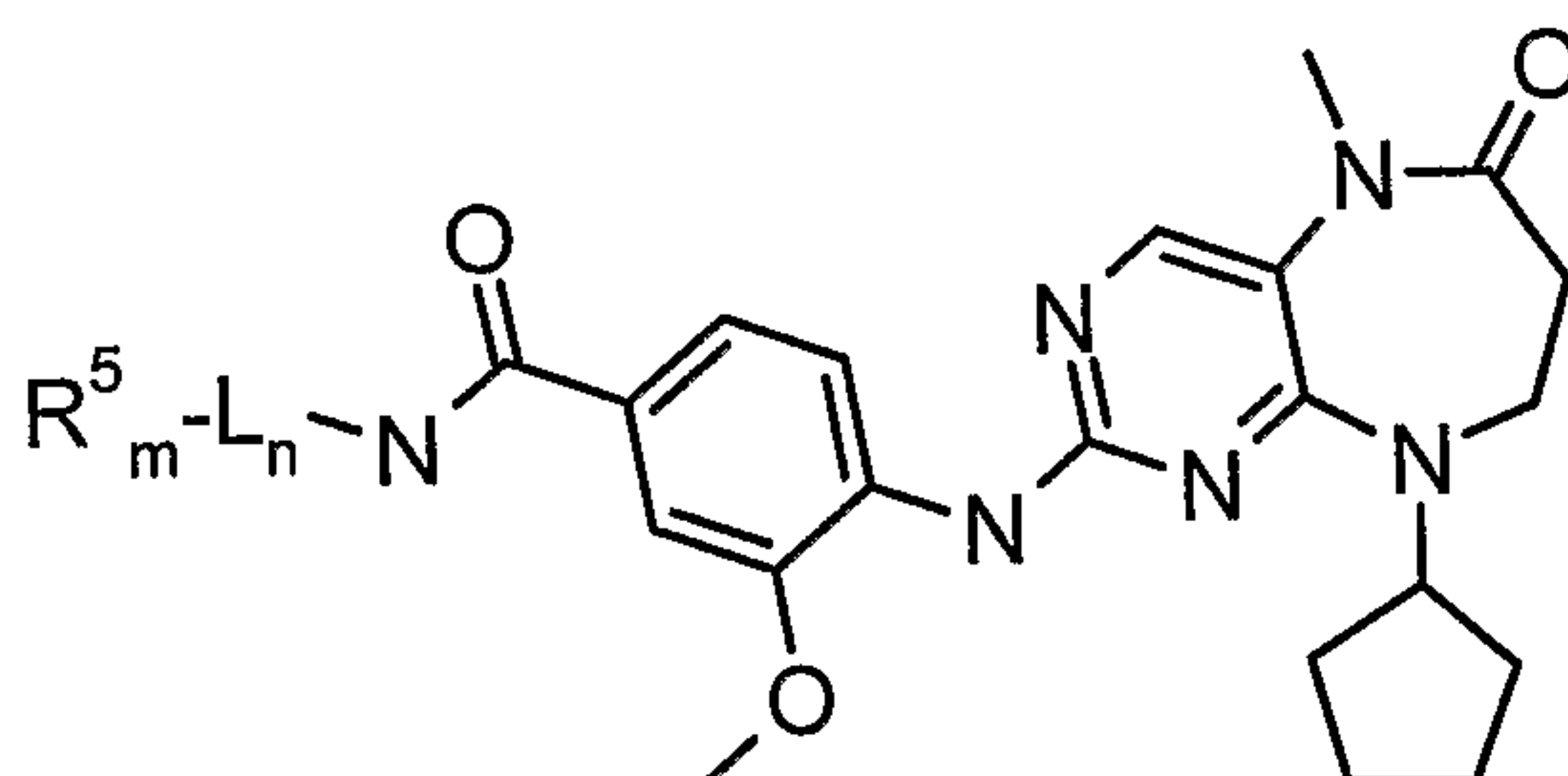
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1-methyl-3-piperidyl)methyl]benzamide

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.92 (m, 1H), 1.44 (m, 1H), 1.73 (m, 10H), 1.94 (m, 2H), 2.13 (s, 3H), 2.64 (m, 5H), 3.15 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.49 (m, 2H), 7.73 (s, 1H), 8.08 (s, 1H), 8.32 (t, 1H), 8.38 (d, 1H)

Example 85:

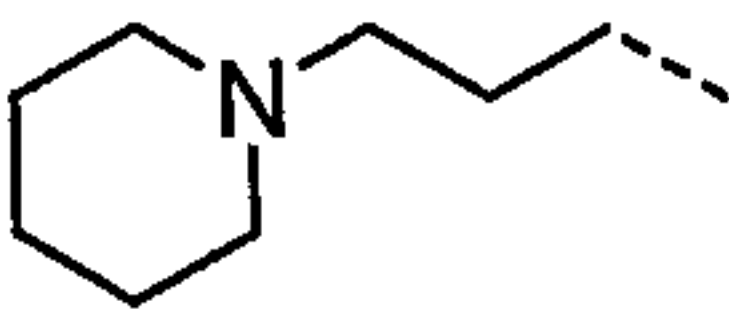
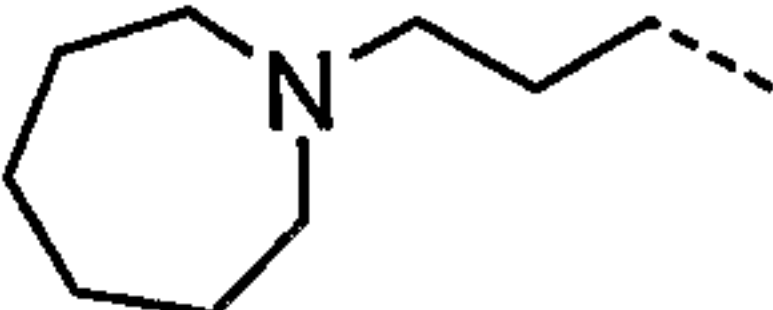
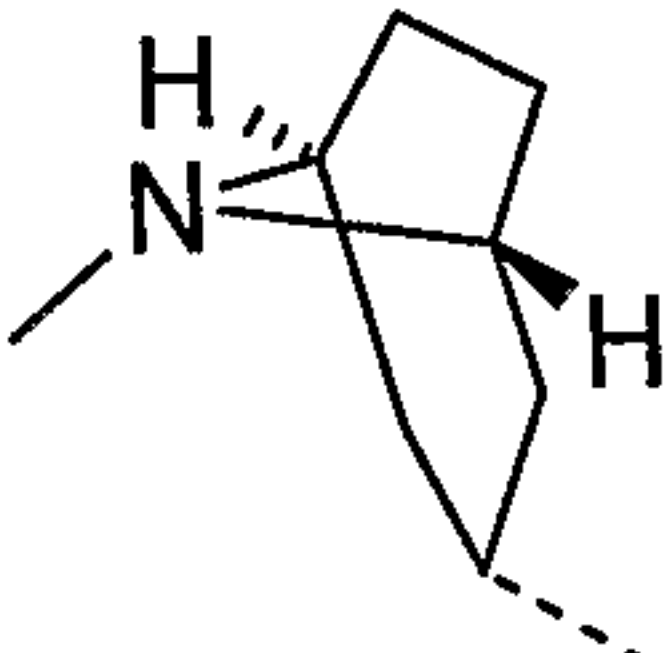
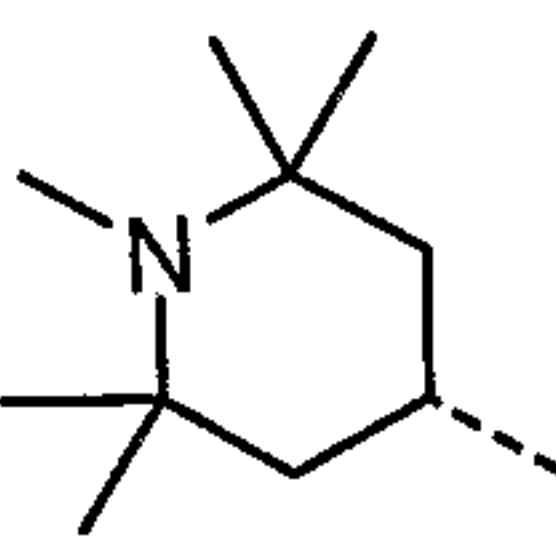
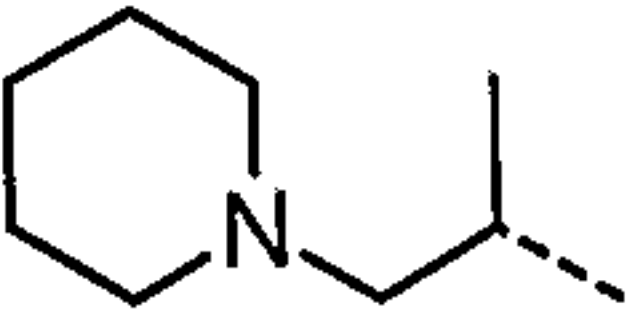
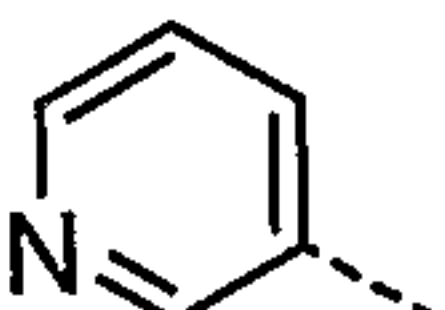
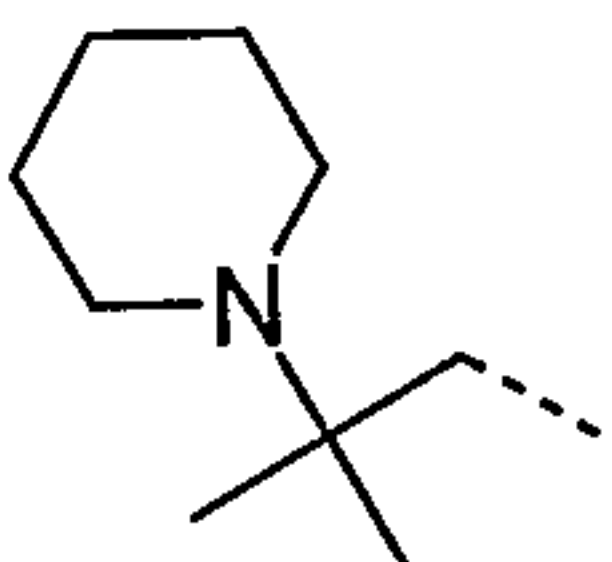
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(1-methyl-2-piperidyl)ethyl]benzamide

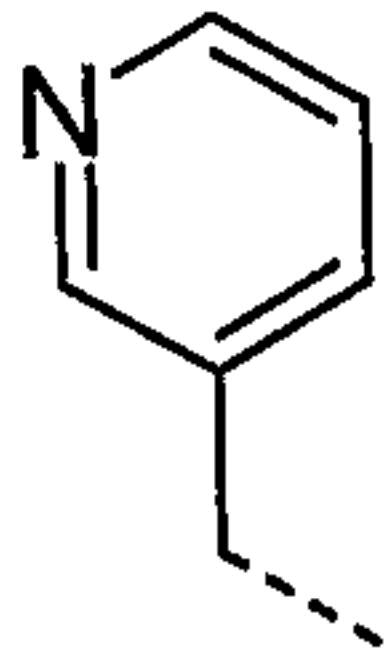
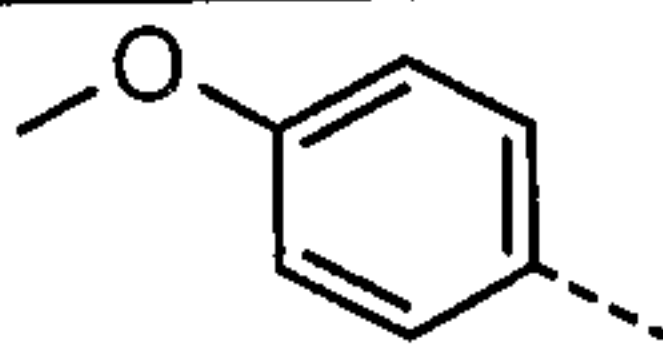
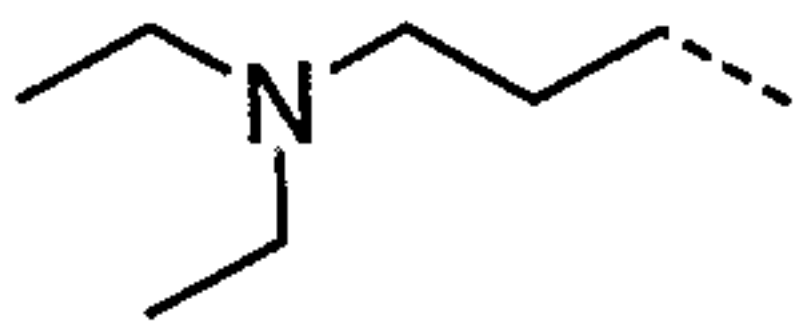
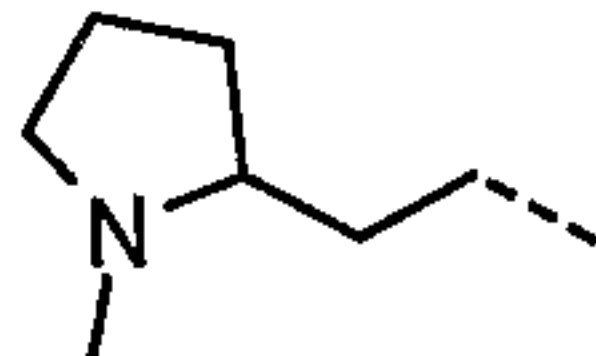
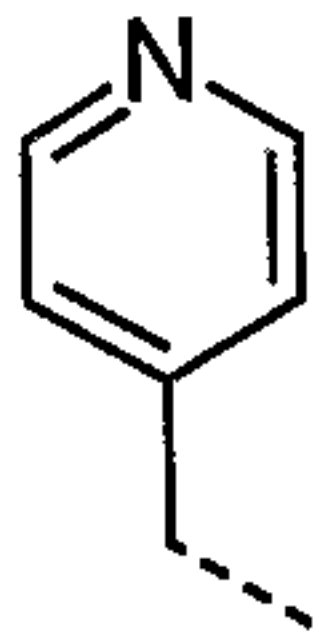
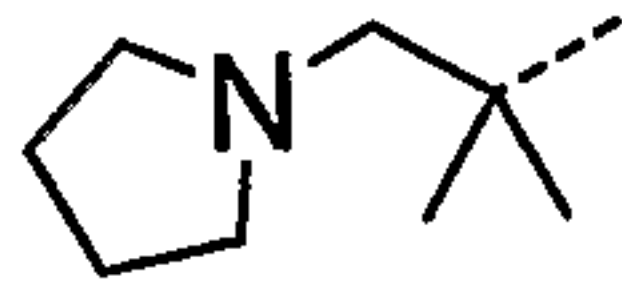
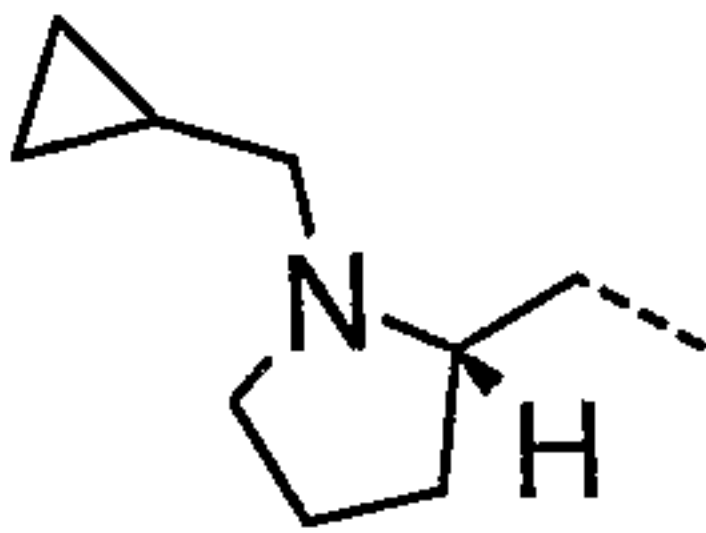
¹H NMR (400.132 MHz, DMSO-d₆) δ 1.45 (m, 14H), 1.95 (m, 4H), 2.21 (s, 3H), 2.59 (m, 2H), 2.76 (m, 1H), 3.17 (s, 3H), 3.31 (m, 2H), 3.63 (m, 2H), 3.94 (s, 3H), 4.81 (m, 1H), 7.46 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.35 (t, 1H), 8.38 (d, 1H)

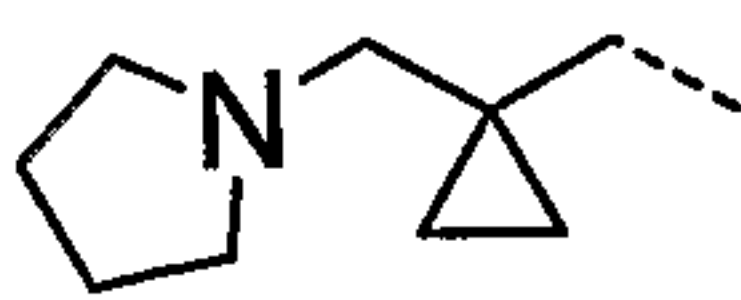
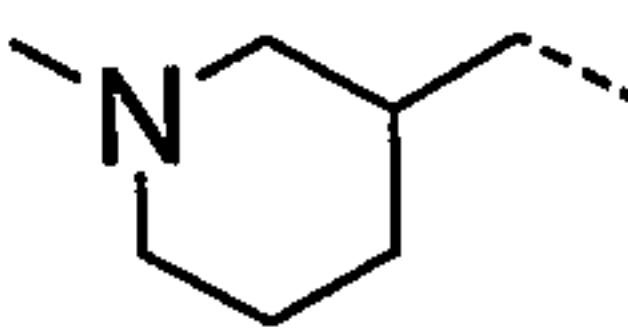
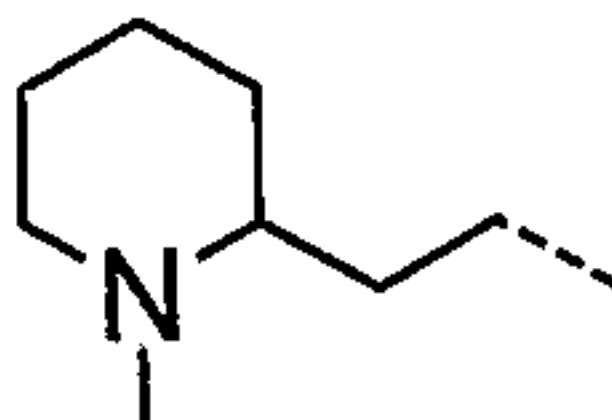


15

Example	R ⁵ _m -L _n -	Supplier or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
67		Aldrich	488	1.97
68		ABCR	522	2.01

Example	R ⁵ _m -L _n -	Supplier or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
69		ABCR	536	2.17
70		ABCR	550	2.33
71		Flurochem	534	1.85
72		ABCR	564	2.28
73		Journal of the Chemical Society (1947), p 1511-13.	536	2.31
74		Aldrich	488	1.96
75		Matrix	550	2.67

Example	R ⁵ _m -L _n -	Supplier or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
76		Aldrich	502	1.81
77		Aldrich	517	2.35
78		Aldrich	524	2.11
79		Aldrich	522	1.83
80		Aldrich	502	1.73
81		Flurochem	536	2.64
82		Intermediate 32	548	2.85

Example	R ⁵ _m -L _n -	Supplier or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
83		Intermediate 33	548	3.01
84		Chembridge	522	2.19
85		Chembridge	536	2.39

Example 86:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-tert-butyl-4-piperidyl)benzamide

A solution of N-[(1S,5R)-3-azabicyclo[3.1.0]hex-6-yl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

(Example 57, 250mg, 0.61mmol), 1-tert-butylpiperidin-4-amine (Activate, 96mg, 0.61mmol),

HATU (349mg, 0.92mmol) and DIPEA (321uL, 1.83mmol) in DMF (5 mL) was stirred at

room temperature overnight. The reaction mixture was loaded on to an SCX-3 column pre-

wet with methanol. The column was washed with methanol and then with 2% 7N

ammonia/methanol to elute the crude product. The product containing fractions were

evaporated and the resultant material purified by reverse phase HPLC to give the title

compound as a white solid (137mg, 40.8%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.04 (9H, s), 1.55 (2H, s), 1.62 - 1.63 (3H, m), 1.73 (3H, d), 1.80 (2H, d), 1.95 (2H, t), 2.10 (2H, t), 2.60 (2H, t), 3.01 (2H, d), 3.18 (3H, s), 3.62 -3.64

(2H, t), 3.72 (1H, m), 3.95 (3H, s), 4.79 - 4.84 (1H, m), 7.46 (1H, d), 7.50 (1H, d), 7.73 (1H, s), 8.02 (1H, d), 8.09 (1H, s), 8.39 (1H, d); MS m/z 549[M+H]⁺.

5

Example 87:

(1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylic acid

10 To a solution of Methyl (1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylate (Example 65, 1.21 g, 2.25 mmol) in 4:1 THF / water (20 mL) was added lithium hydroxide (472 mg, 11.25 mmol) and the reaction mixture stirred at room temperature overnight. The solvent was evaporated and the residue diluted
15 with water. 1M citric acid was added until precipitation ceased (pH 3 – 4) and the resultant suspension stirred for 20 minutes. The resulting cream precipitate was filtered off, washed with water followed by isohexane and dried under vacuum to yield the title compound (1.08 g, 92%)

¹H NMR (399.902 MHz, DMSO-d₆) δ 1.62 - 1.95 (m, 12H), 2.07 (m, 1H), 2.59 (m, 3H), 2.72 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.28 (m, 1H), 4.81 (m, 1H), 7.51 (m, 2H),
20 7.74 (s, 1H), 8.09 (s, 1H), 8.38 (d, 1H), 8.85 (s, 1H); MS m/z 523 [M+H]⁺.

Example 88:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[(1R,3S)-3-(dimethylcarbamoyl)cyclopentyl]-3-methoxy-benzamide

25 A solution of (1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylic acid (Example 87, 100 mg, 0.19 mmol), HATU (80 mg, 0.21 mmol) and DIPEA (100 uL, 0.73 mmol) in DMF (3 mL) was stirred at room
30 temperature for 10 minutes. Dimethylamine solution in THF (1 mL) was added and the reaction mixture stirred at room temperature overnight. Solvent was evaporated and the

resultant material purified by reverse phase HPLC to yield the title compound as a yellow solid (80 mg, 86%)

¹H NMR (400.132 MHz, CDCl₃) δ 1.62 (m, 2H), 1.75 (m, 4H), 1.84 (m, 2H), 2.06 (m, 6H), 2.67 (m, 2H), 2.99 (s, 3H), 3.11 (s, 3H), 3.31 (m, 4H), 3.69 (m, 2H), 3.99 (s, 3H), 4.58 (m, 1H), 4.91 (m, 1H), 7.53 (m, 2H), 7.67 (s, 1H), 7.93 (s, 1H), 8.44 (d, 1H), 8.51 (d, 1H); MS m/z 550 [M+H]⁺.

Example 89:

N-cyclohexyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino] benzamide

A solution of 4-amino-N-cyclohexyl-benzamide (TimTec, 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140mg, 0.5mmol) and p-toluenesulphonic acid monohydrate (238mg, 1.25mmol) in 4-methyl-2-pentanol (3ml) was heated at 140°C for 3h. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto an SCX-3 column and washed with methanol. The product was eluted with ammonia/methanol and the product containing fractions were concentrated. Purification by preparative, reverse phase chromatography (Note 1) gave the title compound as a white solid (35mg, 15%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 – 1.19 (1H, m), 1.26 - 1.37 (4H, m), 1.60 – 1.85 (11H, m), 1.97 - 2.01 (2H, m), 2.59 (2H, m), 3.18 (3H, s), 3.62 - 3.65 (2H, m), 3.72 – 1.76 (1H, m), 4.85 (1H, m), 7.75 - 7.81 (4H, m), 7.93 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 463 [M+H]⁺.

Example 90:

N-cyclohexyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

A solution of HATU (147 mg, 0.385 mmol) in DMA (1 mL) was added to a mixture of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 144mg, 0.35 mmol), DIPEA (183 uL, 0.385 mmol) and Cyclohexylamine (Aldrich, 44 mg, 0.44 mmol) in DMA (1 mL). The resulting mixture

was stirred at room temperature overnight. The mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated *in vacuo*. The resultant material was purified by preparative reverse phase HPLC to yield the title compound as a white solid (7 mg, 4%).

5 m/z 493 [M+H]⁺. Retention Time 2.57 minutes

Example 91:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-methyl-benzamide

10 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 100mg, 0.24 mmol), 2M Methylamine in THF (365 uL, 0.73 mmol), HATU (111 mg, 0.29mmol) and DIPEA (127 uL, 0.73 mmol) and DMF (3 mL) were combined and stirred at ambient temperature overnight. Solvent was evaporated and the residue partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), and
15 gravity filtered through a PTFE cup. The organic phase was added to a silica column, eluting with a gradient of 0 – 10% MeOH / DCM and solvent evaporated from product containing fractions. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid. (45 mg, 44 %)

¹H NMR (400.132 MHz, CDCl₃) δ1.62 (m, 6H), 1.98 (m, 2H), 2.60 (m, 2H), 2.95 (d, 3H),
20 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.83 (m, 1H), 6.00 (d, 1H), 7.17 (m, 1H), 7.37 (d, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 454 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 91 utilising Ammonium Chloride and 3 additional equivalents of DIPEA and
25 collecting the product as a solid precipitated from the work-up procedure with DCM and saturated aqueous Sodium Bicarbonate solution.

Example 92:

30 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide**

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.73 (m, 6H), 2.00 (m, 2H), 2.64 (m, 2H), 3.23 (s, 3H), 3.68 (m, 2H), 3.99 (s, 3H), 4.86 (m, 1H), 7.22 (s, 1H), 7.57 (m, 2H), 7.78 (s, 1H), 7.92 (s, 1H), 8.13 (s, 1H), 8.44 (d, 1H); MS m/z 411 [M+H]⁺.

5 The following examples were prepared by an analogous process to that used in the preparation of **Example 66**, utilising the appropriate amines. NMR data was obtained on compounds when indicated.

Example 93:

10 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-propyl-benzamide**

Example 94:

15 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(cyclopropylmethyl)-3-methoxy-benzamide**

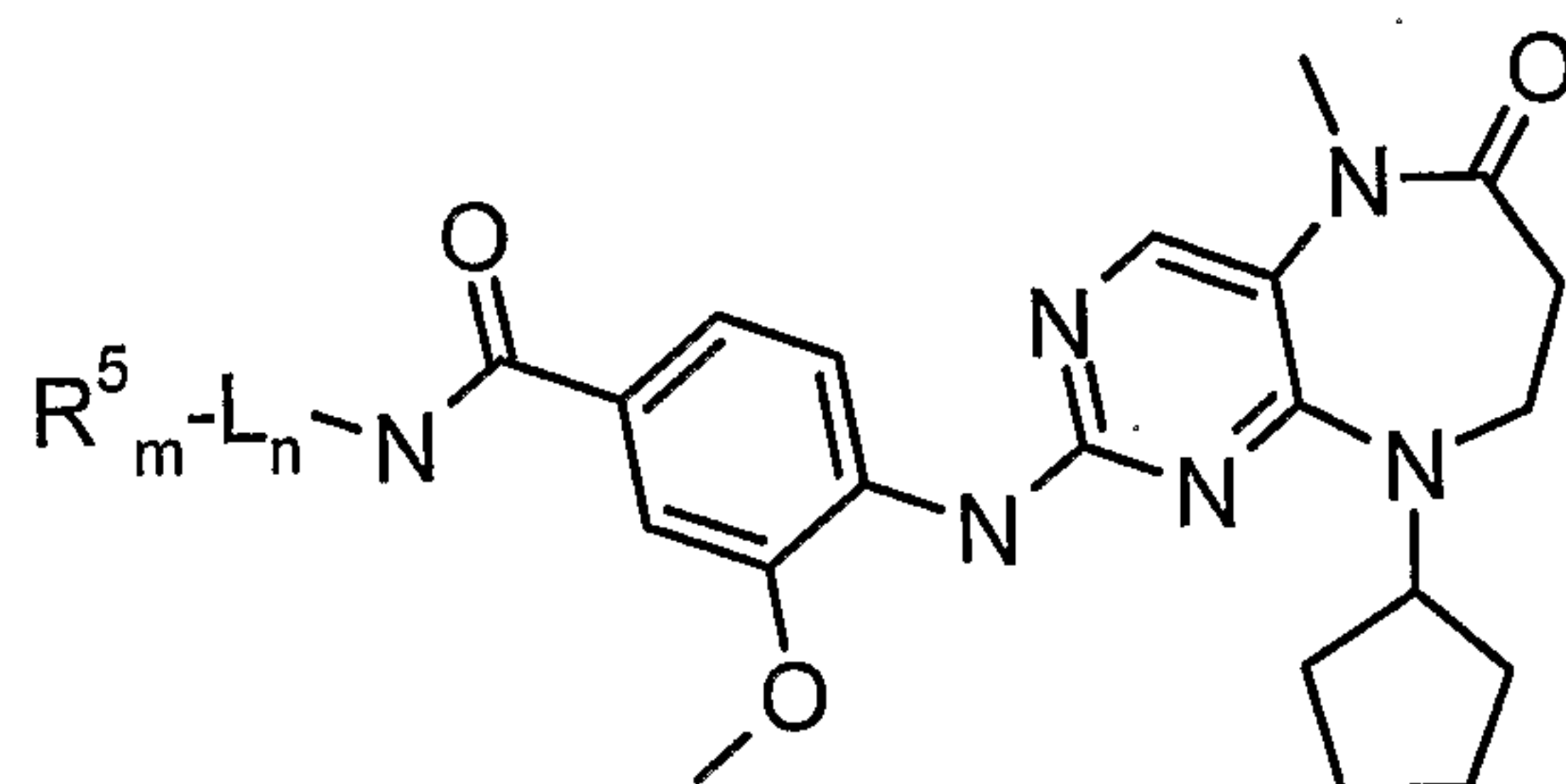
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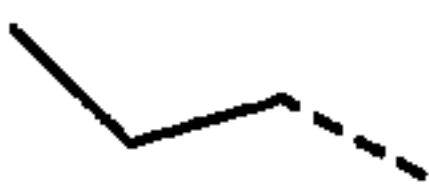
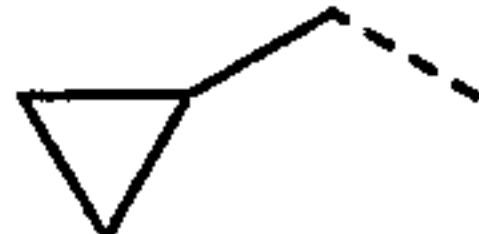
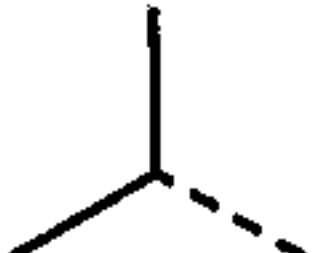
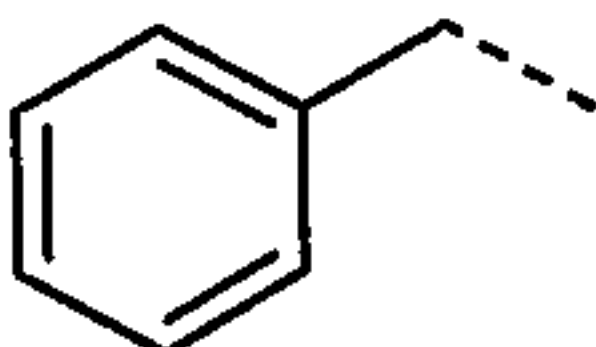
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-propan-2-yl-benzamide

20 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.19 (d, 6H), 1.67 (m, 6H), 1.95 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.12 (m, 1H), 4.82 (m, 1H), 7.49 (m, 2H), 7.72 (s, 1H), 8.04 (d, 1H), 8.08 (s, 1H), 8.38 (d, 1H)

Example 96:

25 **N-benzyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide**



Example	R ⁵ _m -L _n -	Supplier Or Source	MS m/z [M+H] ⁺	Retention time (Minutes)
93		Aldrich	453	2.04
94		Aldrich	465	2.09
5		Aldrich	453	2.04
96		ABCR	501	2.31

Example 97:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-N-cyclohexyl-benzamide (TimTec, 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100mg, 0.36 mmol), the 4-aminobenzamide (Aldrich, 59 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) were heated together in 4-methyl-2-pentanol (4ml) at 120°C for 22 hours. The reaction was cooled to ambient temperature and passed down a 5g SCX-2 column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and solvent evaporated. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid (37 mg, 27%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.67 (m, 6H), 1.97 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 4.84 (m, 1H), 7.08 (s, 1H), 7.77 (s, 1H), 7.79 (s, 4H), 8.08 (s, 1H), 9.46 (s, 1H); MS m/z 381 [M+H]⁺.

- 5 The following example was prepared by an analogous process to that used in the preparation of Example 66 utilising the appropriate amine.

Example 98:

- 10 **N-cyclobutyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide**

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.67 (m, 8H), 1.95 (m, 2H), 2.09 (m, 2H), 2.23 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.43 (m, 1H), 4.82 (m, 1H), 7.48 (m, 2H), 7.72 (s, 1H), 8.09 (s, 1H), 8.41 (m, 2H); MS m/z 465 [M+H]⁺.

15

Example 99:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-phenyl-benzamide

- 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one
20 (Intermediate 1, 100 mg, 0.36 mmol), 4-amino-3-methoxy-N-phenyl-benzamide (Apin, 104 mg, 0.43 mmol) and p-toluenesulphonic acid monohydrate (137 mg, 0.72 mmol) were vortexed and heated together in 4-methyl-2-pentanol (4 mL) at 100⁰C for 24 hours.. The crude reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with MeOH. The column was washed with MeOH and the product eluted with 2M NH₃/MeOH. Solvent was
25 evaporated and the resultant material was purified by reverse phase HPLC to yield the title compound as a white solid (64 mg, 36 %). MS m/z 487 [M+H]⁺. Retention Time 3.81 minutes

Example 100:

- 30 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-propan-2-yl-benzamide**

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 134mg, 0.48mmol), 4-amino-N-propan-2-yl-benzamide (Butt Park, 86 mg, 0.48 mmol) and p-toluenesulphonic acid monohydrate (227 mg, 1.19 mmol) in 4-methyl-2-pentanol (4 mL) were heated at 140°C for 2h. The reaction mixture was loaded onto an SCX-3
5 column pre-wet with methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then eluted with 2% 7N ammonia/methanol.. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a white solid (121 mg, 60%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.17 (6H, d), 1.63 (4H, m), 1.74 (2H, m), 1.97 – 1.99 (2H, d), 2.58 – 2.61 (2H, t), 3.18 (3H, s), 3.62 – 3.65 (2H, t), 4.07 – 4.13 (1H, m), 4.85 (1H, m),
10 7.71 – 7.82 (4H, m), 7.95 – 7.97 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 423 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the preparation of Example 100 utilising the appropriate aniline.

15

Example 101:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-phenyl-benzamide

Amine available from Aldrich

20 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.64 - 1.67 (4H, m), 1.72 - 1.75 (2H, m), 1.99 (2H, m), 2.60 (2H, t), 3.19 (3H, s), 3.63 (2H, t), 4.87 (1H, m), 7.09 (1H, t), 7.35 (2H, m), 7.76 - 7.79 (2H, d), 7.90 (4H, s), 8.11 (1H, s), 9.55 (1H, s), 10.00 (1H, s); MS m/z 423 [M+H]⁺.

Example 102:

25 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-methyl-benzamide**

Amine available from TimTec

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.63 (4H, m), 1.70 – 1.74 (2H, m), 1.97 (2H, m), 2.58 – 2.61 (2H, t), 2.78 (3H, d), 3.18 (3H, s), 3.62 – 3.65 (2H, t), 4.84 (1H, m), 7.75 (2H, d), 7.81
30 (2H, d), 8.09 (1H, s), 8.20 (1H, d), 9.46 (1H, s); MS m/z 395 [M+H]⁺.

Example 103:

6-cyclopentyl-9-[[2-methoxy-4-(2-pyrrolidin-1-ylethylamino)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140 mg, 0.5 mmol) 2-methoxy-N'-(2-pyrrolidin-1-ylethyl)benzene-1,4-diamine (Intermediate 35, 141 mg, 0.6 mmol), and p-toluenesulphonic acid monohydrate (227 mg, 1.19 mmol) in 4-methyl-2-pentanol (4 mL) were heated by microwave irradiation at 160 °C for 1 hour. The reaction mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the material produced was purified by normal phase chromatography using 0-10% ammonia/methanol to yield the title compound as a solid (100 mg, 42 %).

¹H NMR (500.13 MHz, DMSO-d₆) δ 1.55 - 1.62 (4H, m), 1.68 - 1.75 (6H, m), 1.85 - 1.92 (2H, m), 2.54 - 2.56 (6H, m), 2.67 (2H, t), 3.15 - 3.19 (5H, m), 3.58 - 3.60 (2H, m), 3.80 (3H, s), 4.64 - 4.71 (1H, m), 4.87 (1H, t), 6.19 (1H, dd), 6.36 (1H, d), 7.12 (1H, s), 7.67 (1H, d), 7.93 (1H, s); MS m/z 480 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the preparation of Example 103, utilising the appropriate aniline. NMR data is recorded where obtained.

Example 104:

6-cyclopentyl-9-[[2-methoxy-4-[methyl-(1-methyl-4-piperidyl)amino]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 105:

6-cyclopentyl-9-[[2-methoxy-4-[4-(2-methoxyethyl)piperazin-1-yl]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 106:

6-cyclopentyl-9-[[2-methoxy-4-[4-(1-piperidyl)-1-piperidyl]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 107:

6-cyclopentyl-9-[[4-(2-dimethylaminoethylamino)-2-methoxy-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (400.13 MHz, CDCl₃) δ 1.55 - 1.76 (7H, m), 1.99 - 2.02 (2H, m), 2.31 (6H, s), 2.60 - 2.66 (4H, m), 3.19 (2H, t), 3.27 (3H, s), 3.64 - 3.68 (2H, m), 3.85 (3H, s), 4.80 - 4.88 (1H, m), 6.23 - 6.26 (1H, m), 6.29 (1H, d), 7.09 (1H, s), 7.88 (1H, s), 8.03 (1H, d).

Example 108:

9-[[4-(4-cyclohexylpiperazin-1-yl)-2-methoxy-phenyl]amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (400.13 MHz, CDCl₃) δ 1.10 - 1.37 (4H, m), 1.55 - 1.78 (8H, m), 1.81 - 1.89 (2H, m), 1.95 - 2.05 (4H, m), 2.44 (1H, s), 2.65 - 2.67 (2H, m), 2.85 (4H, s), 3.24 (4H, s), 3.28 (3H, s), 3.66 - 3.69 (2H, m), 3.89 (3H, s), 4.82 - 4.91 (1H, m), 6.54 - 6.57 (2H, m), 7.24 (1H, s), 7.90 (1H, s), 8.19 (1H, d)

Example 109:

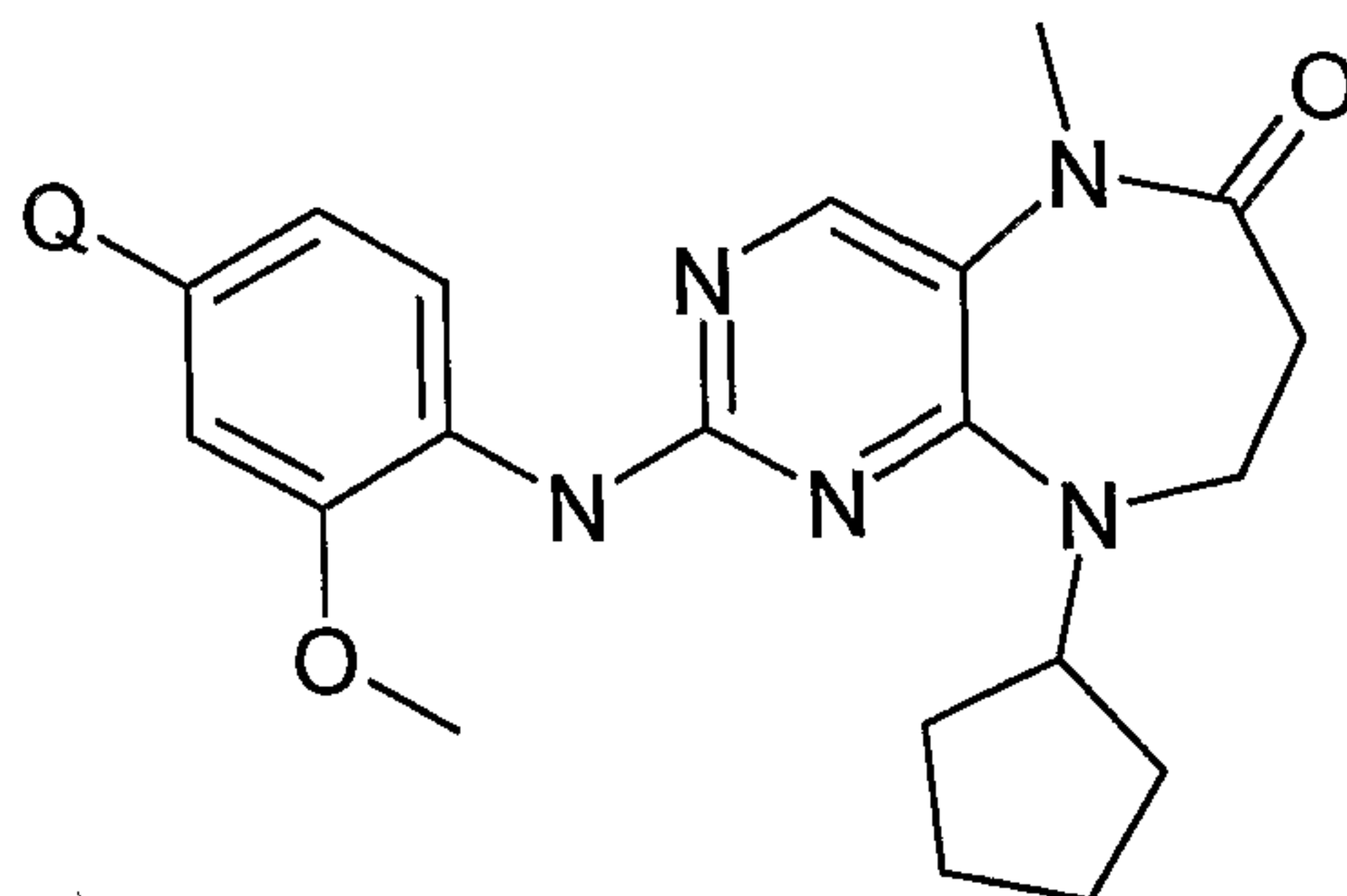
6-cyclopentyl-9-[[2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (400.13 MHz, CDCl₃) δ 1.53 - 1.78 (6H, m), 1.97 - 2.08 (4H, m), 2.42 (3H, s), 2.62 - 2.68 (4H, m), 2.75 - 2.78 (2H, m), 3.27 (3H, s), 3.50 (2H, t), 3.58 - 3.62 (2H, m), 3.64 - 3.67 (2H, m), 3.87 (3H, s), 4.81 - 4.88 (1H, m), 6.27 (1H, d), 6.28 (1H, s), 7.06 (1H, s), 7.88 (1H, m), 8.02 (1H, d)

Example 110:

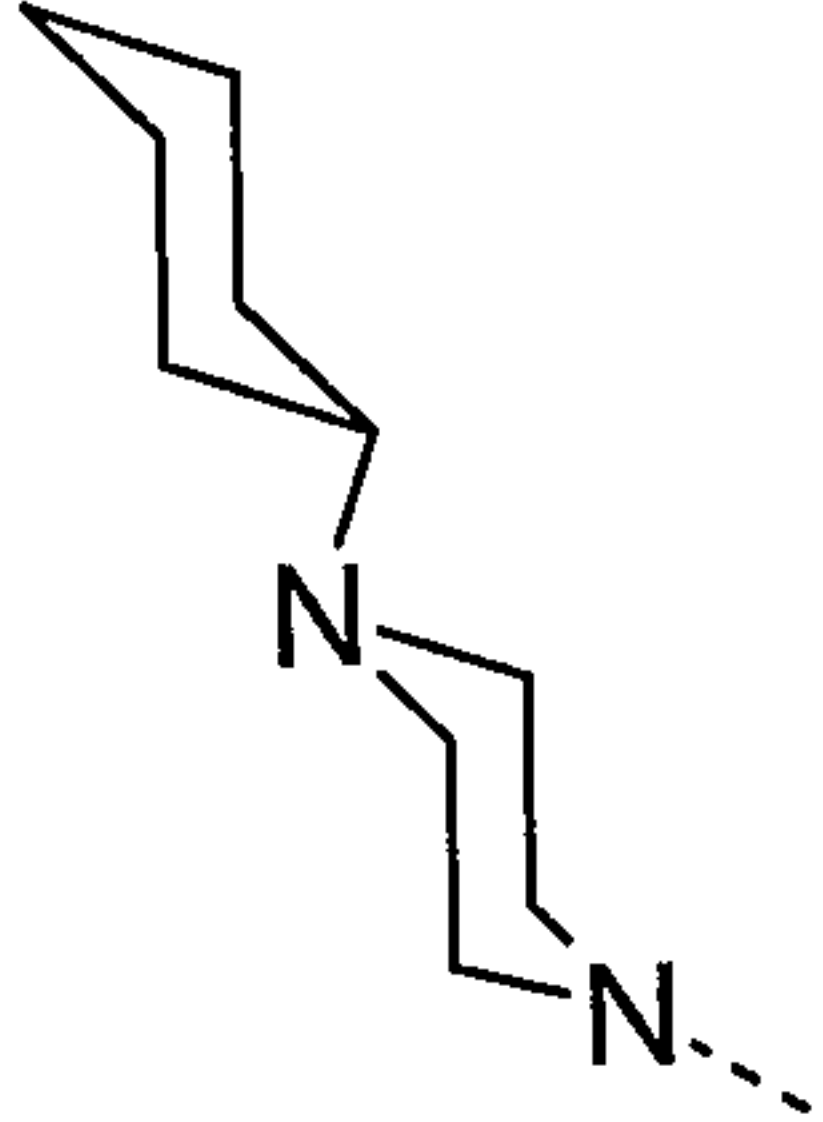
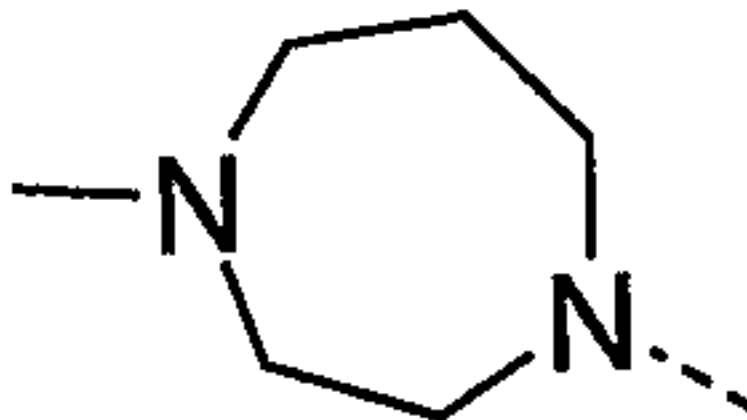
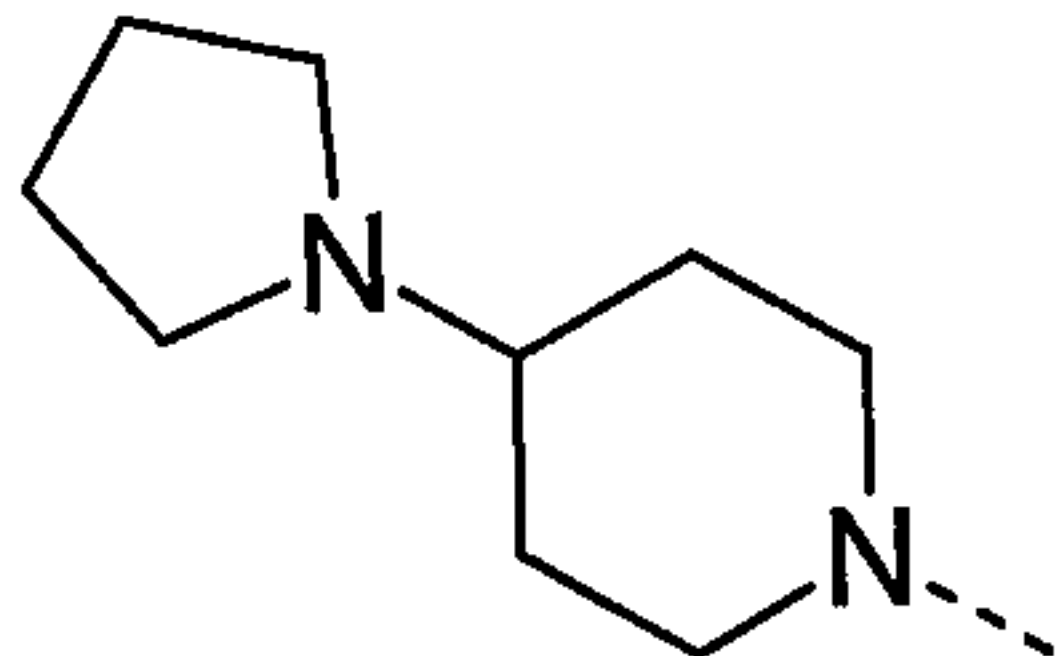
6-cyclopentyl-9-[[2-methoxy-4-(4-pyrrolidin-1-yl-1-piperidyl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

102



5

Exempl e	Q	Source	MS m/z [M+H] ⁺	Retention time (Minutes)
104		Intermediate 36	494	2.10
105		Intermediate 37	510	2.14
106		Intermediate 38	534	2.82
107		Intermediate 39	454	2.00

Exempl e	Q	Source	MS m/z [M+H] ⁺	Retention time (Minutes)
108		Intermediate 40	534	3.49
109		Intermediate 41	480	2.33
110		Intermediate 42	520	2.68

5

Example 111:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoic acid

To a solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-
 10 8,10,12-trien-5-one (Intermediate 1, 10.62 g, 36 mmol) and 4-amino-3-methoxybenzoic acid
 (Aldrich, 6.795 g, 40.7 mmol) in ethanol (150 mL) was added water (450 mL) and conc
 hydrochloric acid 96 mL, 72 mmol). The mixture was heated under reflux for 36 hours. The
 reaction was cooled and a brown solid precipitate formed which was filtered, triturated with
 cold acetonitrile and dried *in vacuo* to give the title compound (10.1 g, 68 %).

15 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.55 - 1.75 (6H, m), 1.87 - 1.95 (2H, m), 2.71 - 2.75 (2H,
 m), 3.18 (3H, s), 3.71 - 3.76 (2H, m), 3.95 (3H, s), 4.79 - 4.93 (1H, m), 7.58 - 7.62 (2H, m),
 8.19 (1H, d), 8.19 (1H, s), 9.37 (1H, s); MS m/z 412 [M+H]⁺.

Example 112:**6-cyclopentyl-2-methyl-9-[(2,4,6-trimethoxyphenyl)amino]-2,6,8,10-****5 tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

2,4,6-trimethoxyaniline (Maybridge, 104 mg, 0.56 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.56 mmol) and p-toluenesulphonic acid monohydrate (268 mg, 1.41 mmol) in 4-methyl-2-pentanol (4 mL) were heated at 140°C for 2h. The reaction solution was loaded on to an SCX-
10 3 column pre-wet with methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with 2% 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a white solid (140mg, 58%)
¹H NMR (399.9 MHz, DMSO-d₆) δ1.32 – 1.68 (8H, m), 2.46 – 2.48 (2H, t), 3.13 (3H, s), 3.50
15 (2H, t), 3.70 (6H, s), 3.79 (3H, s), 4.32 (1H, m), 6.25 (2H, s), 7.37 (1H, s), 7.85 (1H, s); MS
m/z 429 [M+H]⁺.

20 Example 113:**6-cyclopentyl-9-[[2-methoxy-4-[(1-methyl-4-piperidyl)oxy]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one
25 (Intermediate 1, 150 mg, 0.53 mmol), 2-methoxy-4-[(1-methyl-4-piperidyl)oxy]aniline (Intermediate 43 (124 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (255 mg, 1.34 mmol) heated in 4-methyl-2-pentanol (4 mL) at 140°C for 2h. The reaction solution was loaded on to an SCX-2 column pre-wet with methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with 2% 7N
30 ammonia/methanol to elute the crude product. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a red gum (189 mg, 82 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.53 – 1.56 (4H, m), 1.60 (2H, d), 1.63 – 1.68 (4H, m), 1.84 (2H, d), 1.92 (2H, d), 2.20 (3H, s), 2.18 – 2.22 (2H, m), 2.63 (2H, t), 3.15 (3H, s), 3.56 –

3.59 (2H, t), 3.81 (3H, s), 4.33 (1H, m), 4.64 (1H, m), 6.49 – 6.52 (1H, m), 6.62 (1H, d), 7.51 (1H, s), 7.82 (1H, d), 7.98 (1H, s); MS m/z 481 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the preparation of Example 113 utilising the appropriate aniline indicated.

Example 114:

6-cyclopentyl-9-[[2-methoxy-4-(1-methylpyrrolidin-3-yl)oxy-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Starting aniline - 2-methoxy-4-(1-methylpyrrolidin-3-yl)oxy-aniline Intermediate 45

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.54 (3H, d), 1.58 (1H, s), 1.66 (2H, s), 1.79 – 1.83 (2H, m), 1.85 (1H, s), 2.25 – 2.29 (1H, m), 2.30 (3H, s), 2.43 (1H, m), 2.53 – 2.56 (2H, t), 2.61 – 2.65 (1H, m), 2.66 – 2.68 (1H, m), 2.69 – 2.70 (1H, m), 2.81 – 2.85 (1H, m), 3.15 (3H, s), 3.56 – 3.59 (2H, m), 3.81 (3H, s), 4.65 (1H, m), 4.86 – 4.89 (1H, m), 6.41 – 6.44 (1H, m), 6.56 (1H, d), 7.51 (1H, s), 7.82 (1H, d), 7.98 (1H, s); MS m/z 467 [M+H]⁺.

Example 115:

6-cyclopentyl-9-[[2-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Starting aniline - 2-methoxy-4-(2-morpholin-4-ylethoxy)aniline Intermediate 47

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.55 (3H, d), 1.59 (1H, s), 1.67 (2H, s), 1.85 (2H, s), 2.48 (4H, d), 2.53 – 2.56 (2H, t), 2.69 (2H, t), 3.15 (3H, s), 3.59 (2H, d), 3.59 (4H, d), 3.83 (3H, s), 4.08 (2H, t), 4.67 (1H, s), 6.48 – 6.51 (1H, m), 6.63 (1H, d), 7.50 (1H, s), 7.86 (1H, d), 7.98 (1H, s); MS m/z 497 [M+H]⁺.

Example 116:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-(trifluoromethyl)benzonitrile

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 157 mg, 0.56 mmol), 4-amino-2-methyl-benzonitrile (Aldrich, 95 mg, 0.51 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were

dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (330 mg, 1.01 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (28 mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100°C for 8 h. The mixture was cooled, filtered and the
5 filtrate absorbed onto an SCX-3 column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase chromatography to give the title compound as a white solid. (21mg, 10%)

¹H NMR (399.9 MHz, DMSO-d₆) δ1.57 - 1.72 (6H, m), 1.92 - 2.00 (2H, m), 2.61 (2H, m),
10 3.19 (3H, s), 3.64 - 3.66 (2H, m), 4.82 - 4.90 (1H, m), 7.99 - 8.07 (2H, m), 8.16 (1H, s), 8.50 (1H, d), 10.15 (1H, s); MS m/z 431 [M+H]⁺.

Example 117:

**4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-
15 yl)amino]-N-(2-hydroxyethyl)benzenesulfonamide**

4-amino-N-(2-hydroxyethyl)benzenesulfonamide (Maybridge; 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140 mg, 0.5 mmol) and p-toluenesulphonic acid monohydrate (238 mg, 1.25 mmol) were heated at 140°C in 4-methyl-2-pentanol (3 mL) for 3 hours. The mixture was
20 allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto and SCX-3 column and washed with methanol. The product with eluted with ammonia/methanol and the product containing fractions were concentrated. Purification by preparative, reverse phase chromatography gave the title compound as a white solid (122mg, 53%)..

¹H NMR (399.9 MHz, DMSO-d₆) δ1.59 - 1.74 (6H, d), 1.96 - 2.01 (2H, m), 2.57 - 2.61 (2H, m), 2.78 (2H, q), 3.19 (3H, s), 3.35 - 3.40 (2H, m), 3.62 - 3.65 (2H, m), 4.63 (1H, t), 4.80 -
25 4.88 (1H, m), 7.33 (1H, t), 7.64 - 7.68 (2H, m), 7.90 - 7.94 (2H, m), 8.11 (1H, s), 9.65 (1H, s); MS m/z 461 [M+H]⁺.

30 The following example was prepared by an analogous process to that used in the preparation of Example 117 utilising the appropriate aniline available from Aldrich.

Example 118:

6-cyclopentyl-9-[[4-(2-dimethylaminoethoxy)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.55 – 1.71 (6H, m), 1.89 – 1.95 (2H, m), 2.22 (6H, s), 2.55 - 2.57 (2H, m), 2.61 (2H, t), 3.16 (3H, s), 3.58 - 3.61 (2H, m), 4.00 (2H, t), 4.72 - 4.81 (1H, m), 6.82 - 6.86 (2H, m), 7.56 - 7.60 (2H, m), 8.01 (1H, s), 8.95 (1H, s); MS m/z 425 [M+H]⁺.

Example 119:

N-[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]acetamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), N-(4-aminophenyl)acetamide (Aldrich, 64 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 120°C for 22 hours. The reactions were cooled to ambient temperature and then passed down a 5g SCX-2 column pre-wet with methanol. The products were eluted with 2M NH₃/MeOH and the solvent evaporated. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solids (22 mg, 16%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.64 (m, 6H), 1.94 (m, 2H), 2.01 (s, 3H), 2.56 (m, 2H), 3.16 (s, 3H), 3.60 (m, 2H), 4.78 (m, 1H), 7.43 (d, 2H), 7.61 (d, 2H), 8.02 (s, 1H), 9.06 (s, 1H), 9.74 (s, 1H); MS m/z 495 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the preparation of Example 119 utilising the appropriate substituted anilines. NMR analysis was undertaken where indicated.

Example 120:

6-cyclopentyl-9-[(4-methoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.62 (m, 6H), 1.92 (m, 2H), 2.55 (m, 2H), 3.16 (s, 3H), 3.59 (m, 2H), 3.60 (s, 2H), 3.72 (s, 3H), 4.76 (m, 1H), 6.83 (d, 2H), 7.59 (d, 2H), 8.00 (s, 1H), 8.93 (s, 1H)

5

Example 121:

6-cyclopentyl-2-methyl-9-[(4-morpholin-4-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.63 (m, 6H), 1.92 (m, 2H), 2.55 (m, 2H), 3.02 (m, 4H), 3.15 (s, 3H), 3.59 (m, 2H), 3.74 (m, 4H), 4.76 (m, 1H), 6.85 (d, 2H), 7.56 (d, 2H), 7.99 (s, 1H), 8.89 (s, 1H); MS m/z 423 [M+H]⁺.

10

Example 122:

6-cyclopentyl-9-[(4-dimethylaminophenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

15

Example 123:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzenesulfonamide

20

Example 124:

9-[(1-acetyl-2,3-dihydroindol-5-yl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

25

Example 125:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-methoxyethyl)benzenesulfonamide

30

^1H NMR (400.132 MHz, DMSO- d_6) δ 1.66 (m, 6H), 1.96 (m, 2H), 2.59 (m, 2H), 2.88 (m, 2H), 3.17 (s, 3H), 3.18 (s, 3H), 3.30 (m, 2H), 3.63 (m, 2H), 4.83 (m, 1H), 7.44 (t, 1H), 7.66 (d, 2H), 7.91 (d, 2H), 8.10 (s, 1H), 9.64 (s, 1H)

5 **Example 126:**

9-[(3-chloro-4-morpholin-4-yl-phenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 127:

10 **6-cyclopentyl-2-methyl-9-[(4-methylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

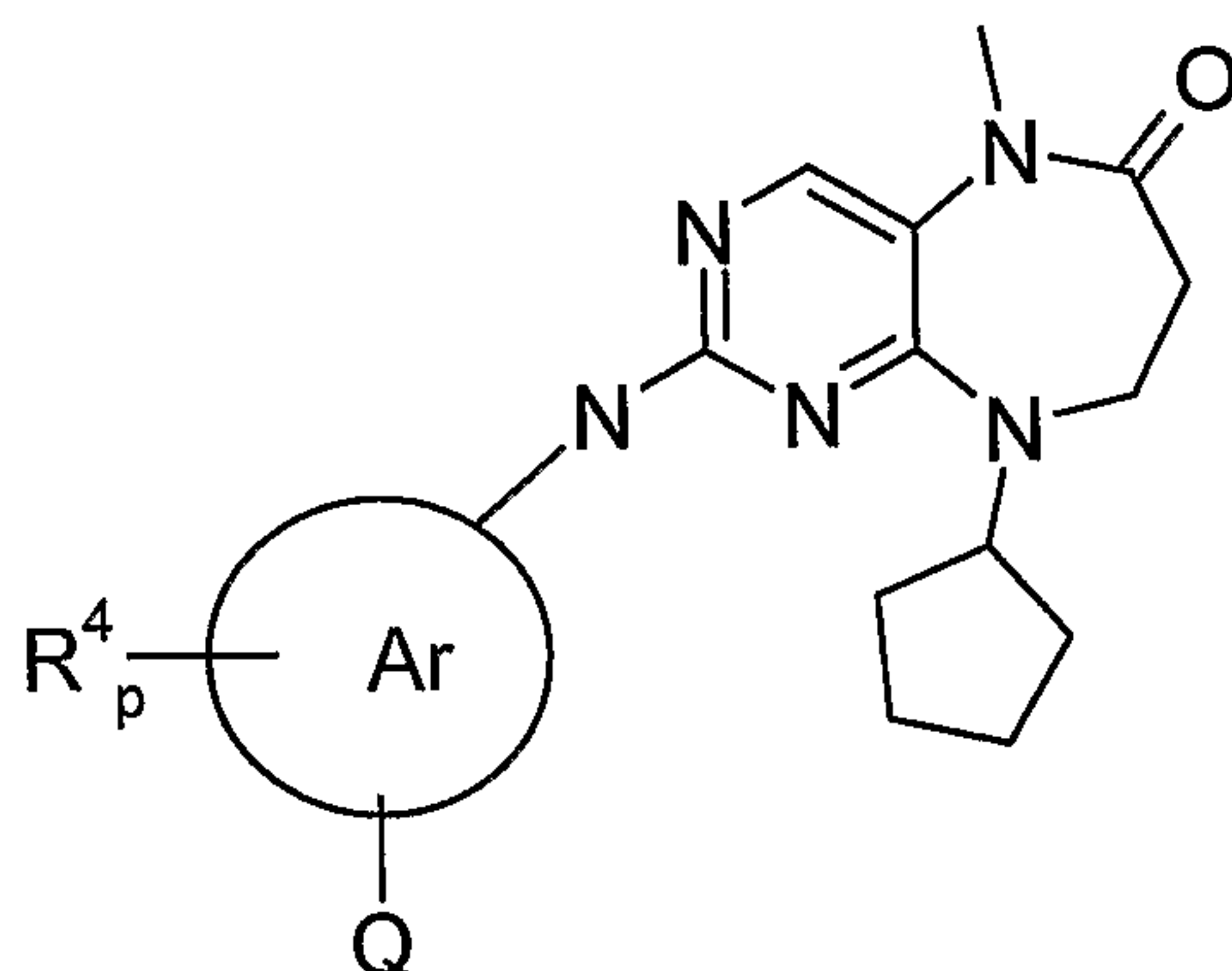
^1H NMR (400.132 MHz, DMSO- d_6) δ 1.67 (m, 6H), 1.98 (m, 2H), 2.60 (m, 2H), 3.15 (s, 3H), 3.18 (s, 3H), 3.64 (m, 2H), 4.85 (m, 1H), 7.77 (d, 2H), 7.98 (d, 2H), 8.11 (s, 1H), 9.74 (s, 1H)

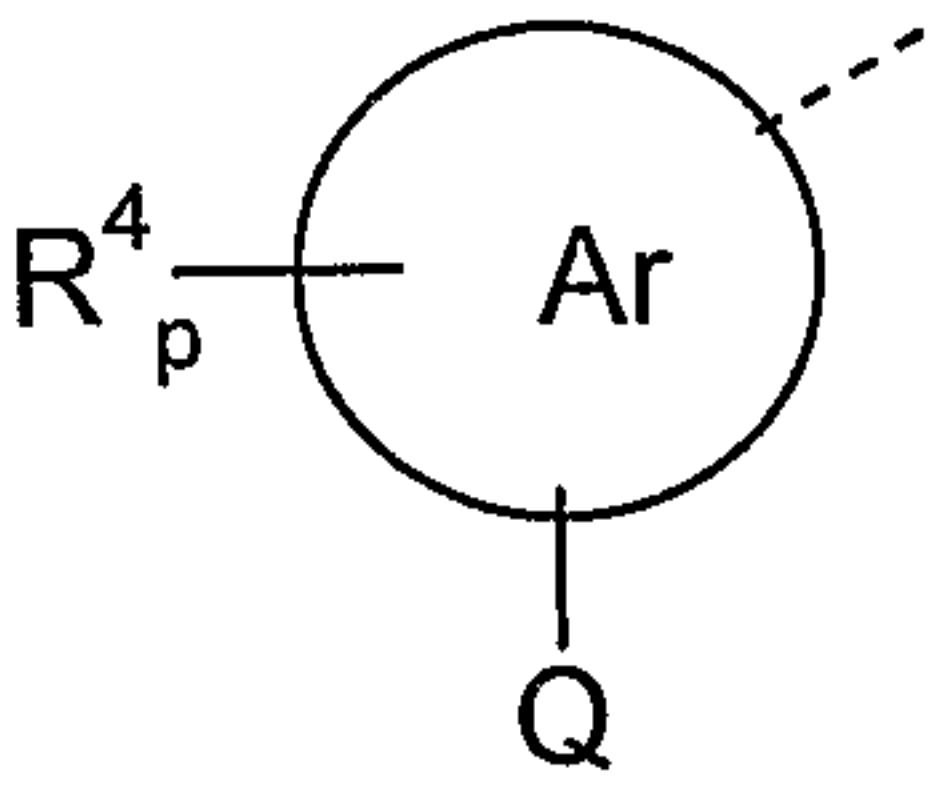
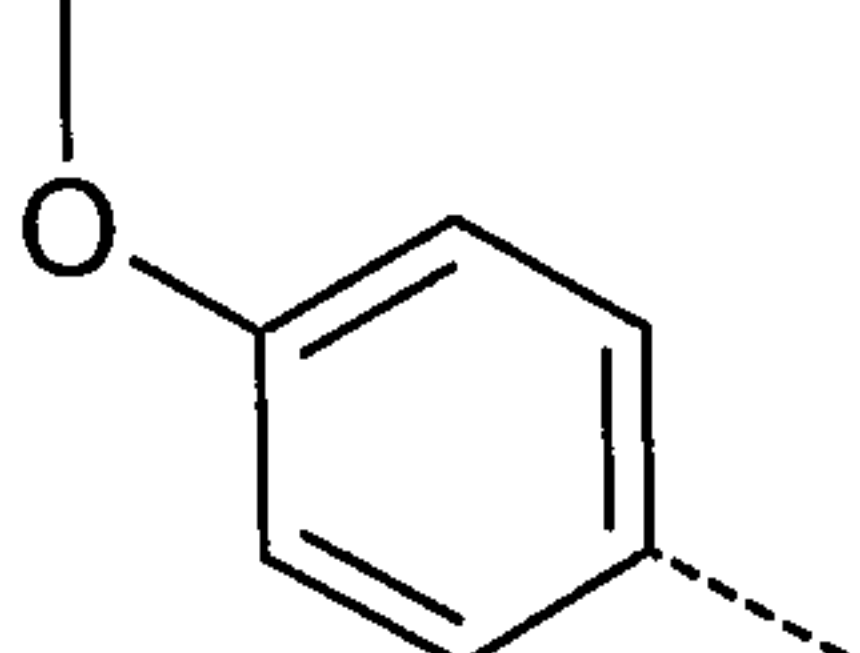
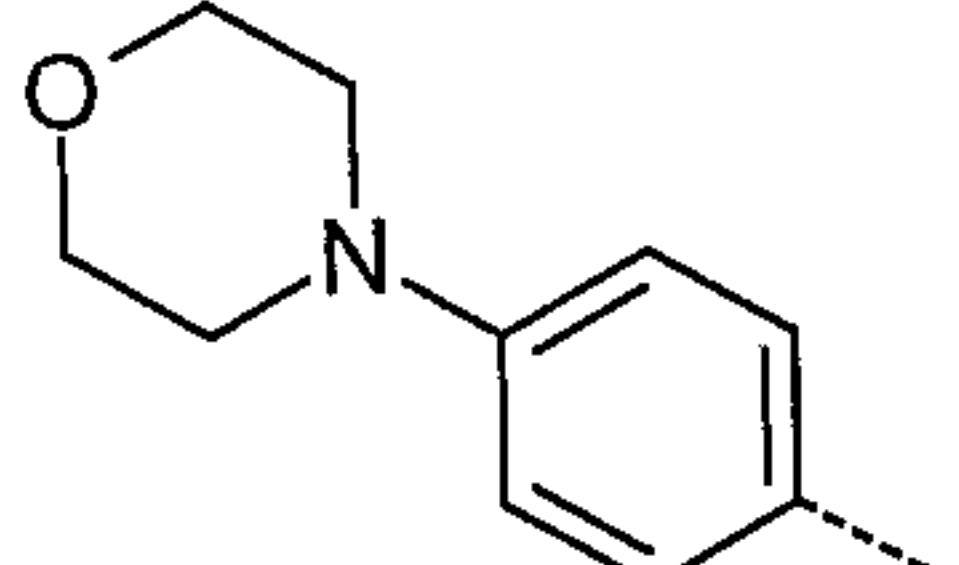
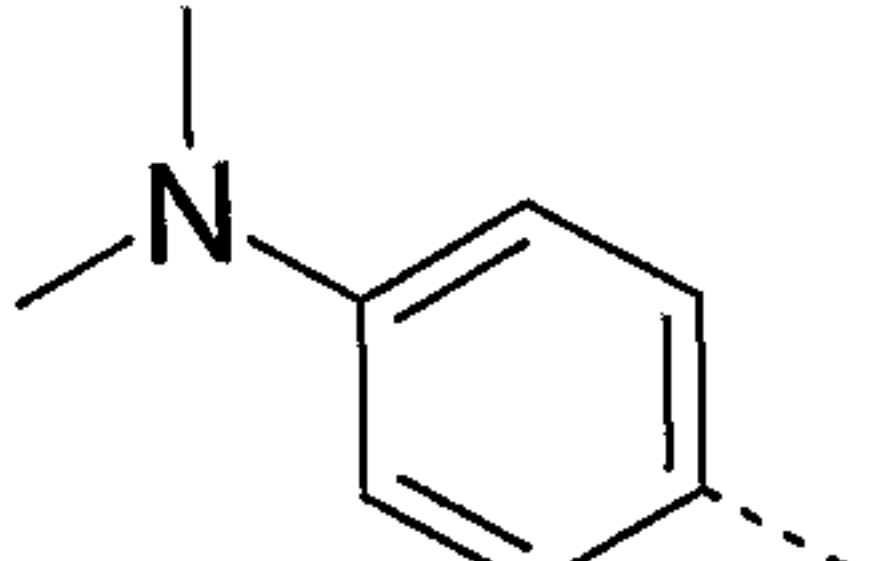
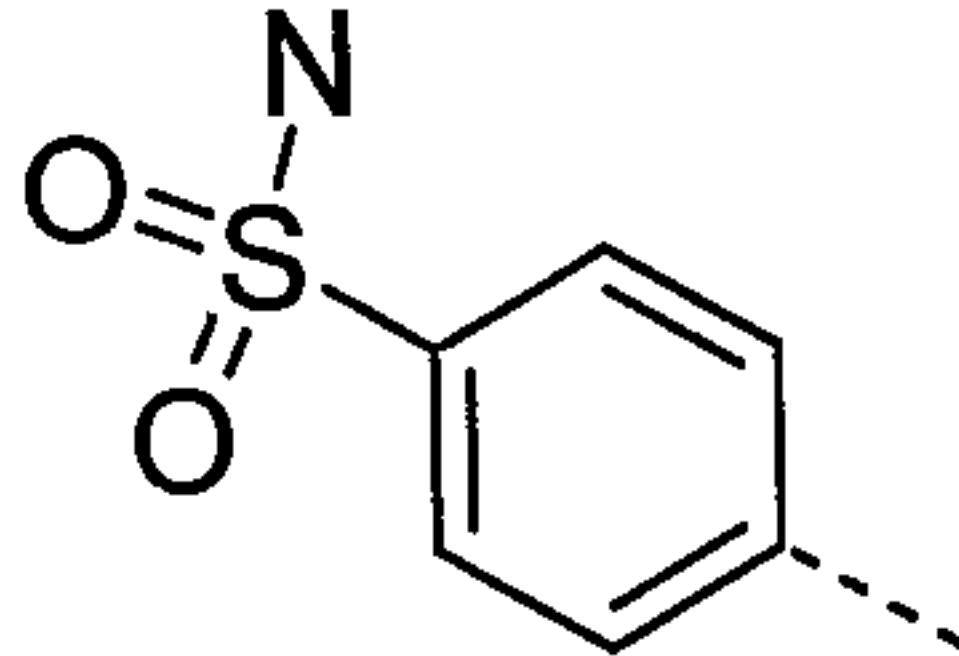
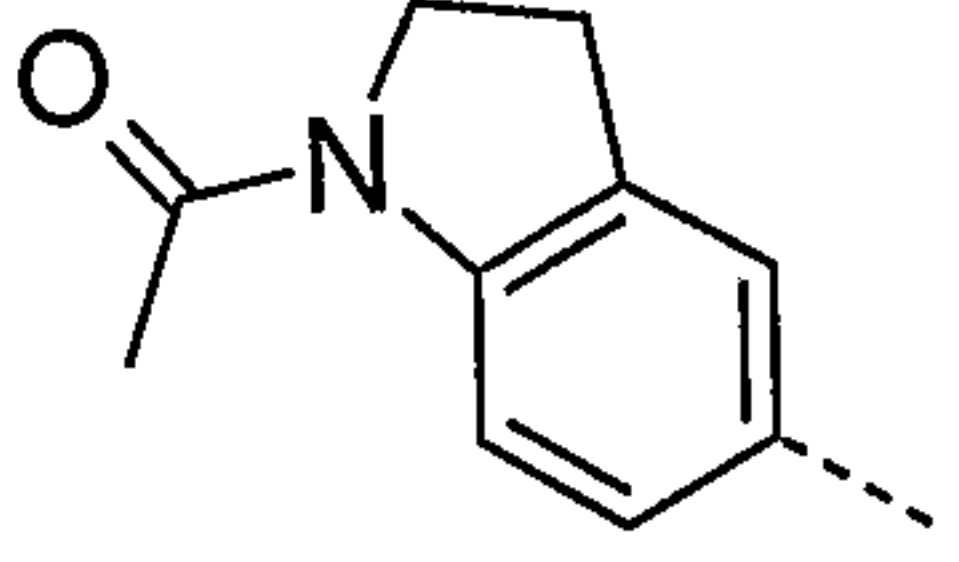
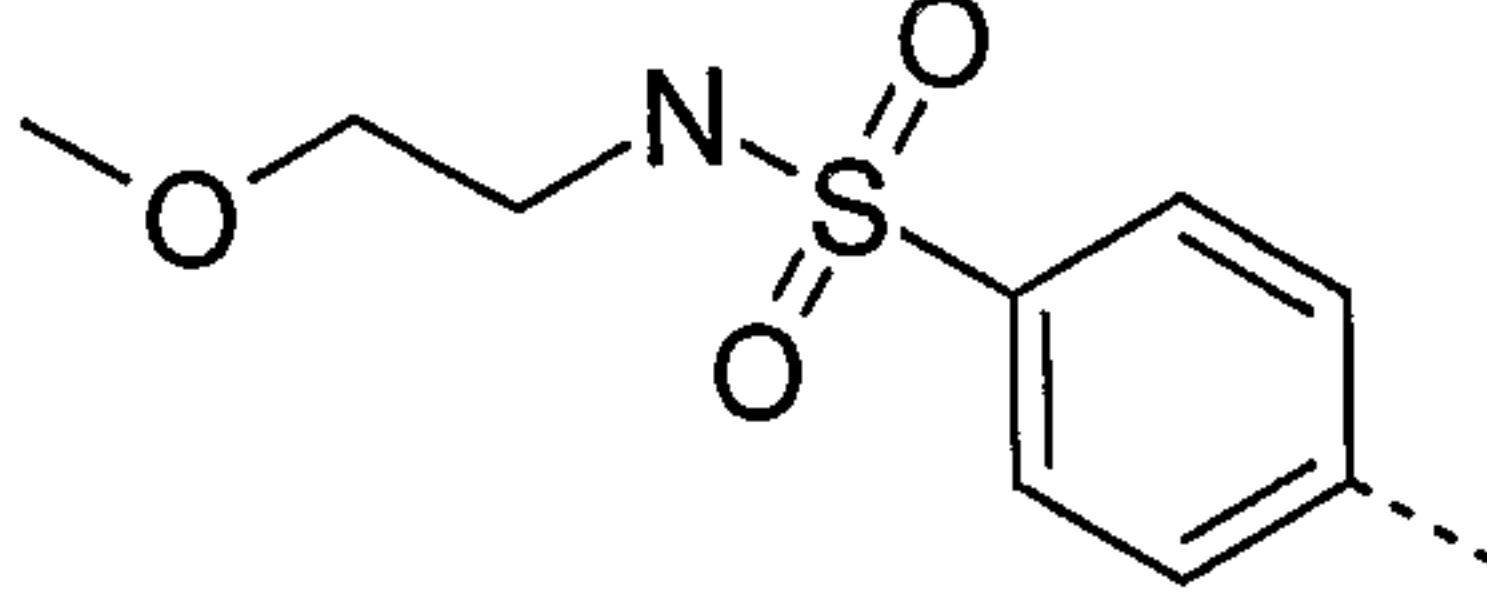
15

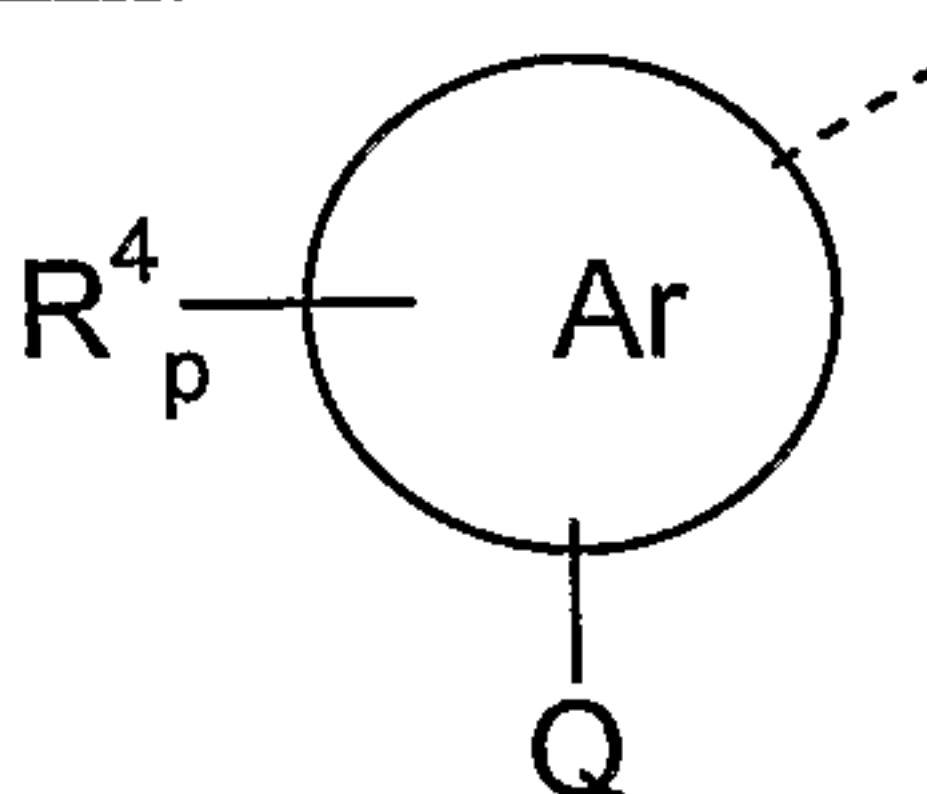
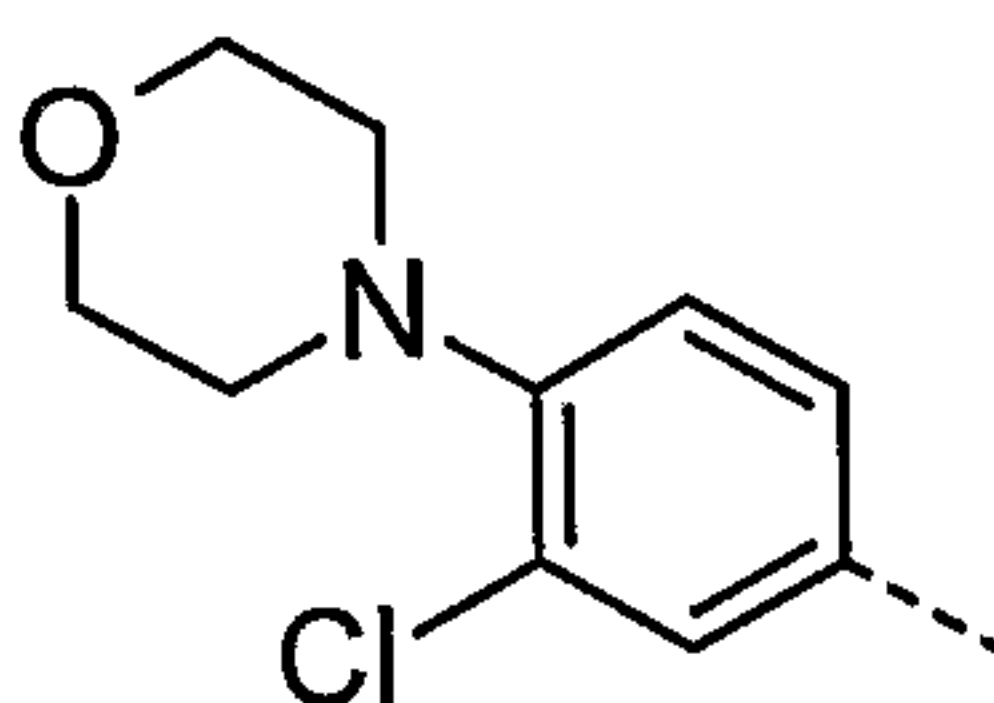
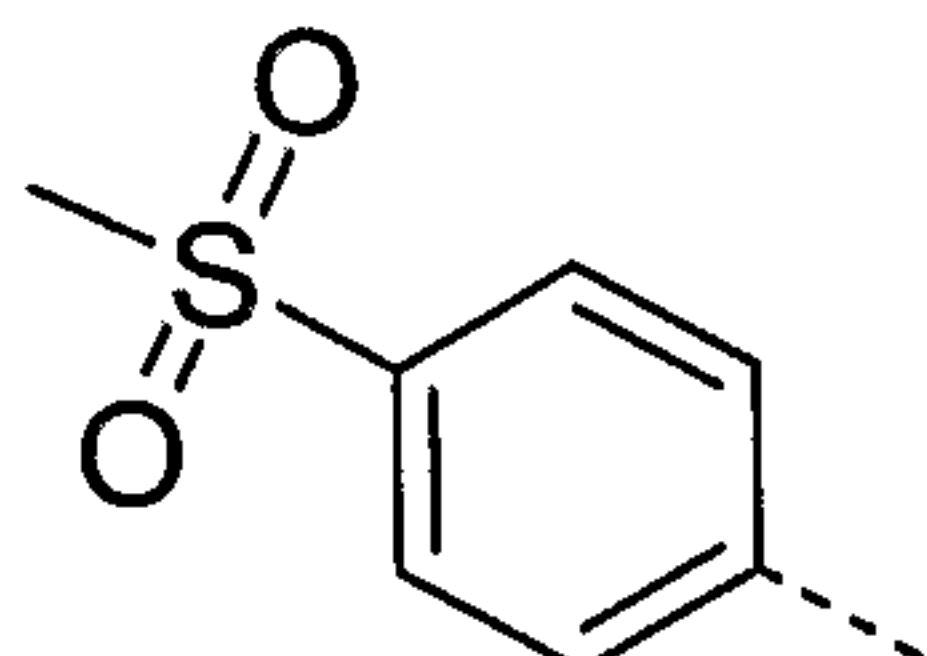
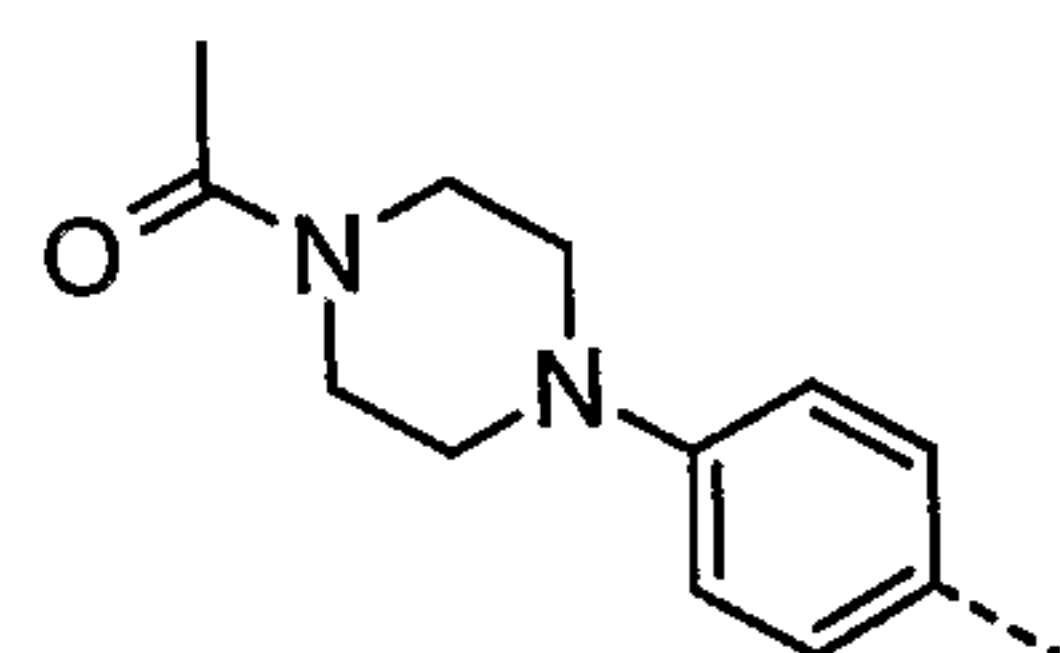
Example 128:

9-[[4-(4-acetylpiperazin-1-yl)phenyl]amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

20



Example		Supplier or Source	MS m/z [M+H] +	Retention Time (Minutes)
120		Aldrich	368	2.16
121		Aldrich	423	1.95
122		Aldrich	381	3.14
123		ABCR	417	2.6
124		Flurochem	421	2.75
125		WO2005/11602 5	475	2.81

Example		Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)
126		Flurochem	457	3.26
127		Flurochem	416	2.78
128		Flurochem	464	2.65

Example 129:**6-cyclopentyl-2-methyl-9-[(3,4,5-trimethoxyphenyl)amino]-2,6,8,10-****5 tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

3,4,5-trimethoxyaniline (Aldrich, 104 mg, 0.56 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.56 mmol) and p-toluenesulphonic acid monohydrate (268 mg, 1.41 mmol) were heated at 140°C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction solution was loaded onto an SCX-3 column pre-wet methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with 2% 7N ammonia/methanol to elute the crude product. The product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a purple solid (130mg, 54%).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.50 – 1.52 (2H, m), 1.57 – 1.61 (2H, m), 1.70 (2H, m), 1.95 (2H, m), 2.55 – 2.58 (2H, t), 3.17 (3H, s), 3.59 (2H, t), 3.63 (3H, s), 3.76 (6H, s), 4.86 (1H, d), 7.09 (2H, s), 8.04 (1H, s), 8.97 (1H, s); MS m/z 429 [M+H]⁺.

- 5 The following example was prepared by an analogous process to that used in the preparation of Example 129 utilising the appropriate substituted anilines available as indicated.

Example 130:

6-cyclopentyl-2-methyl-9-[(2,3,4-trimethoxyphenyl)amino]-2,6,8,10-

10 **tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

Substituted aniline available from **Apin**

¹H NMR (399.9 MHz, DMSO-d₆) δ1.53 - 1.56 (2H, m), 1.58 (2H, d), 1.67 - 1.68 (2H, m), 1.88 (2H, t), 2.55 - 2.57 (2H, m), 3.16 (3H, s), 3.58 - 3.60 (2H, t), 3.79 (3H, s), 3.78 - 3.82 (6H, s), 4.69 (1H, m), 6.74 (1H, d), 7.70 (2H, t), 8.00 (1H, s); MS m/z 429 [M+H]⁺.

15

Example 131:

9-[[4-chloro-3-(hydroxymethyl)phenyl]amino]-6-cyclopentyl-2-methyl-2,6,8,10-

tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

20 Substituted aniline available from **Aldrich**

¹H NMR (399.9 MHz, DMSO-d₆) δ1.60 (3H, d), 1.62 - 1.62 (1H, m), 1.67 (2H, d), 1.96 (2H, s), 2.53 - 2.59 (2H, t), 3.17 (3H, s), 3.60 - 3.63 (2H, t), 4.53 (2H, d), 4.88 (1H, m), 5.27 (1H, t), 7.24 (1H, d), 7.62 - 7.65 (1H, m), 7.96 (1H, d), 8.05 (1H, s), 9.31 (1H, s); MS m/z 402 [M+H]⁺.

25

Example 132:

6-cyclopentyl-2-methyl-9-[(2-pyridin-3-yl-1H-benzoimidazol-5-yl)amino]-2,6,8,10-

tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

30 (Intermediate 1, 134 mg, 0.50 mmol), 2-pyridin-3-yl-1H-benzoimidazol-5-amine (Flurochem, 117 mg, 0.55 mmol) and cesium carbonate (328 mg, 1.00 mmol) were added to dioxane (4

mL) and the suspension bubbled with nitrogen for 10 minutes.

Bis(dibenzylideneacetone)palladium (28 mg, 0.03 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were added and the mixture heated to 110 °C overnight. The mixture was filtered and the filtrate purified by column

5 chromatography with a 5% 7N ammonia in methanol/DCM solvent system. Product containing fractions were combined and evaporated to give the title compound as a solid (73 mg, 32 %)

¹H NMR (499.8 MHz, DMSO-d₆ @ 373K) δ 1.64 (4H, m), 1.73 (2H, m), 2.00 (2H, m), 2.53 - 2.56 (2H, t), 3.21 (3H, s), 3.62 - 3.65 (2H, t), 4.82 - 4.85 (1H, m), 7.53 - 7.55 (3H, m), 8.04
10 (2H, s), 8.45 (1H, d), 8.64 - 8.65 (1H, m), 8.71 (1H, s), 9.32 (1H, d), 12.51 (1H, s); MS m/z 455 [M+H]⁺.

Example 133:

**N-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-
15 9-yl)amino]phenyl]methyl]pyridine-2-carboxamide**

N-[(4-aminophenyl)methyl]pyridine-2-carboxamide (Intermediate 49: 114mg, 0.5mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 141 mg, 0.5 mmol) and p-toluenesulphonic acid monohydrate (239 mg, 1.25 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140°C for 2 hours. The mixture was
20 cooled and diluted with methanol / DCM and absorbed on to an SCX-3 column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase chromatography to give the title compound as a white solid (63mg, 27%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.54 - 1.71 (6H, m), 1.89 - 1.96 (2H, m), 2.56 - 2.58 (2H,
25 m), 3.16 (3H, s), 3.59 - 3.61 (2H, m), 4.44 (2H, d), 4.79 (1H, m), 7.23 (2H, d), 7.60 - 7.63 (1H, m), 7.65 - 7.67 (2H, m), 7.99 - 8.08 (3H, m), 8.64 - 8.66 (1H, m), 9.13 (1H, s), 9.18 (1H, t); MS m/z 472 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the
30 preparation of Example 133 utilising the appropriate substituted anilines available from ABCR

Example 134:

6-cyclopentyl-2-methyl-9-[[4-(1-piperidylsulfonyl)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.34 – 1.39 (2H, m), 1.52 – 1.75 (10H, m), 1.94 – 2.00 (2H, m), 2.57 – 2.61 (2H, m), 2.87 (4H, t), 3.19 (3H, s), 3.62 – 3.65 (2H, m), 4.84 (1H, m), 7.59 (2H, d), 7.94 – 7.96 (2H, m), 8.11 (1H, s), 9.71 (1H, s); MS m/z 485 [M+H]⁺.

Example 135:

6-cyclopentyl-2-methyl-9-[[4-(2-morpholin-4-ylethoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.54 – 1.72 (6H, m), 1.89 – 1.95 (2H, m), 2.48 (4H, m), 2.66 – 2.70 (2H, m), 2.68 – 2.69 (2H, m), 3.16 (3H, s), 3.59 (6H, m), 4.05 (2H, t), 4.76 (1H, m), 6.84 – 6.87 (2H, m), 7.57 – 7.60 (2H, m), 8.01 (1H, s), 8.95 (1H, s); MS m/z 467 [M+H]⁺.

Example 136:

tert-butyl N-[[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]methyl]carbamate

20

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 155 mg, 0.55 mmol), tert-butyl N-[(3-aminophenyl)methyl]carbamate (Chembasics, 111 mg, 0.50 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were dissolved in 1,4-dioxane (7.5 mL) Caesium carbonate (326 mg, 1.0 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes.

25

Tris(dibenzylideneacetone) palladium (II) (28 mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100°C for 8h. The mixture was cooled, filtered and the filtrate absorbed onto an SCX-3 column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by normal phase chromatography (1% methanol/DCM) to give the title compound as a white solid (57 mg, 24 %).

30

¹H NMR (399.9 MHz, DMSO-d₆) δ1.41 (9H, s), 1.59 - 1.71 (6H, m), 1.96 (2H, m), 2.58 (2H, m), 3.17 (3H, s), 3.61 (2H, m), 4.09 (2H, d), 4.85 (1H, m), 6.80 (1H, d), 7.18 (1H, t), 7.30 (1H, t), 7.57 (1H, d), 7.62 (1H, s), 8.04 (1H, s), 9.16 (1H, s); MS m/z 467 [M+H]⁺.

5

The following example was prepared by an analogous process to that used in the preparation of Example 136 utilising the appropriate substituted aniline available from Flurochem.

Example 137:

10 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-methyl-isoindole-1,3-dione**

¹H NMR (399.9 MHz, DMSO-d₆) δ1.61 - 1.77 (6H, m), 1.95 - 1.98 (2H, m), 2.61 - 2.63 (2H, m), 3.04 (3H, s), 3.20 (3H, s), 3.65 - 3.68 (2H, m), 4.78 (1H, m), 7.39 (1H, d), 7.74 (1H, t), 8.16 (1H, s), 8.81 (1H, d), 9.14 (1H, s); MS m/z 421 [M+H]⁺.

15

Example 138:

N-[2-[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methoxy-phenyl]ethyl]acetamide

N-[2-(3-amino-4-methoxy-phenyl)ethyl]acetamide (Compound 4- Organic Process Research
20 & Development 2004, 8, 628-642, 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140 mg, 0.5 mmol) and p-toluenesulphonic acid monohydrate (238 mg, 1.25 mmol) were heated at 140°C in 4-methyl-2-pentanol (3 mL) for 3 hours. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto an SCX-3
25 column and washed with methanol. The product with eluted with ammonia/methanol and the product containing fractions were concentrated. Purification by preparative, reverse phase chromatography gave the title compound as a white solid (45 mg, 20 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.55 - 1.70 (6H, m), 1.79 (3H, s), 1.93 - 1.96 (2H, m), 2.56 - 2.59 (2H, m), 2.64 (2H, t), 3.17 (3H, s), 3.20 - 3.26 (2H, m), 3.61 - 3.63 (2H, m), 3.86
30 (3H, s), 4.85 (1H, m), 6.78 - 6.81 (1H, m), 6.95 (1H, d), 7.55 (1H, s), 7.86 (1H, t), 8.05 (1H, s), 8.12 (1H, d); MS m/z 453 [M+H]⁺.

Example 139:

6-cyclopentyl-9-[(2-methoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

5 2-methoxyaniline (Aldrich, 22 mg, 0.18 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 50 mg, 0.18 mmol) and p-toluenesulphonic acid monohydrate (84 mg, 0.44 mmol) were heated in 4-methyl-2-pentanol (1 mL) at 135°C for 24 hours. The mixture was cooled and diluted with methanol / DCM and absorbed on to an SCX-3 column, washed with methanol and eluted with ammonia in
10 methanol. Product containing fractions were concentrated and purified by preparative reverse phase chromatography to give the title compound as a white solid (42 mg, 64 %). MS m/z 368 [M+H]⁺, Retention Time 2.61 mins.

The following examples were prepared by an analogous process to that used in the
15 preparation of Example 139, utilising the appropriate substituted anilines available as indicated.

Example 140:

6-cyclopentyl-9-[(2-ethoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-
20 **8,10,12-trien-3-one**

Example 141:

6-cyclopentyl-2-methyl-9-[(2-methylsulfanylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

25

Example 142:

6-cyclopentyl-9-[(2-hydroxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

30 **Example 143:**

6-cyclopentyl-9-[(2-ethylphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 144:

5 9-[(2-benzoylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 145:

10 2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzenesulfonamide

Example 146:

15 6-cyclopentyl-2-methyl-9-[(2-phenoxyphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 147:

9-[(2-bromophenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

20 **Example 148:**

6-cyclopentyl-2-methyl-9-[(2-phenylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 149:

25 6-cyclopentyl-2-methyl-9-[(2-methylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 150:

30 6-cyclopentyl-2-methyl-9-[(2-propan-2-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 151:

9-[(2-butylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-
5 8,10,12-trien-3-one

Example 152:

6-cyclopentyl-2-methyl-9-[[2-(1-piperidyl)phenyl]amino]-2,6,8,10-
tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10 **Example 153:**

6-cyclopentyl-2-methyl-9-[[2-(4-tert-butylphenoxy)phenyl]amino]-2,6,8,10-
tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 154:

15 2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-
yl)amino]-N-ethyl-benzenesulfonamide

Example 155:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-
20 yl)amino]-N-methyl-benzenesulfonamide

Example 156:

6-cyclopentyl-2-methyl-9-[[2-(2-morpholin-4-ylethylamino)phenyl]amino]-2,6,8,10-
tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

25

Example 157:

9-[(2-benzylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-
8,10,12-trien-3-one

30 **Example 158:**

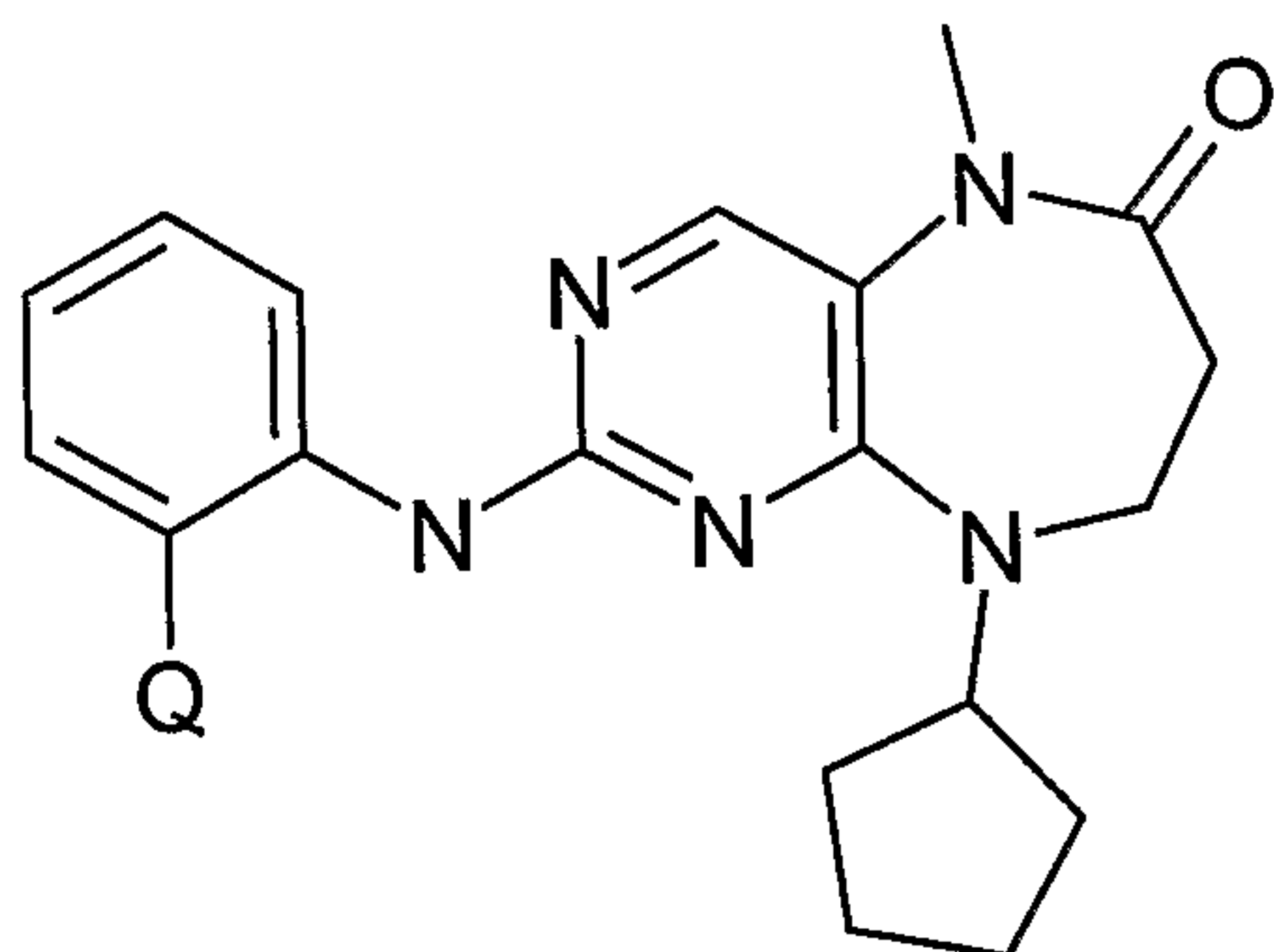
6-cyclopentyl-2-methyl-9-[(2-pyrrol-1-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 159:

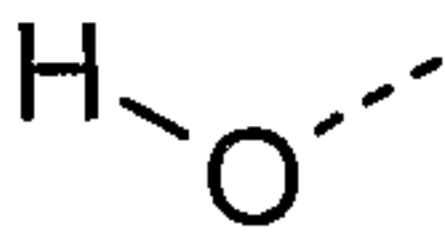
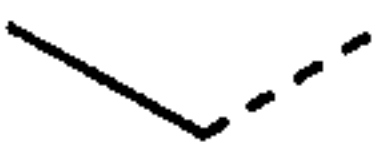
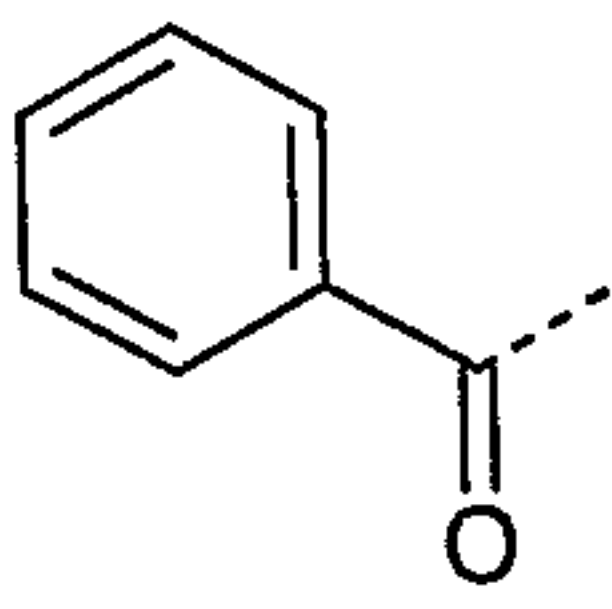
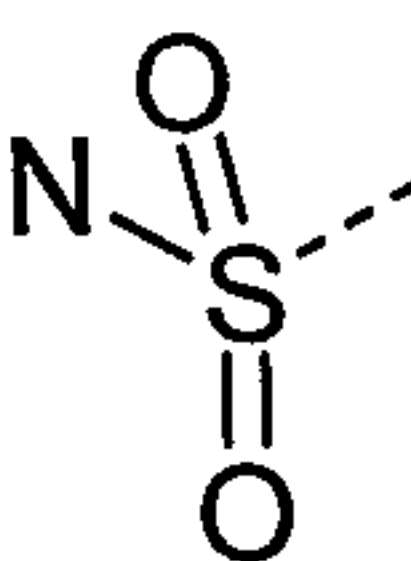
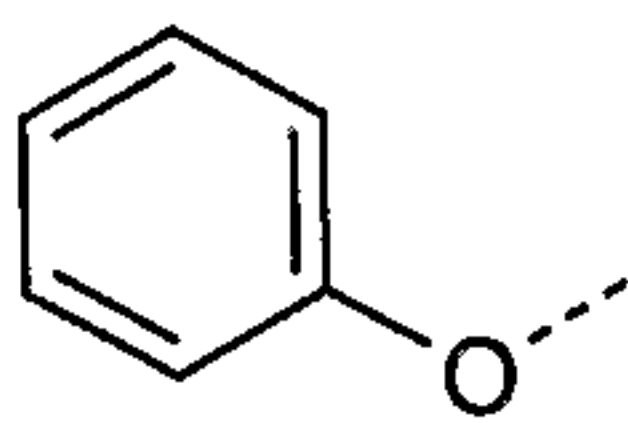
5 6-cyclopentyl-2-methyl-9-[[2-(4-methylphenoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 160:

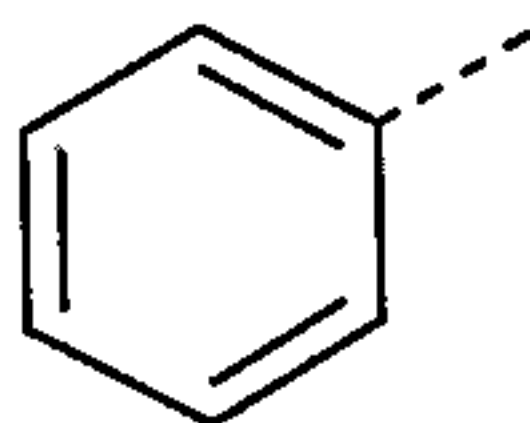
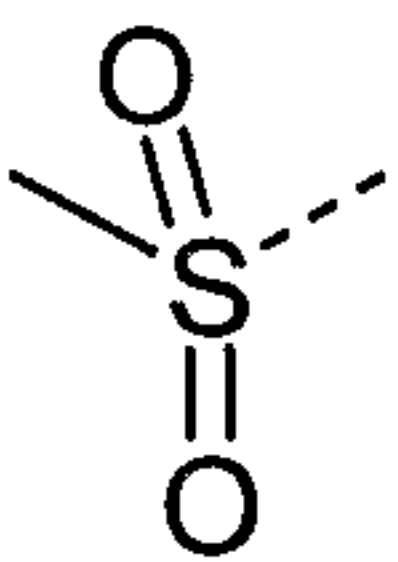
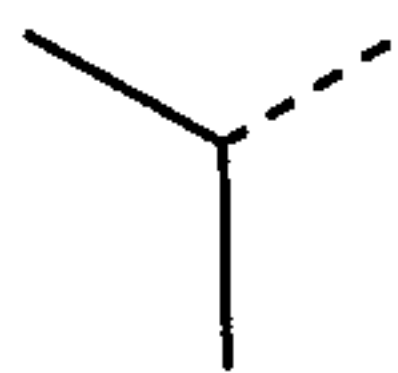
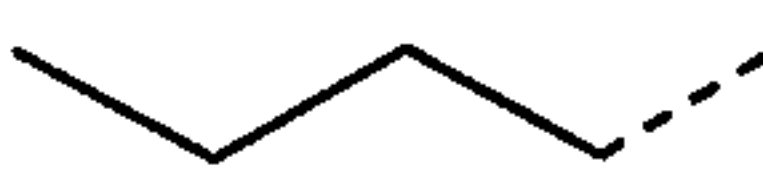
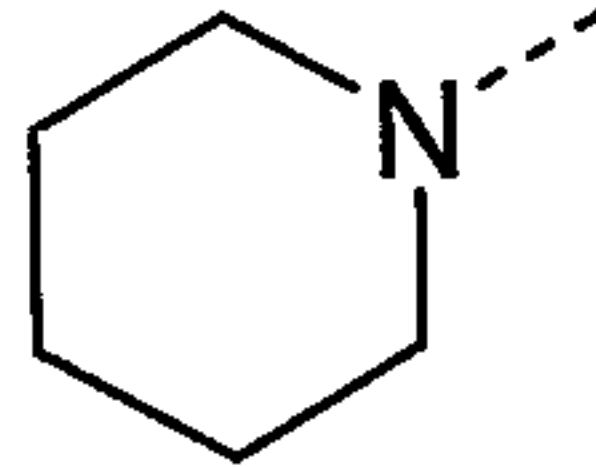
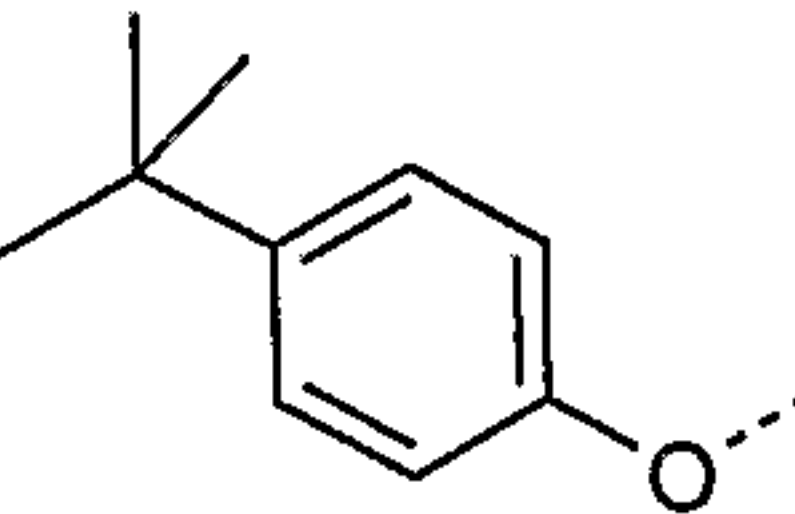
10 6-cyclopentyl-2-methyl-9-[[2-(morpholin-4-ylmethyl)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

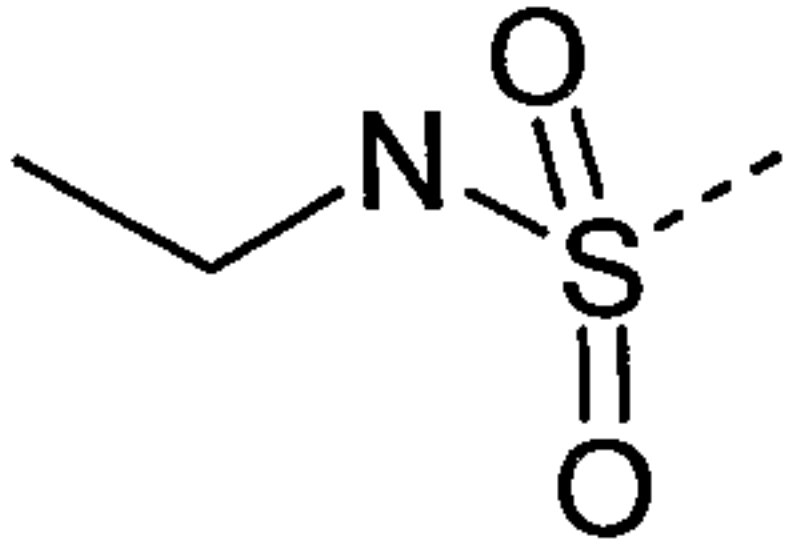
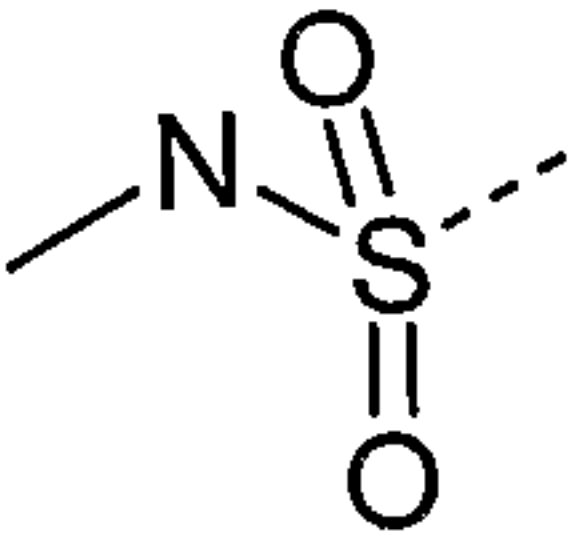
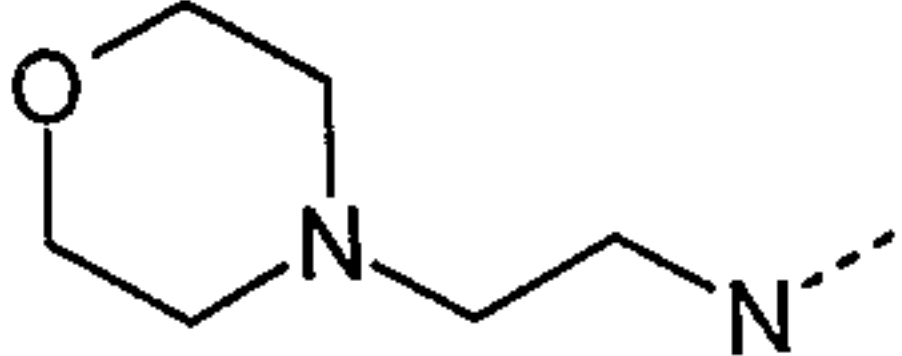
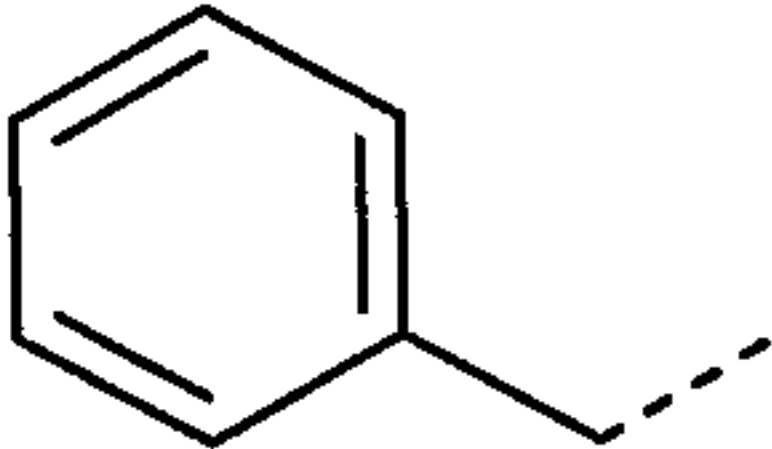
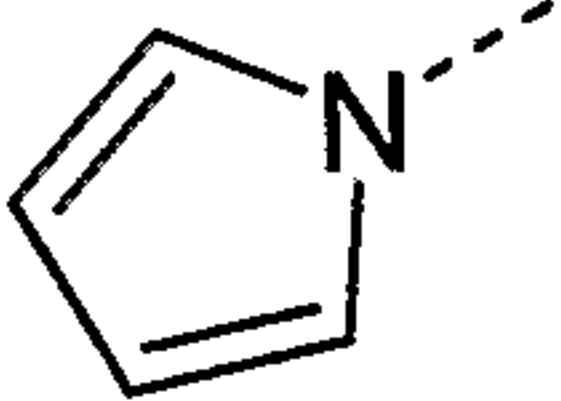
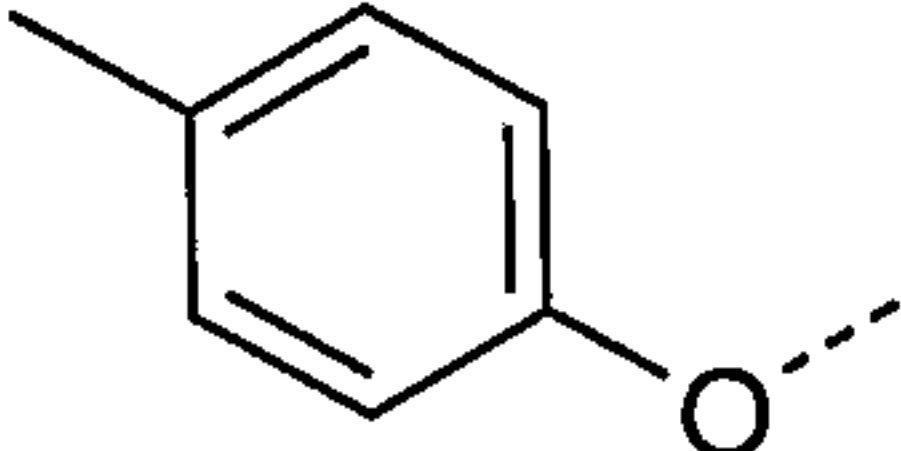


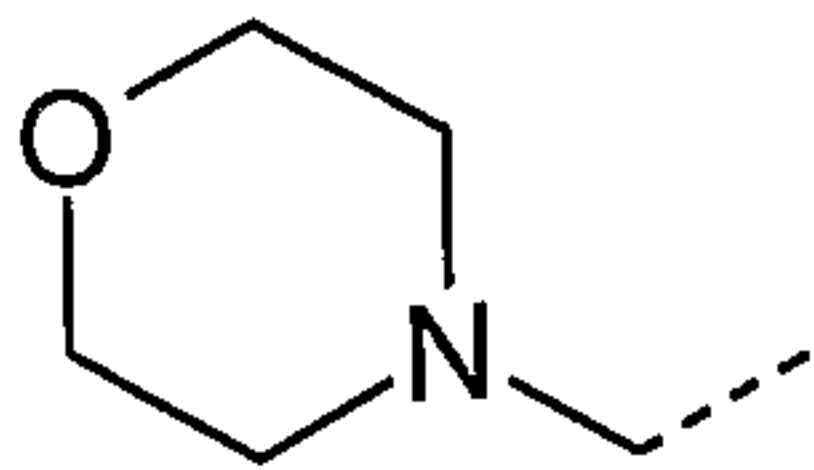
Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)
140		Aldrich	382	2.81
141		Aldrich	384	2.76

Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)
142		Aldrich	354	2.01
143		Aldrich	366	2.7
144		Aldrich	442	3.11
145		Aldrich	417	1.99
146		Aldrich	430	3.11
147		Aldrich	418	2.82

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Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	RetentionTime (Minutes)
148		ABCR	414	3
149		Enamine	416	2.38
150		Aldrich	380	2.81
151		ABCR	394	3.07
152		ABCR	421	3.4
153		Tim Tec	486	3.73

Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)
154		Farmaco, Edizione Scientifica (1957), 12 41-8	445	2.5
155		Zelinsky	431	2.38
156		Journal of the American Chemical Society (1948), 70 416	466	2.26
157		Aldrich	428	2.99
158		Aldrich	401	2.84
159		Tim Tec	444	3.31

Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)
160		Maybridge	437	2.73

Example 161:**6-cyclopentyl-9-[(3-methoxyphenyl)amino]-2-methyl-2,6,8,10-****5 tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

3-methoxyaniline (Aldrich, 22 mg, 0.18 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, (50 mg, 0.18 mmol), and p-toluene sulphonic acid (84 mg, 0.44 mmol) were combined in 4-methyl-2-pentanol (1 mL).

The solution was heated at reflux under a blanket of nitrogen for 12 hours. The reaction mixture was cooled and passed through an SCX-2 column washed with methanol. The crude product were washed off with 7N ammonia in methanol and then concentrated *in vacuo*. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid. (39 mg, 59%); MS m/z 368 [M+H]⁺, Retention Time 2.46 mins.

15 The following examples were prepared by an analogous process to that used in the preparation of Example 161 utilising the appropriate substituted anilines available as indicated.

Example 162:**20 6-cyclopentyl-9-[(3-ethoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one****Example 163:**

6-cyclopentyl-2-methyl-9-[(3-methylsulfanylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 164:

5 3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzonitrile

Example 165:

10 9-[(3-acetylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 166:

15 6-cyclopentyl-9-[(3-ethylphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 167:

3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

20 **Example 168:**

6-cyclopentyl-9-[(3-ethynylphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 169:

25 9-[(3-benzoylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 170:

30 3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzenesulfonamide

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Example 171:

6-cyclopentyl-2-methyl-9-[(3-phenylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

5 **Example 172:**

6-cyclopentyl-2-methyl-9-[(3-methylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 173:

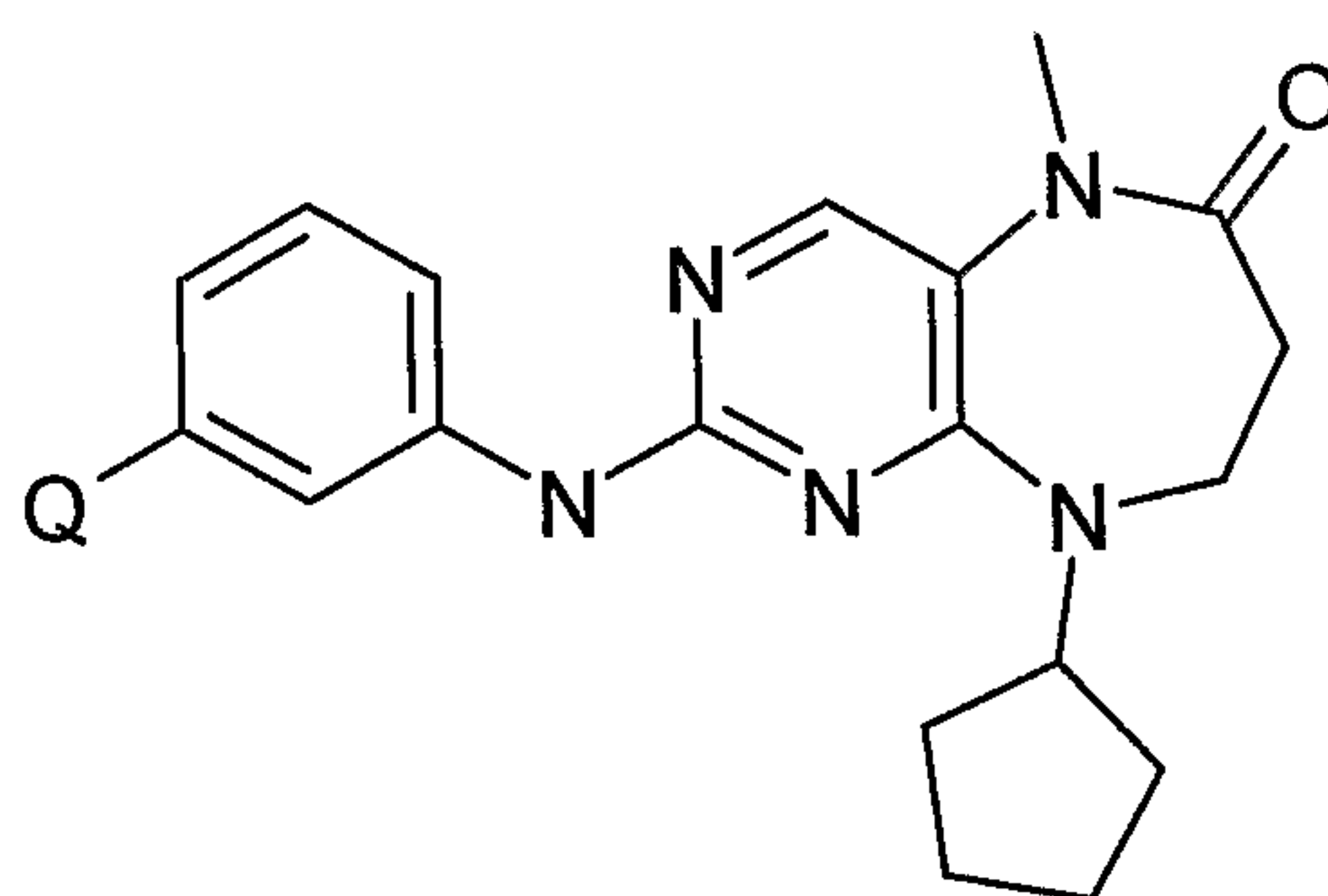
10 **6-cyclopentyl-9-[[3-(hydroxymethyl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

Example 174:

15 **6-cyclopentyl-2-methyl-9-[(3-propan-2-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

Example 175:

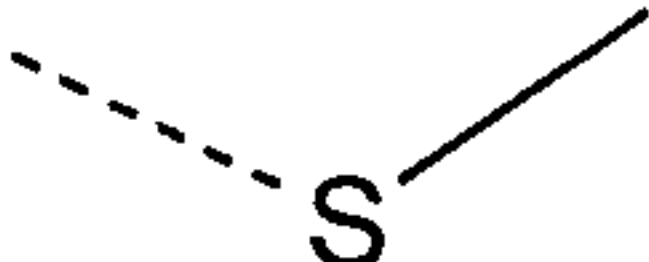
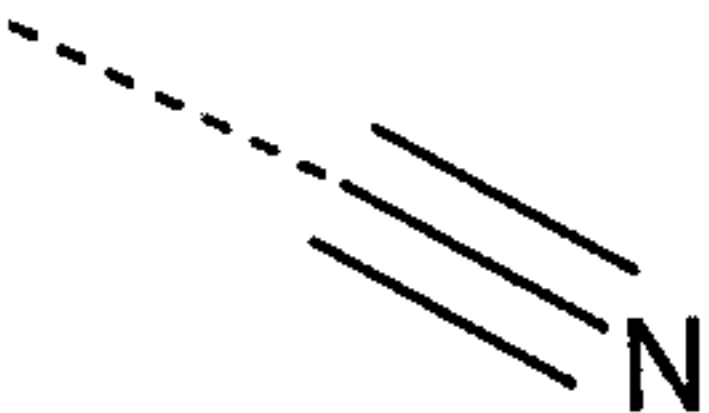
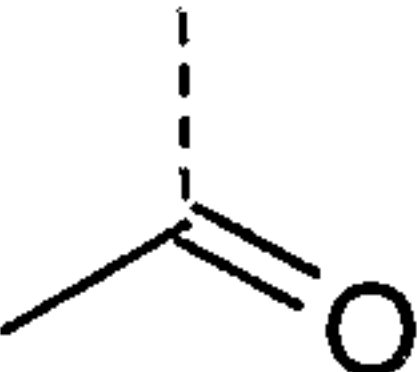
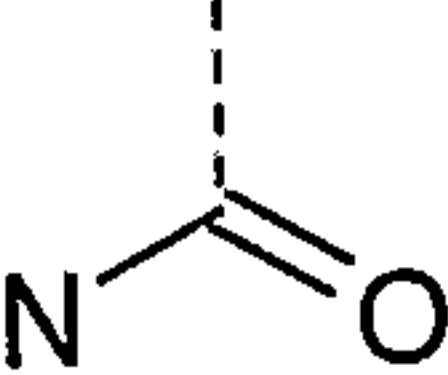
N-[2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]benzenesulfonamide



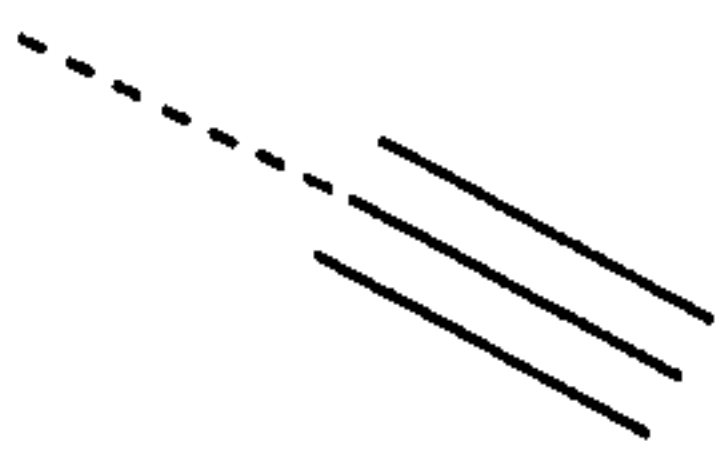
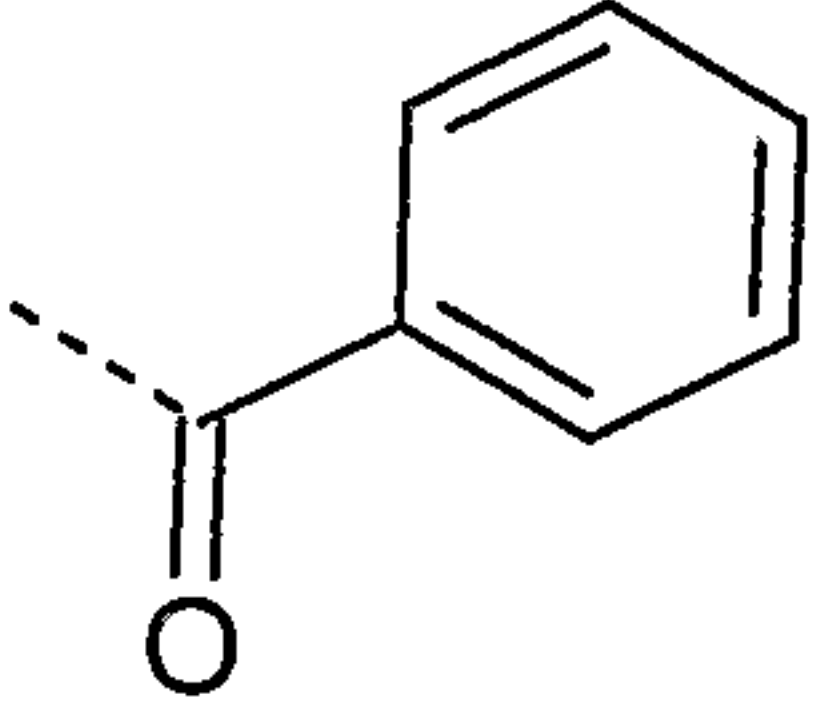
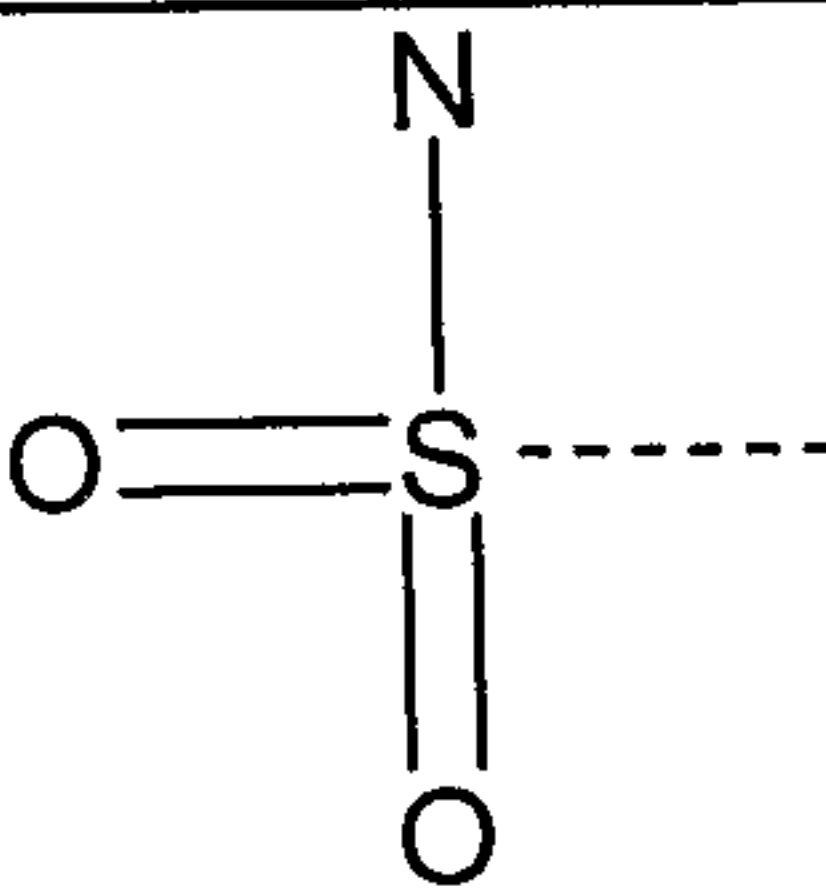
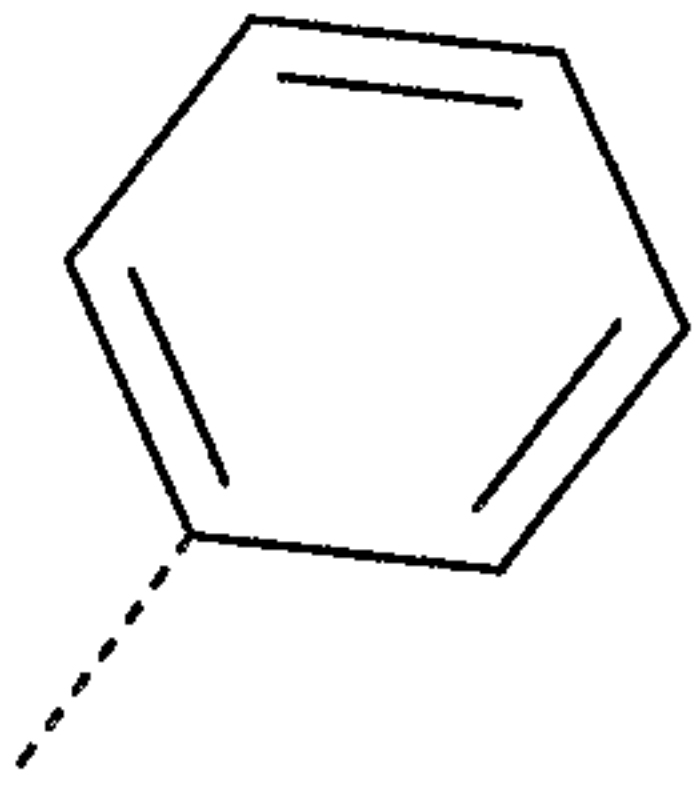
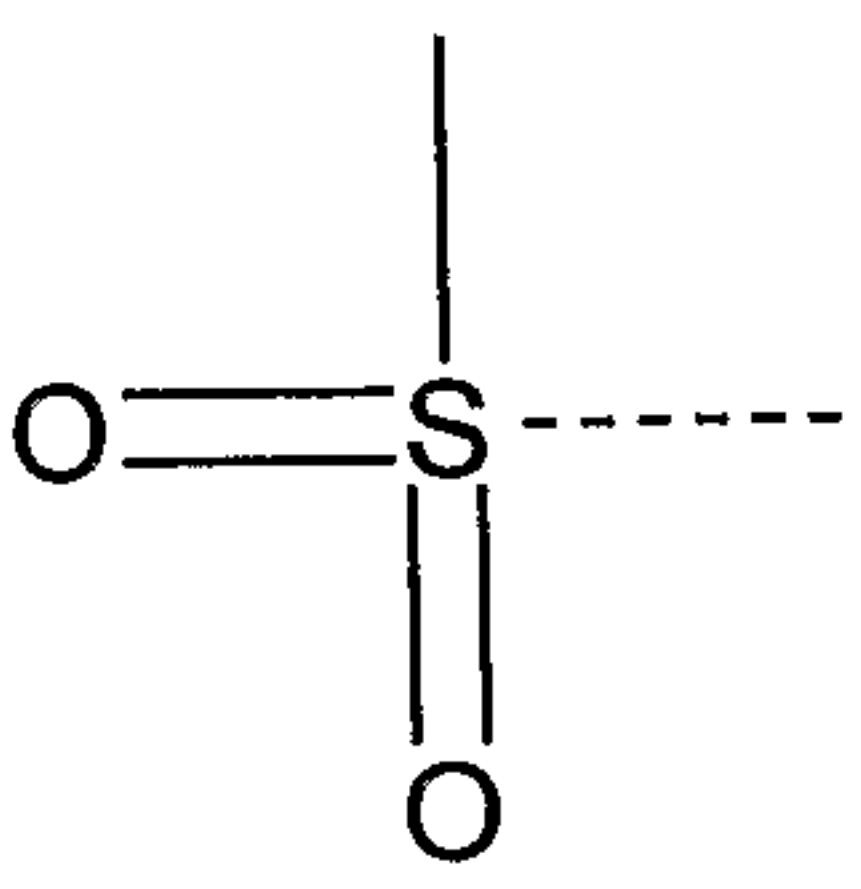
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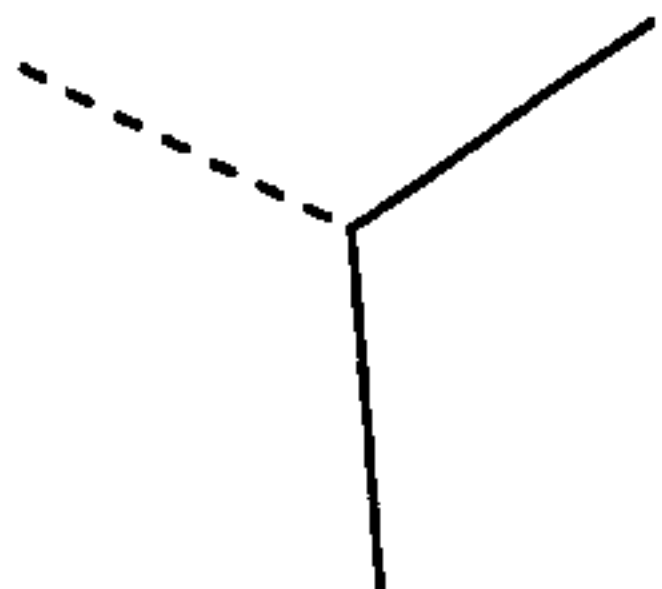
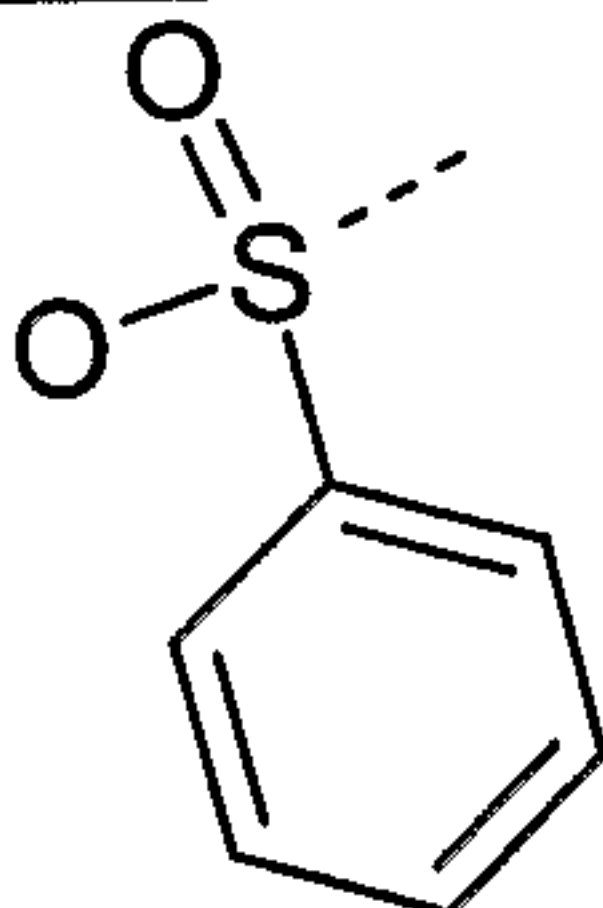
Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)

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Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	RetentionTime (Minutes)
162		Aldrich	382.23	2.63
163		Aldrich	384.19	2.65
164		Aldrich	363.18	2.4
165		Aldrich	380.23	2.3
166		Aldrich	366.21	2.78
167		Aldrich	381.2	1.78

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Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	RetentionTime (Minutes)
168		Aldrich	362.17	2.57
169		Aldrich	442.3	2.72
170		ABCR	417.21	1.87
171		ABCR	414.26	2.94
172		Enamine	416.21	2.09
173		Aldrich	368.16	1.96

Example	Q	Substituted Aniline Supplier or Source	MS m/z [M+H] ⁺	Retention Time (Minutes)
174		ABCR	380.26	2.92
175		Journal of the Chemical Society (1938), 899-905.	492.19	1.61

Example 176:

N-[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methoxy-phenyl]acetamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), N-(3-amino-4-methoxy-phenyl)acetamide (Aldrich, 77 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) heated together in 4-methyl-2-pentanol (4ml) at 120°C for 22 hours. The reactions were cooled to ambient temperature and then passed down a 5g SCX-2 column pre-wet with methanol. The column was eluted with 2M NH₃/MeOH and the solvent evaporated. The resultant material was purified by reverse phase HPLC to give the title compound as a white solid (46 mg, 30%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.58 (m, 6H), 1.88 (m, 2H), 1.99 (s, 3H), 2.56 (m, 2H), 3.17 (s, 3H), 3.59 (m, 2H), 3.83 (s, 3H), 4.85 (m, 1H), 6.93 (d, 1H), 7.05 (d, 1H), 7.56 (s, 1H), 8.02 (s, 1H), 8.37 (s, 1H), 9.68 (s, 1H); MS m/z 425 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the preparation of Example 176 utilising the appropriate substituted anilines available from Aldrich

5 **Example 177:**

N-[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]acetamide

MS m/z 395 [M+H]⁺. Retention Time 2.65 mins

10 **Example 178:**

6-cyclopentyl-9-[[5-(hydroxymethyl)-2-methyl-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

MS m/z 382 [M+H]⁺. Retention Time 2.76 mins

15 **Example 179:**

6-cyclopentyl-9-[[3-(2-hydroxyethyl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 134 mg, 0.48 mmol), 2-(3-aminophenyl)ethanol (ABChem Inc, 92 mg, 0.48
20 mmol) and p-toluenesulphonic acid monohydrate (227 mg, 1.19 mmol) were heated at 140°C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction solution was loaded onto an SCX-3 column pre-wet with Methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with 2% 7N ammonia/methanol to elute the crude product. Fraction containing products were evaporated and the resultant material
25 purified by reverse phase HPLC to give the title compound as a white solid (92 mg, 50 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.59 – 1.60 (4H, m), 1.69 – 1.71 (2H, m), 1.96 – 1.98 (2H, m), 2.53 – 2.59 (2H, t), 2.69 (2H, t), 3.18 (3H, s), 3.60 (2H, t), 3.62 (2H, t), 4.62 (1H, s), 4.87 (1H, ms), 6.77 (1H, d), 7.14 (1H, t), 7.46 – 7.49 (1H, m), 7.66 (1H, t), 8.04 (1H, s), 9.10 (1H, s); MS m/z 382 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 183 utilising the appropriate substituted aniline available from sources as indicated

5 **Example 180:**

6-cyclopentyl-2-methyl-9-[[3-(2-morpholin-4-ylethoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Substituted aniline available from ABCR

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.61 (4H, d), 1.71 (2H, s), 1.97 (2H, s), 2.48 (4H, m), 2.59
10 (2H, t), 2.68 (2H, t), 3.17 (3H, s), 3.59 (4H, m), 3.62 (2H, m), 4.05 (2H, t), 4.80 – 4.90 (1H, m), 6.49 - 6.52 (1H, d), 7.13 (1H, t), 7.20 (1H, d), 7.51 (1H, t), 8.05 (1H, s), 9.13 (1H, s); MS m/z 467 [M+H]⁺.

Example 181:

15 **3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methoxy-N-(1-methyl-4-piperidyl)benzamide**

Synthetic route for substituted aniline available from WO06/018220

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.48 – 1.62 (8H, m), 1.71 – 1.77 (2H, d), 1.80 – 2.00 (4H, m), 2.17 (3H, s), 2.56 (2H, t), 2.77 (2H, d), 3.17 (3H, s), 3.59 (2H, t), 3.71 (1H, m), 3.91 (3H,
20 s), 4.74 – 4.79 (1H, m), 7.05 (1H, d), 7.48 - 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, d), 8.04 (1H, s), 8.57 (1H, d); MS m/z 509 [M+H]⁺.

Example 182:

25 **6-cyclopentyl-9-[[5-(3-dimethylaminopyrrolidin-1-yl)-2-methoxy-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.53 mmol), 1-(3-amino-4-methoxy-phenyl)-N,N-dimethyl-pyrrolidin-3-amine (Intermediate 50; 141 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (255 mg, 1.34 mmol) were combined and heated in 4-methyl-2-pentanol (4 mL)
30 at 140°C for 2 hours. The reaction mixture was loaded onto a 20g SCX-2 column was pre-wet with methanol. The column was washed with methanol twice to remove p-Toluene Sulphonic

acid and then washed twice with 2% 7N ammonia/methanol to elute the crude product..

Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a white solid (140mg, 51.6%).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.48 – 1.62 (8H, m), 1.71 – 1.77 (2H, d), 1.80 – 2.00 (4H, m), 2.17 (3H, s), 2.56 (2H, t), 2.77 (2H, d), 3.17 (3H, s), 3.59 (2H, t), 3.71 (1H, m), 3.91 (3H, s), 4.74 – 4.79 (1H, m), 7.05 (1H, d), 7.48 - 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, d), 8.04 (1H, s), 8.57 (1H, d); MS m/z 508 [M+H]⁺.

Example 183:

10 6-cyclopentyl-2-methyl-9-[(3-morpholin-4-ylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.53 mmol), 3-(morpholinosulphonyl)aniline (Fluorochem; 130 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (255 mg, 1.34 mmol) were combined and heated at 140°C in 4-methyl-2-pentanol (4 mL) for 2 hours. The mixture was cooled and methanol and dichloromethane added to dissolve the solid that formed. The mixture was absorbed on to an SCX –3 column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated to give a white crystalline solid. This was suspended in methanol and filtered off and dried at 140°C under vacuum in a desiccator to give the title compound as a white crystalline solid (200mg, 77%)

¹H NMR (399.9 MHz, DMSO-d₆) δ1.57 – 1.70 (6H, m), 1.94 - 2.00 (2H, m), 2.57 - 2.60 (2H, m), 2.88 (4H, m), 3.18 (3H, s), 3.61 - 3.66 (6H, m), 4.91 (1H, m), 7.22 - 7.25 (1H, m), 7.53 (1H, t), 7.99 - 8.02 (1H, m), 8.09 (1H, s), 8.23 (1H, t), 9.57 (1H, s)
MS m/z 487 [M+H]⁺.

Example 184:

3-chloro-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 52, 100 mg, 0.35 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 124 mg, 0.44 mmol) and p-toluenesulphonic acid monohydrate

(168 mg, 0.88 mmol) were heated at 140°C in 4-methyl-2-pentanol (2.5 mL) for 3 hours. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto and SCX-3 column and washed with methanol. Elution of the product with ammonia / methanol, concentration and column chromatography (2% 7N ammonia in methanol/DCM) gave material that was further purified by reverse phase HPLC to give the title compound as a white foam (87 mg, 47 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.54 - 1.69 (6H, m), 1.86 - 1.89 (2H, m), 2.44 (6H, m), 2.59 (2H, m), 3.18 (3H, s), 3.37 - 3.42 (2H, m), 3.57 - 3.63 (6H, m), 4.69 - 4.77 (1H, m), 7.78 - 7.81 (1H, m), 7.97 (1H, d), 8.09 (1H, s), 8.20 (1H, s), 8.27 (1H, d), 8.40 (1H, t); MS m/z 528 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 184 utilising 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide Intermediate 55.

Example 185:

3-chloro-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.55 - 1.68 (8H, m), 1.77 (2H, s), 1.86 - 1.98 (4H, m), 2.18 (3H, s), 2.59 (2H, m), 2.78 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.69 - 3.77 (1H, m), 4.73 (1H, m), 7.79 - 7.82 (1H, m), 8.00 (1H, d), 8.09 (1H, s), 8.19 (2H, d), 8.26 (1H, d); MS m/z 512 [M+H]⁺.

Example 186:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-hydroxy-N-(1-methyl-4-piperidyl)benzamide

To pyridine (1 mL) was cautiously added conc HCl (1 mL). The mixture was heated at 200°C until no more water was evolved. The mixture was cooled and 4-[(2-Cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-(1-

methyl-4-piperidyl)benzamide (Example 1, 100 mg, 0.2 mmol) was added and the solution reheated and stirred at 200°C for 30 minutes. The solution was cooled and water added followed by pH adjustment to neutral pH by addition of NaHCO₃.

The aqueous solution was adsorbed on an SCX-3 column pre-wet with MeOH. The column
5 was washed with MeOH and water and MeOH. Product was removed from the column by addition of NH₃/MeOH (2N). Combined fractions were evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a gum which on trituration with DCM / hexane gave an amorphous solid (17 mg, 17 %)

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.50-1.85 (m, 10H), 1.85-2.10 (m, 4H), 2.20 (s, 3H),
10 2.55-2.68 (m, 2H), 2.70-2.85 (m, 2H), 3.20 (s, 3H), 3.55-3.70 (m, 2H), 3.60-3.80 (m, 1H), 4.75-4.90 (m, 1H), 7.28-7.35 (d, 1H), 7.38 (s, 1H), 7.83 (s, 1H), 7.95-8.05 (d, 1H), 8.08 (s, 1H), 8.13-8.23 (d, 1H), 10.2-10.5 (bs, 1H); MS m/z 494 [M+H]⁺.

Example 187:

15 **4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2,6-difluoro-N-(1-methyl-4-piperidyl)benzamide**

10-amino-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 57, 75 mg, 0.29 mmol), 4-bromo-2,6-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 58, 105 mg, 0.31 mmol) and caesium carbonate (187 mg,
20 0.57 mmol) were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Bis(dibenzylideneacetone)palladium (16 mg, 0.028 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (15 mg, 0.026 mmol) were added and the mixture heated to 100 °C overnight. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with DCM and the filtrate added to a 5g SCX-2 column pre-wet with
25 MeOH (2 column volumes), flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH and evaporated to a brown gum. The resultant material was purified by reverse phase HPLC to yield the title compound as a cream solid (107 mg, 73%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.59 (m, 4H), 1.72 (m, 4H), 2.04 (m, 4H), 2.16 (m, 2H),
30 2.29 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.01 (m, 1H), 4.86 (m, 1H), 5.83 (d, 1H), 7.10 (s, 1H), 7.28 (s, 1H), 7.31 (s, 1H), 7.93 (s, 1H); MS m/z 514 [M+H]⁺.

Example 188:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

5 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59, 87 mg, 0.32 mmol) and caesium carbonate (211 mg, 0.65 mmol) were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Bis(dibenzylideneacetone)palladium (11 mg, 0.019 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (17 mg, 0.029 mmol) were added and the mixture heated to 100 °C overnight. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with DCM and the filtrate added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), washed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH and evaporated to a brown gum. The resultant material
10 was purified by reverse phase HPLC to yield the title compound as a white solid (34 mg, 19%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.60 (m, 4H), 1.75 (m, 4H), 2.05 (m, 4H), 2.17 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.30 (s, 3H), 3.71 (m, 2H), 4.01 (m, 1H), 4.88 (m, 1H), 6.59 (m, 1H), 7.29 (m, 1H), 7.82 (m, 1H), 7.96 (s, 1H), 8.46 (m, 1H); MS m/z 515
20 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 188 utilising 4-amino-2-fluoro-N-(1-methyl-4-piperidyl)benzamide Intermediate 61.

25

30 **Example 189:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

¹H NMR (399.902 MHz, CDCl₃) δ 1.59 (m, 4H), 1.73 (m, 4H), 2.05 (m, 4H), 2.18 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.03 (m, 1H), 4.88 (m, 1H), 6.56 (m, 1H), 7.12 (m, 2H), 7.87 (m, 1H), 7.94 (s, 1H), 8.01 (m, 1H); MS m/z 496 [M+H]⁺.

Example 190:

methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-hydroxy-benzoate

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 180 mg, 0.64 mmol) and methyl 3-hydroxy-4-aminobenzoate (ABCR, 123 mg, 0.73 mmol) was taken up in ethanol (4 mL) and water (12 mL). To this was added concentrated hydrochloric acid (36%; 130 µl). The reaction was heated to 80°C and stirred overnight.. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~30 mL with water and the solution basified to pH 9 by addition of a few drops of aq. Ammonia. The resultant mixture was extracted with DCM (2 x 50 mL). A solid persisted at the phase boundary. This solid was collected by suction filtration and dried to give the title compound as a purple/grey solid (64 mg).

20 Combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to a pink/brown solid which was taken up in small amount (~5 mL) of DCM and sonicated for 5 minutes. The solid was then collected by suction filtration and dried to give the title compound as a dusky pink solid (79 mg)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.56 - 1.75 (m, 6H), 1.94 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.80 (s, 3H), 4.82 (m, 1H), 7.44 (m, 2H), 7.84 (s, 1H), 8.09 (s, 1H), 8.35 (d, 1H), 10.53 (s, 1H); MS m/z 412 [M+H]⁺.

30 **Example 191:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

A solution of 4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 108mg, 0.43mmol) in EtOH (2 mL) was added to 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol). Water (6 mL) was added followed by concentrated hydrochloric acid (36%, 70 ul) and the solution heated at 80°C for 28 hours and then left to cool over the weekend. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol. Product was eluted with 2M NH₃/MeOH. Solvent evaporation gave crude product as a gum which was purified by reverse phase HPLC to yield the title compound as a white solid (71 mg, 40 %)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.68 (m, 6H), 1.97 (m, 2H), 2.44 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (m, 2H), 3.58 (m, 4H), 3.63 (m, 2H), 4.84 (m, 1H), 7.77 (m, 4H), 8.08 (s, 1H), 8.16 (t, 1H), 9.45 (s, 1H); MS m/z 494 [M+H]⁺.

15

Example 192:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-diethylaminoethyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), 4-amino-N-(2-diethylaminoethyl)benzamide (Timtec, 101 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 100°C for 24 hours. The crude reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with MeOH. The column was washed with MeOH and the product eluted with 2M NH₃/MeOH. Solvent evaporation gave material that was purified by reverse phase HPLC to yield the title compound as a white solid (123 mg, 71 %)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.98 (t, 6H), 1.66 (m, 6H), 1.96 (m, 2H), 2.52 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.30 (s, 2H), 3.63 (m, 2H), 4.84 (m, 1H), 7.73 (d, 2H), 7.80 (d, 2H), 8.08 (s, 1H), 8.12 (t, 1H), 9.45 (s, 1H); MS m/z 480 [M+H]⁺.

30

Example 193:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methyl-N-(1-methyl-4-piperidyl)benzamide

A solution of 4-amino-3-methyl-N-(1-methyl-4-piperidyl)benzamide (Intermediate 63, 53 mg, 0.214 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 60 mg, 0.214 mmol) and p-toluenesulphonic acid monohydrate (102 mg, 0.535 mmol) in 4-methyl-2-pentanol (4 mL) was heated at 100 °C overnight. The reaction was cooled to room temperature (solid formed) dissolved in MeOH and added to a 2g SCX-2 column pre-wet with MeOH (2 column volumes). The column was washed with MeOH (2 column volumes) and then product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant material was taken up in DCM and purified on silica eluting with a gradient of 0 – 10% MeOH / DCM then 10% MeOH / DCM. Fractions containing product were combined and evaporated to a clear gum to which ether was added and re-evaporated to a white solid which was further purified by reverse phase HPLC.

¹H NMR (399.902 MHz, CDCl₃) δ 1.54 - 1.70 (m, 6H), 1.75 (m, 2H), 2.02 (m, 4H), 2.17 (m, 2H), 2.31 (s, 3H), 2.37 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.29 (s, 3H), 3.68 (m, 2H), 3.99 (m, 1H), 4.85 (m, 1H), 5.86 (d, 1H), 6.79 (s, 1H), 7.59 (m, 2H), 7.92 (s, 1H), 8.32 (d, 1H); MS m/z 492 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 193 utilising 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide Intermediate 65

Example 194:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

¹H NMR (399.902 MHz, CDCl₃) δ 1.53 - 1.80 (m, 8H), 2.03 (m, 4H), 2.16 (m, 2H), 2.30 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.69 (m, 2H), 3.97 (m, 1H), 4.87 (m, 1H), 5.85 (d, 1H), 7.22 (m, 1H), 7.52 (m, 2H), 7.95 (s, 1H), 8.57 (m, 1H); MS m/z 496 [M+H]⁺.

Example 195:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-methoxyethoxy)-N-(1-methyl-4-piperidyl)benzamide

To a suspension of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-(2-methoxyethoxy)benzoic acid (Intermediate 66, 55 mg, 0.12 mmol) in DMF (2 mL) was added DIPEA (42 μ L, 0.16 mmol) and the mixture stirred for 5 minutes. HATU (60 mg, 0.16 mmol) was added to the resultant straw coloured solution. The solution was stirred for a further 10 minutes before addition of 4-amino-1-methylpiperidine (18 mg, 0.16 mmol) in DMF (0.5 mL). The reaction was stirred at ambient temperature for 6 hours and the crude reaction mixture was purified by reverse phase HPLC to afford the title compound as a white solid (50 mg, 76 %)

^1H NMR (400.132 MHz, DMSO- d_6) δ 1.55 - 1.83 (m, 10H), 1.89 - 2.10 (m, 4H), 2.23 (s, 3H), 2.59 (m, 2H), 2.84 (m, 2H), 3.18 (s, 3H), 3.38 (s, 3H), 3.64 (m, 2H), 3.73 - 3.81 (m, 3H), 4.26 (m, 2H), 4.79 (m, 1H), 7.51 (d, 1H), 7.54 (m, 1H), 7.81 (s, 1H), 8.06 (d, 1H), 8.09 (s, 1H), 8.42 (d, 1H); MS m/z 552 $[\text{M}+\text{H}]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 195 utilising a 2.0M methylamine solution in THF

Example 196:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-methoxyethoxy)-N-methyl-benzamide

^1H NMR (400.132 MHz, CDCl_3) δ 1.55 - 1.81 (m, 6H), 2.03 (m, 2H), 2.67 (m, 2H), 3.01 (d, 3H), 3.29 (s, 3H), 3.47 (s, 3H), 3.69 (m, 2H), 3.80 (m, 2H), 4.28 (m, 2H), 4.88 (m, 1H), 6.07 (m, 1H), 7.28 (m, 1H), 7.46 (m, 1H), 7.80 (s, 1H), 7.95 (s, 1H), 8.52 (d, 1H); MS m/z 469

Example 197:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)-3-propan-2-yloxy-benzamide

To a solution of 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoic acid (Intermediate 69; 49 mg, 0.11 mmol) in DMF (2 mL) was added DIPEA (42 μ L, 0.24 mmol) and HATU (61 mg, 0.16 mmol). The solutions were stirred for 5 minutes before addition of 4-amino-1-methylpiperidine (ABCR, 16 mg, 0.14 mmol). The reaction mixture was stirred, at ambient temperature, overnight.

The crude reaction mixture was purified by reverse phase HPLC to afford the title compound as a white solid (29 mg, 49%)

^1H NMR (400.132 MHz, DMSO- d_6) δ 1.36 (d, 6H), 1.54 - 1.80 (m, 10H), 1.94 (m, 4H), 2.17 (s, 3H), 2.59 (m, 2H), 2.78 (m, 2H), 3.18 (s, 3H), 3.64 (m, 2H), 3.74 (m, 1H), 4.78 (m, 2H), 7.48 (m, 1H), 7.52 (m, 1H), 7.67 (s, 1H), 8.04 (d, 1H), 8.08 (s, 1H), 8.41 (d, 1H); MS m/z 536 $[\text{M}+\text{H}]^+$.

15

Example 198:

N-cyclohexyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-dimethylaminoethoxy)benzamide

To a stirred solution of Methyl 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-(2-dimethylaminoethoxy)benzoate (Intermediate 72; 41 mg, 0.08 mmol) in Ethanol (2 mL) was added a solution of lithium hydroxide (8 mg, 0.33 mmol) in water (1 mL). The reaction was heated at 100°C by microwave irradiation with stirring, for 30 minutes, cooled, evaporated and the residue diluted with water (5 mL). The resultant solution was treated with a few drops of 2M HCl (aq.) so as to adjust pH to 2-3. The aqueous solution was evaporated to dryness to give the carboxylic acid as a pale yellow gum, which was dissolved in DMF (1 mL) and treated with DIPEA (25 μ L, 0.14 mmol) and HATU (40 mg, 0.11 mmol). Cyclohexylamine (11 μ L, 0.10 mmol) was added and reaction mixture left to stir, at ambient temperature, overnight.

The crude reaction mixture was purified by reverse phase HPLC to afford the title compound as an off white solid (14 mg, 32 %)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.10 - 1.37 (m, 6H), 1.55 - 1.99 (m, 12H), 2.28 (s, 6H), 2.59 (m, 2H), 2.65 (t, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.77 (m, 1H), 4.21 (t, 2H), 4.80 (m, 1H), 7.50 (m, 1H), 7.55 (m, 1H), 7.98 (d, 1H), 8.09 (s, 1H), 8.39 (m, 1H), 8.41 (s, 1H); MS m/z 551 [M+H]⁺.

5

Example 199:**4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide**

To a solution of 4-amino-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide
10 (Intermediate 74, 104 mg, 0.33 mmol) 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 91 mg, 0.32 mmol) in anhydrous 1,4-dioxane (4 mL) was added caesium carbonate (222 mg, 0.68 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone) palladium (II) (21 mg, 0.07 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (21 mg, 0.11 mmol). The reaction was heated by microwave
15 irradiation at 150°C for 60 minutes. Further portions of 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (19 mg) & Tris(dibenzylideneacetone) palladium (II) (25 mg) added and mixture heated on hot plate at 100°C overnight. The reaction mixture was cooled and diluted to 10 mL with DCM. Insoluble material was filtered and the filter cake washed
20 with DCM. Evaporation to dryness of filtrate afforded a brown gum, which was taken up in methanol and poured onto an SCX-2 cartridge (5g, Silicycle). The Cartridge was washed with methanol (~75 mL) before eluting products with 2M ammonia in methanol (~50 mL). The ammoniacal fraction was evaporated to afford a brown gum which was purified by reverse phase HPLC to yield the title compound as a white solid (25 mg, 4 %)

25 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.51 - 1.97 (m, 14H), 2.17 (s, 3H), 2.59 (m, 2H), 2.78 (m, 2H), 3.18 (s, 3H), 3.62 (m, 2H), 3.74 (m, 1H), 4.74 (m, 1H), 7.86 (m, 2H), 8.08 (s, 1H), 8.25 (d, 1H), 8.30 (d, 1H), 8.57 (s, 1H) MS m/z 562 [M+H]⁺.

30 **Example 200:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-ethoxy-N-(1-methyl-4-piperidyl)benzamide

A solution of HATU (63 mg, 0.165 mmol) in DMA (1 mL) was added to a mixture 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-ethoxy-benzoic acid (Intermediate 75, 64 mg, 0.15 mmol), DIPEA (79 μ L, 0.45 mmol) and the amine in DMA (1 mL). The resulting mixture was stirred at room temperature overnight. The reaction mixture was added to an SCX-3 column pre-wet with Methanol, washed with methanol and product eluted with Ammonia in Methanol. Product containing fractions were evaporated and the resultant material purified by column chromatography, eluting with 0-10% 7N methanolic ammonia in DCM, to give the title compound as clear glass (64 mg, 82 %).

^1H NMR (399.9 MHz, CDCl_3) δ 1.51 (3H, t), 1.61 - 1.82 (8H, m), 2.03 - 2.09 (2H, m), 2.21 - 2.29 (4H, m), 2.38 (3H, s), 2.67 - 2.70 (2H, m), 2.90 - 2.93 (2H, m), 3.31 (3H, s), 3.70 - 3.73 (2H, m), 4.00 - 4.08 (1H, m), 4.22 (2H, q), 4.92 (1H, quin), 6.07 (1H, d), 7.27 (1H, dd), 7.42 (1H, d), 7.72 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 522 $[\text{M}+\text{H}]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 200 utilising the appropriate amines available from Aldrich

Example 201:

N-(1-azabicyclo[2.2.2]oct-8-yl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-ethoxy-benzamide

^1H NMR (399.9 MHz, CDCl_3) δ 1.51 (3H, t), 1.55 - 1.89 (10H, m), 2.06 - 2.03 (6H, m), 2.67 - 2.70 (2H, m), 2.84 - 2.97 (4H, m), 3.07 - 3.13 (1H, m), 3.31 (3H, s), 3.44 - 3.50 (1H, m), 3.70 - 3.73 (2H, m), 4.20 - 4.26 (1H, m), 4.22 (2H, q), 4.91 (1H, quin), 6.55 (1H, d), 7.34 (1H, dd), 7.47 (1H, d), 7.72 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 533 $[\text{M}+\text{H}]^+$.

Example 202:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-dimethylaminoethyl)-3-ethoxy-benzamide

¹H NMR (399.9 MHz, CDCl₃) δ1.52 (3H, t), 1.62 - 1.82 (6H, m), 2.04 - 2.09 (2H, m), 2.39 (6H, s), 2.64 - 2.71 (4H, m), 3.31 (3H, s), 3.58 - 3.62 (2H, m), 3.70 - 3.73 (2H, m), 4.24 (2H, q), 4.92 (1H, quin), 7.01 (1H, s), 7.38 (1H, dd), 7.49 (1H, d), 7.71 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 494 [M+H]⁺.

5

Example 203:

3-chloro-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

10 10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76, 100mg, 0.39mmol) and 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 79; 127 mg, 0.47 mmol) were suspended in 4-methyl-2-pentanol (3 mL) and p-toluenesulphonic acid monohydrate (74 mg, 0.97 mmol) added. The mixture was heated at 140°C for 4 hours. The mixture was cooled causing a white solid to
15 formed. The whole mixture was diluted with MeOH to give a solution which was absorbed on to an SCX-3 column, washed with methanol and eluted with ammonia/methanol. Concentration and column chromatography (1-2-3-5% NH₃ in MeOH/DCM) of the product containing fractions gave the title compound as a white solid (58mg, 31%).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.23 (6H, d), 1.54 - 1.64 (2H, m), 1.75 - 1.78 (2H, m),
20 1.91 - 1.97 (2H, m), 2.18 (3H, s), 2.60 (2H, m), 2.78 (2H, d), 3.18 (3H, s), 3.61 (2H, m), 3.69 - 3.75 (1H, m), 4.72 - 4.78 (1H, m), 7.81 - 7.84 (1H, m), 7.99 (1H, d), 8.09 (2H, d), 8.21 (1H, d), 8.32 (1H, d); MS m/z 486 [M+H]⁺.

Example 204:

25 **3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzoic acid**

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76; 739 mg, 2.9 mmol), 4-amino-3-methoxy-benzoic acid (Aldrich, 534 mg, 3.2 mmol), 4:1 Water / Etanol (6 mL) and concentrated aqueous hydrochloric acid (0.485 mL,
30 5.8 mmol) were combined and heated at reflux overnight under nitrogen. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with water followed

by diethylether to give the title compound as an off white solid as the Hydrochloride salt (673 mg, 55 %)

¹H NMR (399.9 MHz, DMSO-d₆) : δ_H : 1.25 (d, 6H), 2.73(m, 2H), 3.19 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.89 (m, 1H), 7.59 (s, 1H), 7.67 (d, 1H), 8.20 (m, 2H), 9.55 (s, 1H); MS
5 m/z 386 [M+H]⁺.

Example 205:

3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-[2-(1-piperidyl)ethyl]benzamide

10 To a solution of the hydrochloride salt of 3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzoic acid (Example 204; 127 mg, 0.33 mmol) and 1-(2-aminoethyl)piperidine (Aldrich, 54uL, 0.38 mmol) and DIPEA (157 uL , 0.9 mmol) in anhydrous DMA (10 mL) at room temperature under nitrogen was added HATU (126 mg, 0.33 mmol) as a solid and the resulting solution stirred at room
15 temperature overnight. The reaction mixture was loaded onto a SCX-3 column pre-wet with Methanol and the column washed with Methanol. The column was eluted with Ammonia in Methanol and product containing fractions evaporated. The resultant material was dissolved in dichloromethane and chromatographed with 2-5-10-20% methanol/dichloromethane followed by 7N ammonia/methanol. Evaporation of product containing fractions gave a
20 yellow foam foam which was purified by reverse phase HPLC to yield the title compound as an off white gum (75 mg, 46 %)

¹H NMR (399.9 MHz, DMSO-d₆) : δ_H : 1.25 (d, 6H), 1.39 (m, 2H), 1.50 (m, 6H), 2.40 (m, 6H), 2.60 (m, 2H), 3.19 (s, 3H), 3.37 (m, 2H), 3.61 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.49 (m, 2H), 7.69 (s, 1H), 8.07 (s, 1H), 8.22 (tr, 1H), 8.41 (m, 1H); MS m/z 496 [M+H]⁺.

25

The following examples were prepared by an analogous process to that used in the preparation of Example 205 utilising the appropriate amines available from Aldrich or Matrix

Example 206:

30 **N-(1-azabicyclo[2.2.2]oct-8-yl)-3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide**

Example 207:

N-(2-dimethylaminoethyl)-3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

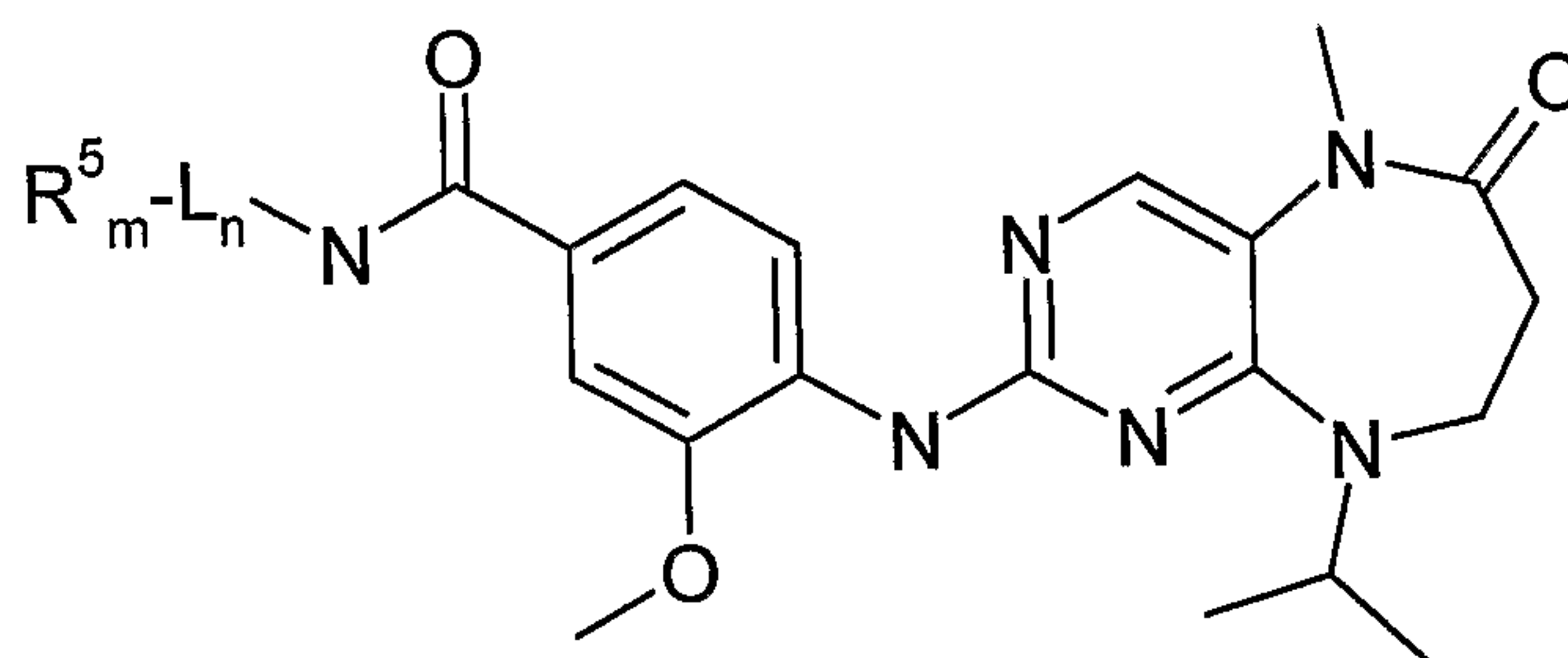
5

Example 208:

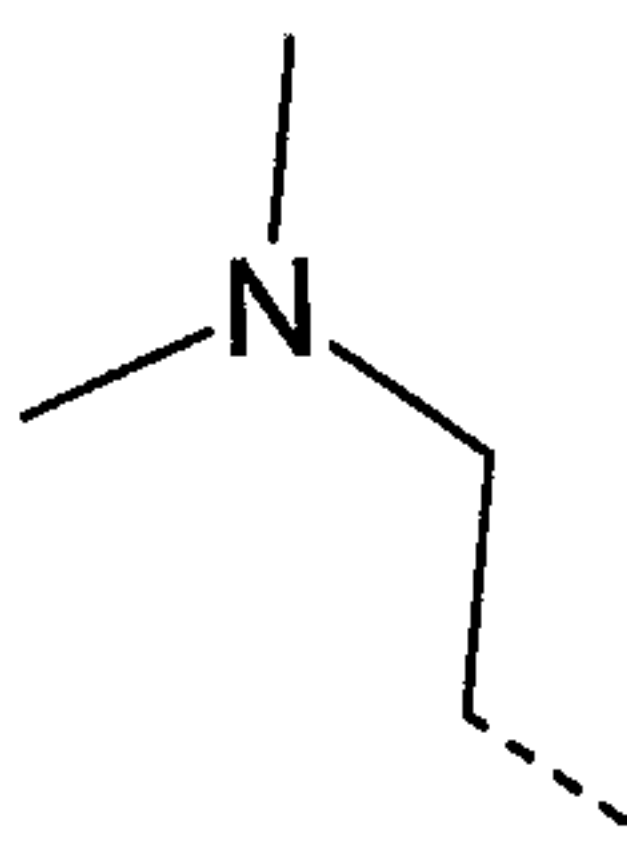
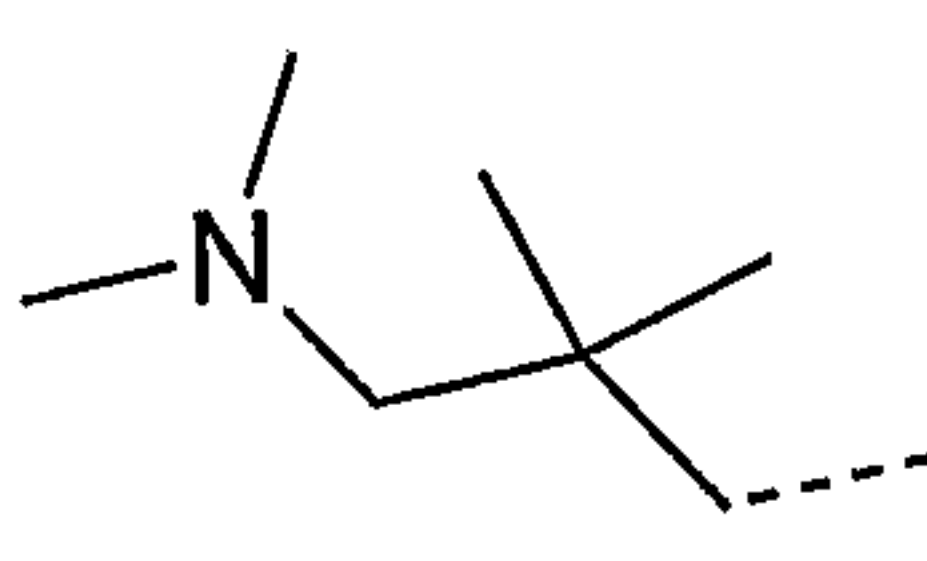
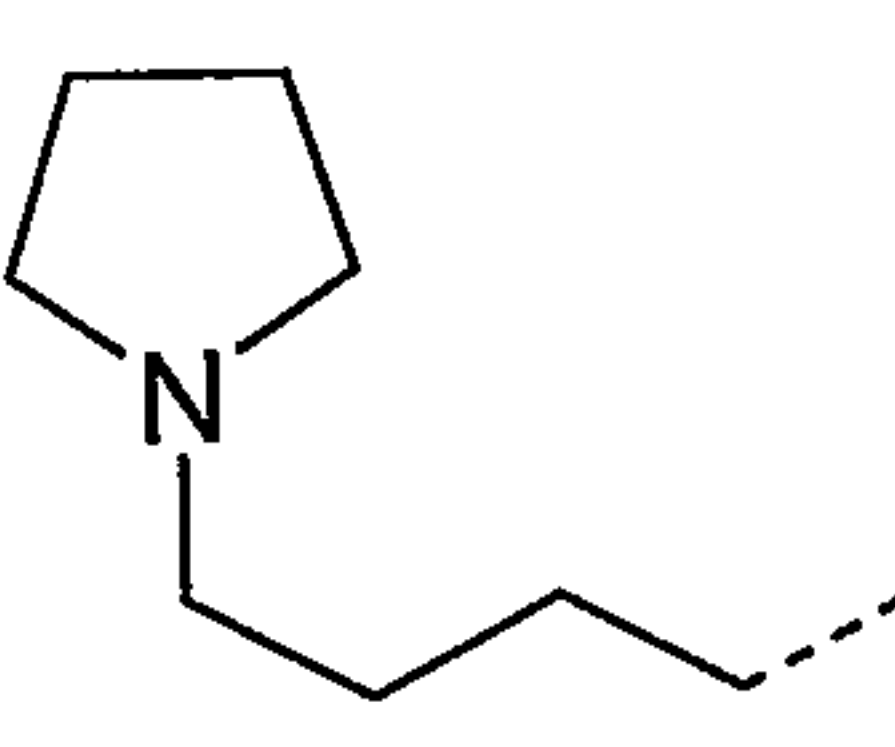
N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

10 **Example 209:**

3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(4-pyrrolidin-1-ylbutyl)benzamide



Example	R ⁵ _m -L _n -	¹ H NMR (400 MHz, DMSO-d ₆)	MS m/z [M+H] ⁺
206		δ _H : 1.23 (d, 6H), 1.30 (m, 1H), 1.60 (m, 2H), 1.85 (m, 2H), 2.60 (m, 2H), 2.70 (m, 4H), 2.90 (m, 1H), 3.11 (m, 1H), 3.20 (s, 3H), 3.62 (m, 2H), 3.95 (m, 4H), 4.81 (m, 1H), 7.49 (s, 1H), 7.56 (d, 1H), 7.30 (s, 1H), 8.06 (m, 2H), 8.42 (d, 1H);	494
207		δ _H : 1.23 (d, 6H), 2.19 (s, 6H), 2.40 (tr, 2H), 2.60 (m, 2H), 3.18 (s, 3H), 3.36 (m, 2H), 3.61 (d, 2H), 3.96 (s, 3H), 4.81 (m, 1H), 7.50 (m, 2H), 7.69 (s, 1H), 8.07 (s, 1H), 8.24 (tr, 1H),	456

Example	R ⁵ _m -L _n -	¹ H NMR (400 MHz, DMSO-d ₆)	MS m/z [M+H] ⁺
		8.41 (d, 1H);	
208		δ _H : 0.89 (s, 6H), 1.25 (d, 6H), 2.20 (s, 2H), 2.29 (s, 6H), 2.61 (m, 2H), 3.20 (m, 5H), 3.61 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.46 (m, 2H), 7.70 (s, 1H), 8.08 (s, 1H), 8.41 (m, 2H)	498
209		δ _H : 1.26 (d, 6H), 1.52 (m, 4H), 1.68 (m, 4H), 2.40 (m, 6H), 2.60 (m, 2H), 3.18 (s, 3H), 3.30 (m, 2H), 3.60 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.50 (m, 2H), 7.69 (s, 1H), 8.09 (s, 1H), 8.31 (tr, 1H), 8.41 (d, 1H)	510

Example 210:

4-[(6-ethyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-

5 **3-methoxy-N-(1-methyl-4-piperidyl)benzamide**

10-chloro-2-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

Intermediate 81; 180 mg, 0.75 mmol), 4-amino-3-methoxy-N-(1-methyl-4-

piperidyl)benzamide (WO06/018220, 198 mg, 0.75 mmol) and p-toluenesulphonic acid (357

mg, 1.88 mmol) were heated in 4-methyl-2-pentanol (3 mL) to 140 °C for 18 hours. The

10 reaction mixture was allowed to cool to room temperature and loaded onto a 10 g SCX-2

cartridge, washing with methanol (10 mL), water (10 mL) and methanol (10 mL) before the

product was eluted off with 7 N methanolic ammonia which on evaporation of product

containing fractions provided a brown oil which was purified by flash silica chromatography

(Companion, 40 g, 0-10% methanolic ammonia/DCM) to give a pale yellow glass which was

further purified by reverse phase HPLC to yield the title compound as a white solid (192 mg, 49 %).

¹H NMR (399.902 MHz, DMSO-d₆) δ 1.24 (t, 3H), 1.60 (qd, 2H), 1.73 - 1.81 (m, 2H), 1.95 (td, 2H), 2.18 (s, 3H), 2.62 - 2.64 (m, 2H), 2.79 (br d, 2H), 3.18 (s, 3H), 3.62 (q, 2H), 3.70 - 3.79 (m, 3H), 3.96 (s, 3H), 7.49 - 7.53 (m, 2H), 7.70 (s, 1H), 8.05 - 8.08 (m, 2H), 8.41 (d, 1H); MS m/z 468 [M+H]⁺.

Example 211:

3-methoxy-4-[[2-methyl-6-(2-methylpropyl)-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide
 10 10-chloro-6-methyl-2-(2-methylpropyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 84; 65 mg, 0.24 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220, 57 mg, 0.24 mmol) and p-toluene sulphonic acid (110 mg, 0.58 mmol) were taken up in 4-methyl-2-pentanol (1 mL) and heated to 160°C by
 15 microwave irradiation for 1 hour. The reaction mixture was diluted with methanol (5 mL) and water (2 mL) and resultant solution poured onto an SCX-3 cartridge (2 g). The cartridge was washed with methanol (~30 mL) before eluting products with 2M ammonia methanol (~20 mL). The Ammoniacal fraction was evaporated to give an amber gum which was purified by reverse phase HPLC to yield the title compound as a colourless glass (scratches down to a
 20 white solid) (80 mg, 75 %).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.90 (d, 6H), 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 2H), 2.11 (m, 1H), 2.17 (s, 3H), 2.64 (m, 2H), 2.78 (m, 2H), 3.19 (s, 3H), 3.50 (d, 2H), 3.68 - 3.79 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.70 (s, 1H), 8.07 (d, 1H), 8.08 (s, 1H), 8.34 (m, 1H); MS m/z 496 [M+H]⁺.

25

The following examples were prepared by an analogous process to that used in the preparation of Example 211 utilising the appropriate Chloropyrimidines indicated

Example 212A:

4-[(6-butan-2-yl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide
 30

Chloropyrimidine used - 2-butan-2-yl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one Intermediate 87

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.87 (t, 3H), 1.23 (d, 3H), 1.49 - 1.70 (m, 4H), 1.77 (m, 2H), 1.95 (t, 2H), 2.18 (s, 3H), 2.55 - 2.68 (m, 2H), 2.79 (m, 2H), 3.18 (s, 3H), 3.50 (m, 1H), 3.62 (m, 1H), 3.74 (m, 1H), 3.95 (s, 3H), 4.63 (m, 1H), 7.48 - 7.52 (m, 2H), 7.68 (s, 1H), 8.05 - 8.08 (m, 2H), 8.38 (m, 1H); MS m/z 496 [M+H]⁺.

Example 212B:

4-[(6-cyclobutyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used - 10-chloro-2-cyclobutyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one Intermediate 90

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.55 - 1.80 (m, 6H), 1.95 (m, 2H), 2.10 (m, 2H), 2.18 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 2.79 (m, 2H), 3.18 (s, 3H), 3.66 (m, 2H), 3.74 (m, 1H), 3.95 (s, 3H), 4.52 (m, 1H), 7.49 (m, 1H), 7.53 (m, 1H), 7.74 (s, 1H), 8.06 (d, 1H), 8.14 (s, 1H), 8.45 (d, 1H); MS m/z 494 [M+H]⁺.

Example 213:

4-[[6-(cyclopropylmethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used 10-chloro-2-(cyclopropylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one Intermediate 93

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.30 (m, 2H), 0.52 (m, 2H), 1.17 (m, 1H), 1.60 (m, 2H), 1.77 (m, 2H), 1.95 (m, 2H), 2.17 (s, 3H), 2.65 (m, 2H), 2.79 (m, 2H), 3.19 (s, 3H), 3.51 (d, 2H), 3.69 - 3.81 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.71 (s, 1H), 8.06 (d, 1H), 8.09 (s, 1H), 8.39 (m, 1H); MS m/z 494 [M+H]⁺.

Example 214:

3-methoxy-4-[(2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-[(2,4-dimethoxyphenyl)methyl]-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 96; 80 mg, 0.23 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 52 mg, 0.20 mmol) and p-toluene sulphonic acid (110 mg, 0.58 mmol) were taken up in 4-methyl-2-pentanol (1.5 mL) and heated at 160°C by
 5 microwave irradiation for 1 hour. The reaction mixture was dissolved in methanol (5 mL) and water (~5 mL) and poured directly onto an SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~30 mL), before elution of products with 2M ammonia in methanol (~30 mL). Evaporation of ammoniacal fraction gave a brown gum which was purified by reverse phase HPLC to yield the title compound as a white solid (9 mg, 10 %)

10 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.61 (m, 2H), 2.78 (m, 2H), 3.21 (s, 3H), 3.54 (m, 2H), 3.73 (m, 1H), 3.95 (s, 3H), 7.47 (m, 2H), 7.58 (m, 2H), 8.05 (d, 1H), 8.10 (s, 1H), 8.52 (m, 1H); MS m/z 440 [M+H]⁺.

Example 215:

15 **4-[(6-benzyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**

2-benzyl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 99; 42 mg, 0.14 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 33 mg, 0.13 mmol) and p-toluene sulphonic acid
 20 monohydrate (54 mg, 0.28 mmol) were taken up in 4-methyl-2-pentanol (1.5 mL) and heated at 160°C by microwave irradiation for 1 hour. The reaction mixture was dissolved in methanol (5 mL) and water (~5 mL) and poured directly onto an SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~30 mL), before elution of products with 2M ammonia in methanol (~30 mL). Evaporation of the ammoniacal fraction gave an amber film
 25 which was purified by reverse phase HPLC to yield the title compound as an off-white solid (33 mg, 48 %)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.57 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.68 (m, 2H), 2.77 (m, 2H), 3.22 (s, 3H), 3.59 - 3.77 (m, 3H), 3.91 (s, 3H), 4.87 (s, 2H), 7.24 - 7.38 (m, 6H), 7.43 (m, 1H), 7.71 (s, 1H), 8.01 (d, 1H), 8.14 (d, 1H), 8.15 (s, 1H); MS
 30 m/z 531 [M+H]⁺.

Example 216:

3-methoxy-4-[[2-methyl-6-[(2-methyl-1,3-thiazol-4-yl)methyl]-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide
 10-chloro-6-methyl-2-[(2-methyl-1,3-thiazol-4-yl)methyl]-2,6,9,11-

5 tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 101; 58 mg, 0.18 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 49 mg, 0.19 mmol) and p-toluene sulphonic acid (70 mg, 0.37 mmol) were taken up in 4-methyl-2-pentanol (2 mL) and heated to 160°C in microwave by microwave irradiation for 1 hour. The reaction mixture was dissolved in methanol (5 mL) and water (~5 mL) and poured directly onto an
 10 SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~30 mL), before elution of products with 2M ammonia in methanol (~30 mL). Evaporation of the ammoniacal fraction gave an amber film which was purified by reverse phase HPLC to yield the title compound as an off white solid (43 mg, 26 %)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.58 (m, 2H), 1.76 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.67 (s, 3H), 2.72 (m, 2H), 2.77 (m, 2H), 3.21 (s, 3H), 3.68 - 3.77 (m, 3H), 3.92 (s, 3H),
 15 4.85 (s, 2H), 7.23 (m, 1H), 7.29 (m, 1H), 7.44 (d, 1H), 7.71 (s, 1H), 8.04 (d, 1H), 8.08 (d, 1H), 8.13 (s, 1H); MS m/z 551 [M+H]⁺.

The following examples were prepared by an analogous process to that used in the preparation of Example 216 utilising the appropriate Chloropyrimidines indicated

Example 217:

4-[[6-(cyclobutylmethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used - 10-chloro-2-(cyclobutylmethyl)-6-methyl-2,6,9,11-

25 tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 102)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.60 (m, 2H), 1.73 - 2.07 (m, 10H), 2.17 (s, 3H), 2.61 (m, 2H), 2.69 - 2.81 (m, 3H), 3.17 (s, 3H), 3.66 - 3.80 (m, 5H), 3.95 (s, 3H), 7.47 - 7.51 (m, 2H), 7.71 (s, 1H), 8.07 (m, 2H), 8.35 (d, 1H); MS m/z 509 [M+H]⁺.

Example 218:

4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 188mg, 0.75mmol) and 10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one
5 (Intermediate 76; 160mg, 0.63mmol) were heated together in 1:3 EtOH:water (8 ml) in the presence of concentrated hydrochloric acid (126ul) for 24 hours. The reaction was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and the solvent evaporated to give product as a brown gum. This was purified by reverse phase HPLC to give the title compound a white
10 solid. (125 mg, 42 %)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.25 (d, 6H), 2.44 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (m, 2H), 3.59 (m, 6H), 4.85 (m, 1H), 7.78 (m, 4H), 8.06 (s, 1H), 8.15 (t, 1H), 9.42 (s, 1H); MS m/z 468 [M+H]⁺.

15 The following examples were prepared by an analogous process to that used in the preparation of Example 218 utilising the appropriate substituted anilines and Chloropyrimidines as indicated.

Example 219:

20 **3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide**

Prepared from Intermediate 76 and Intermediate 47.

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.29 (d, 6H), 2.49 (m, 6H), 2.52 (s, 3H), 2.65 (m, 2H), 3.44 (m, 2H), 3.65 (m, 6H), 4.00 (s, 3H), 4.87 (m, 1H), 7.54 (m, 2H), 7.74 (s, 1H), 8.12 (s,
25 1H), 8.32 (t, 1H), 8.47 (d, 1H).

Example 220:

3-methoxy-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

Prepared from Intermediate 103 and Intermediate 47.

¹H NMR (400.132 MHz, DMSO-d₆) δ 2.44 (m, 5H), 2.83 (m, 2H), 3.28 (s, 3H), 3.36 (m, 2H), 3.59 (m, 4H), 3.88 (s, 3H), 4.06 (m, 2H), 6.93 (d, 1H), 7.35 (m, 4H), 7.47 (m, 3H), 7.64 (s, 1H), 8.16 (t, 1H), 8.29 (s, 1H).

5

Example 221:

3-methoxy-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

Prepared from Intermediate 103 and an intermediate described in WO06/018220.

10 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.58 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.51 (s, 3H), 2.80 (m, 4H), 3.70 (m, 1H), 3.89 (s, 3H), 4.06 (m, 2H), 6.96 (d, 1H), 7.34 (m, 4H), 7.48 (m, 3H), 7.64 (s, 1H), 7.97 (d, 1H), 8.29 (s, 1H).

15

Example 222:

N-(3-dimethylamino-2,2-dimethyl-propyl)-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

Prepared from Intermediate 76 and Intermediate 22.

20 ¹H NMR (400.132 MHz, DMSO-d₆) δ 0.88 (s, 6H), 1.25 (d, 6H), 2.18 (s, 2H), 2.27 (s, 6H), 2.59 (m, 2H), 3.18 (s, 2H), 3.29 (s, 3H), 3.61 (m, 2H), 4.85 (m, 1H), 7.73 (d, 2H), 7.81 (d, 2H), 8.06 (s, 1H), 8.27 (t, 1H), 9.42 (s, 1H);

Example 223:

25 **N-(3-dimethylamino-2,2-dimethyl-propyl)-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide**

Prepared from Intermediate 103 and Intermediate 22.

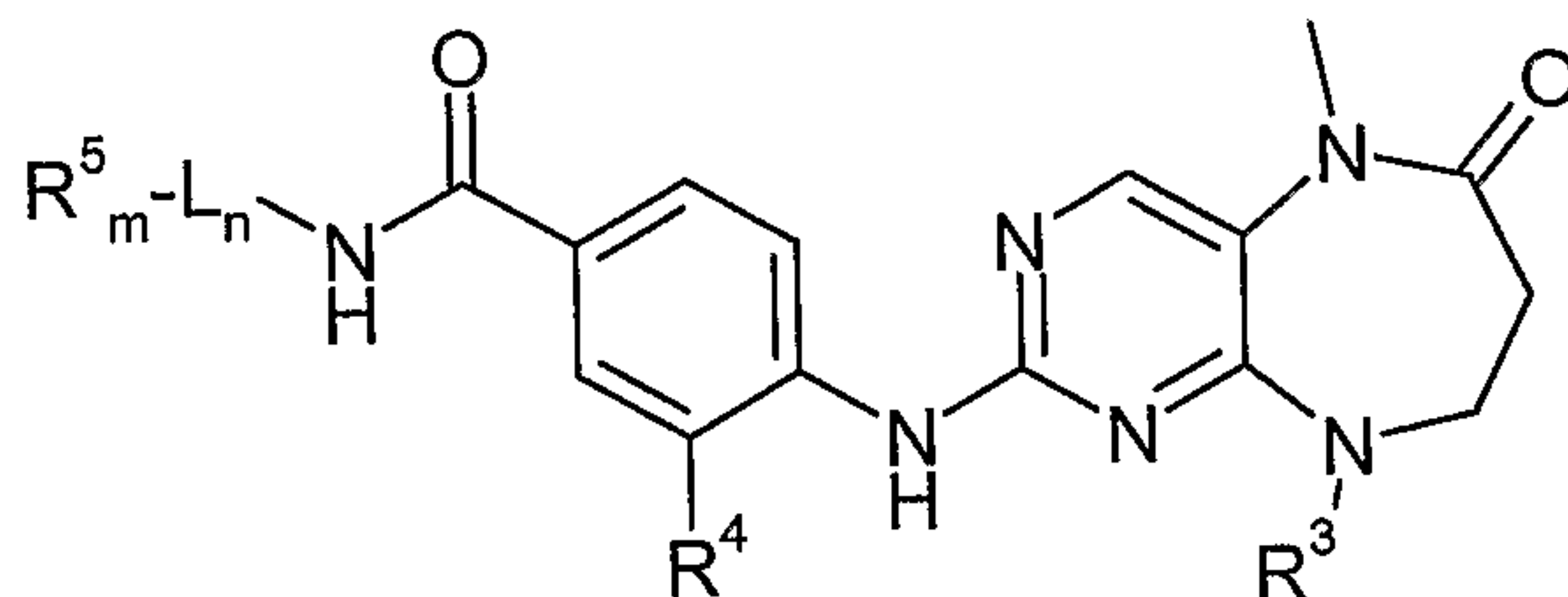
¹H NMR (400.132 MHz, DMSO-d₆) δ 0.87 (s, 6H), 2.18 (s, 2H), 2.28 (s, 6H), 2.81 (m, 2H), 3.14 (d, 2H), 3.28 (s, 3H), 4.06 (m, 2H), 7.33 (m, 7H), 7.47 (m, 2H), 8.21 (t, 1H), 8.31 (s, 30 1H), 9.52 (s, 1H).

Example 224:

4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

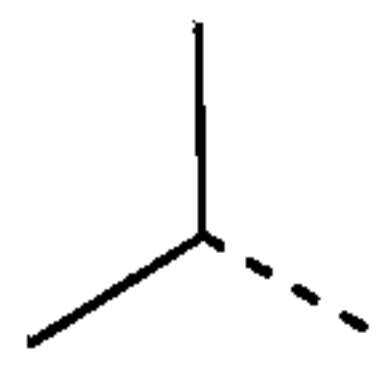
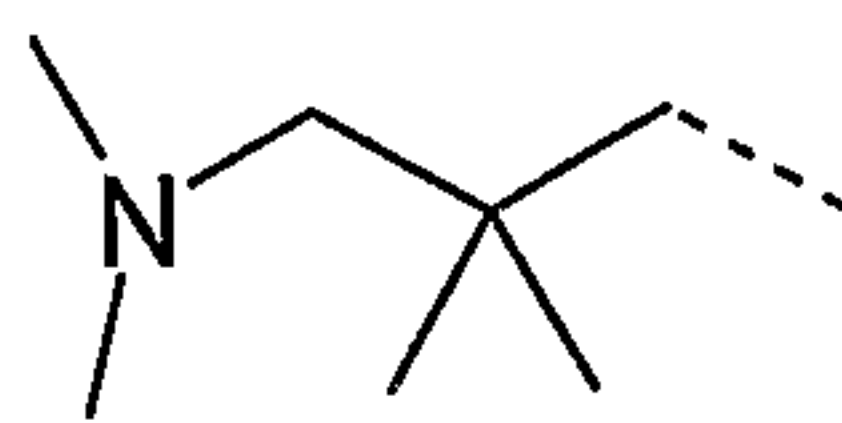
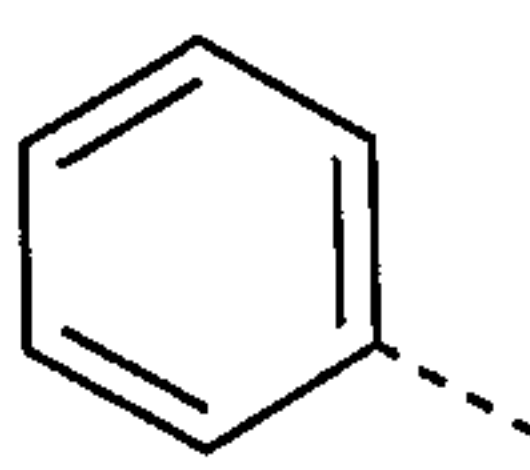
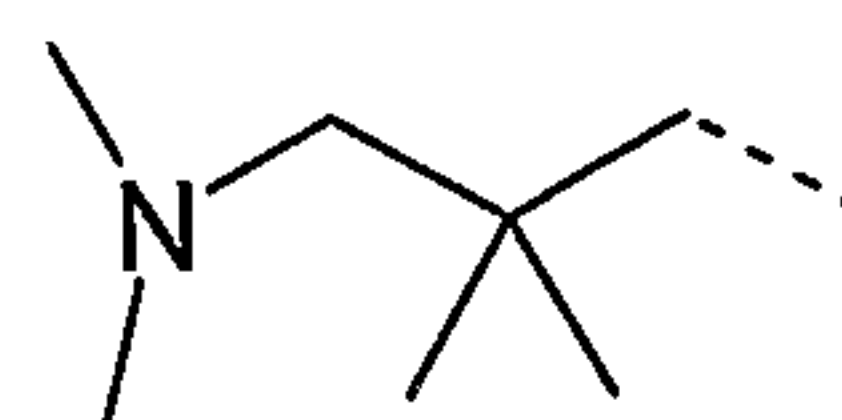
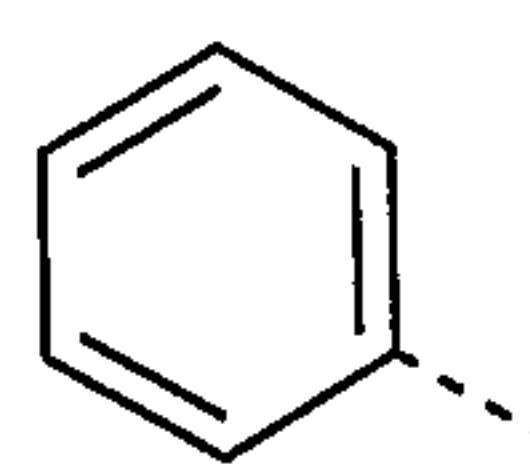
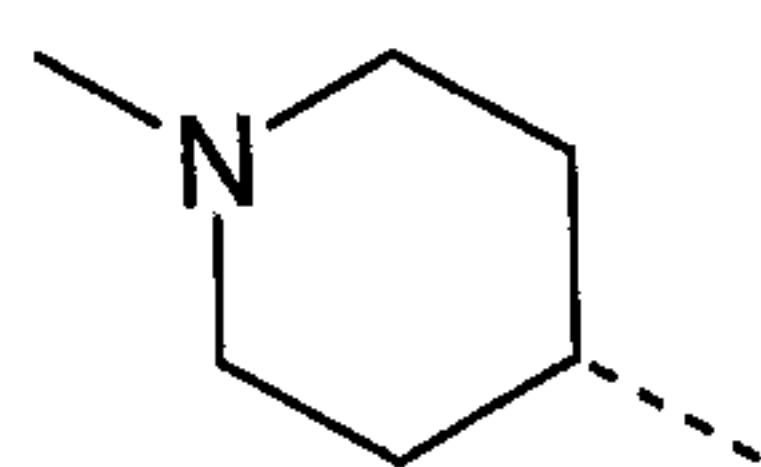
5 Prepared from Intermediate 103 and Intermediate 4.

^1H NMR (400.132 MHz, DMSO- d_6) δ 1.56 (m, 2H), 1.72 (m, 2H), 1.93 (m, 2H), 2.16 (s, 3H), 2.78 (m, 4H), 3.28 (s, 3H), 3.68 (m, 1H), 4.05 (m, 2H), 7.29 (m, 5H), 7.45 (m, 4H), 7.87 (d, 1H), 8.31 (s, 1H), 9.49 (s, 1H)



10

Example	R ³	R ⁴	R ⁵ _m -L _n -	MS m/z [M+H] ⁺
219				498
220				532
221				516

Example	R ³	R ⁴	R ⁵ _m -L _n -	MS m/z [M+H] ⁺
222		H		468
223		H		502
224		H		486

Example 225:

3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)-4-[(2-methyl-3-oxo-6-phenyl-

5 2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 107; 99mg, 0.35mmol), 10-chloro-6-methyl-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 103; 99 mg, 0.35 mmol) and p-toluenesulphonic acid monohydrate (165 mg, 0.87 mmol) were heated at 140°C in 4-methyl-2-pentanol (2.5 mL) for 2 hours. The mixture was allowed to cool forming a dark orange clear solution which was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with methanol to remove p-TsOH. and then eluted with 2% 7N ammonia/methanol to give the crude product which was purified by reverse phase HPLC to yield the title compound as a white solid (15 mg, 8 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ0.88 (6H, s), 2.17 (2H, s), 2.28 (6H, s), 2.82 - 2.85 (2H, m), 3.16 (2H, d), 4.04 - 4.08 (2H, m), 7.21 - 7.24 (1H, m), 7.28 - 7.30 (1H, m), 7.32 - 7.35 (2H, m), 7.46 (1H, s), 7.48 - 7.50 (1H, m), 7.56 (1H, d), 7.82 (1H, d), 8.02 (1H, s), 8.32 (1H, s), 8.37 (1H, t); MS m/z 537 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 225 utilising the appropriate substituted aniline (Intermediate 52)

Example 226:

5 **3-chloro-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide**

¹H NMR (399.9 MHz, DMSO-d₆) δ 2.41 – 2.47 (6H, m), 2.84 (2H, t), 3.33 - 3.41 (2H, m), 3.59 (4H, t), 4.05 - 4.08 (2H, m), 7.24 - 7.27 (1H, m), 7.31 - 7.35 (3H, m), 7.49 (2H, t), 7.55 (1H, q), 7.85 (1H, d), 8.00 (1H, s), 8.31 (2H, s); MS m/z 537 [M+H]⁺.

10

Example 227:

4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

10-chloro-6-methyl-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one
 15 (Intermediate 103; 150 mg, 0.52 mmol), 4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 130 mg, 0.52 mmol) and p-toluenesulphonic acid monohydrate (248 mg, 1.30mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140°C for 2 hours. The reaction mixture was cooled and loaded onto an SCX-3 column pre-wet methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with
 20 2% 7N ammonia/methanol to elute the crude product. The product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a white solid (81 mg, 32.2 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ 2.41 - 2.44 (6H, m), 2.82 (2H, t), 3.35 (3H, s), 3.38 - 3.39 (2H, t), 3.59 (4H, t), 4.06 - 4.08 (2H, t), 7.26 (1H, s), 7.29 (1H, s), 7.31 - 7.35 (2H, m), 7.34 -
 25 7.34 (1H, m), 7.40 - 7.42 (2H, m), 7.49 (2H, t), 8.05 (1H, t), 8.31 (1H, s), 9.53 (1H, s); MS m/z 503 [M+H]⁺.

Example 228:

3-chloro-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide
 30

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76 ;150 mg, 0.59 mmol), 4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 52; 168 mg, 0.59 mmol), and p-toluenesulphonic acid monohydrate (281 mg, 1.47 mmol) were heated in 4-methyl-2-pentanol (4 mL) at 140°C for 2 hours. The reaction mixture was cooled and loaded onto an SCX-3 column pre-wet with Methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with 2% 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as an orange gum (46 mg, 15.6 %).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.20 (6H, d), 2.42 - 2.43 (3H, m), 2.44 - 2.49 (2H, m), 2.60 (2H, t), 3.18 (4H, t), 3.39 (2H, q), 3.60 - 3.62 (6H, m), 4.75 (1H, m), 7.80 - 7.82 (1H, m), 7.96 (1H, d), 8.07 (1H, s), 8.12 (1H, s), 8.32 (1H, d), 8.40 (1H, t); MS m/z 503 [M+H]⁺.

Example 229:

15 **3-methoxy-4-[[6-(2-methoxyethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide**

10-chloro-2-(2-methoxyethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 109; 70 mg, 0.26 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 63 mg, 0.26 mmol), and p-toluenesulphonic acid monohydrate (123 mg, 0.65 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C overnight. The reaction was cooled to room temperature and taken up in MeOH and added to a 2g SCX-2 column pre-wet with MeOH (2 column volumes). The column was washed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant material was dissolved in DCM and purified on silica eluting with a gradient of 0 – 10% MeOH / DCM then 10% MeOH / DCM. Fractions containing product combined and evaporated to a clear gum to which ether was added and re-evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a white solid. (40 mg, 31 %).

¹H NMR (399.902 MHz, CDCl₃) δ 1.58 (m, 2H), 2.06 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.72 (m, 2H), 2.83 (m, 2H), 3.29 (s, 3H), 3.36 (s, 3H), 3.72 (m, 2H), 3.87 (m, 4H), 4.00 (m,

4H), 5.90 (d, 1H), 7.23 (m, 1H), 7.44 (d, 1H), 7.65 (s, 1H), 7.95 (s, 1H), 8.42 (d, 1H); MS m/z 503 [M+H]⁺.

Example 230:

5 **3-methoxy-4-[[6-(1-methoxypropan-2-yl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide**
10-chloro-2-(1-methoxypropan-2-yl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 112 60 mg, 0.21 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 56 mg, 0.21 mmol), and p-toluenesulphonic acid
10 monohydrate (100 mg, 0.53 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C for 16 hrs. The reaction mixture was cooled to room temperature and dissolved in Methanol. The resultant solution was added to a 5g SCX-3 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant residue was dissolved in
15 DCM and purified on silica eluting with a gradient of 5 – 15% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a beige solid. (35 mg, 32%)
¹H NMR (399.902 MHz, CDCl₃) δ 1.32 (d, 3H), 1.58 (m, 2H), 2.05 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.83 (m, 2H), 3.29 (s, 3H), 3.36 (s, 3H), 3.51 (m, 1H), 3.62 (m,
20 1H), 3.73 (m, 2H), 4.00 (m, 4H), 5.00 (m, 1H), 5.90 (d, 1H), 7.23 (m, 1H), 7.43 (m, 1H), 7.65 (s, 1H), 7.94 (s, 1H), 8.47 (d, 1H); MS m/z 503 [M+H]⁺.

Example 231:

4-[[6-(3-furylmethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-
25 **9-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**
10-chloro-2-(3-furylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 116; 67 mg, 0.23 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 60 mg, 0.23 mmol), and p-toluenesulphonic acid monohydrate (109 mg, 0.57 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated
30 at 100 °C for 16 hrs.. The reaction mixture was cooled to room temperature and dissolved in Methanol. The resultant solution was added to a 5g SCX-3 column pre wet with MeOH (2

column volumes). Flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant residue was dissolved in DCM and purified on silica eluting with a gradient of 0 – 15% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by
 5 base modified reverse phase HPLC to give the title compound as a yellow solid. (50 mg, 42%)

¹H NMR (400.132 MHz, CDCl₃) δ 1.57 (m, 2H), 2.04 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.64 (m, 2H), 2.82 (m, 2H), 3.31 (s, 3H), 3.71 (m, 2H), 3.98 (m, 4H), 4.67 (s, 2H), 5.88 (d, 1H), 6.43 (s, 1H), 7.14 (m, 1H), 7.40 (m, 1H), 7.43 (m, 2H), 7.71 (s, 1H), 7.99 (s, 1H), 8.45
 10 (d, 1H); MS m/z 520 [M+H]⁺.

Example 232:

4-[(6-cyclopropyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

15 10-chloro-2-cyclopropyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 117 42mg, 0.16 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 44 mg, 0.216 mmol), and p-toluenesulphonic acid monohydrate (79 mg, 0.41 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C for 16 hrs. The reaction mixture was cooled to room temperature and dissolved in
 20 methanol. The resultant solution was added to a 5g SCX-3 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant residue was dissolved in DCM and purified on silica eluting with a gradient of 0 – 15% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by
 25 base modified reverse phase HPLC to give the title compound as a white solid. (34 mg, 43%)

¹H NMR (400.132 MHz, CDCl₃) δ 0.64 (m, 2H), 0.92 (m, 2H), 1.59 (m, 2H), 2.05 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.67 (m, 2H), 2.86 (m, 3H), 3.26 (s, 3H), 3.82 (m, 2H), 4.00 (m, 4H), 5.90 (d, 1H), 7.22 (m, 1H), 7.44 (d, 1H), 7.82 (s, 1H), 7.99 (s, 1H), 8.76 (d, 1H); MS m/z 503 [M+H]⁺.

Example 233:

N-cyclohexyl-3-methoxy-4-[[2-methyl-6-(1-methyl-4-piperidyl)-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]benzamide

10-chloro-6-methyl-2-(1-methyl-4-piperidyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 118; 39mg, 0.13 mmol), 4-amino-N-cyclohexyl-3-methoxy-
 5 benzamide (Intermediate 119; 31mg, 0.13 mmol) and
 p-toluenesulphonic acid monohydrate (60 mg, 0.31 mmol) were combined in 4-Methyl-2-pentanol (2 mL) and heated at 100 °C for 16 hrs. The reaction mixture was cooled to room temperature and dissolved in Methanol and added to a 5g SCX-3 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) then crude product eluted
 10 with 2M ammonia in MeOH and solvents evaporated. The resultant material was dissolved in DCM and purified on silica eluting with a shallow (25 column volumes) gradient of 0 – 10% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid. (15 mg, 23%).

15 ¹H NMR (400.132 MHz, CDCl₃) δ 1.26 (m, 4H), 1.45 (m, 2H), 1.77 (m, 2H), 1.91 (m, 4H), 2.05 (m, 2H), 2.17 (m, 2H), 2.35 (s, 3H), 2.67 (m, 2H), 3.02 (m, 2H), 3.28 (s, 3H), 3.71 (m, 2H), 3.98 (m, 4H), 4.51 (m, 1H), 5.88 (d, 1H), 7.26 (m, 1H), 7.38 (d, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.45 (d, 1H); MS m/z 522 [M+H]⁺.

20

Example 234:

4-[(6-cyclopentyl-2,5-dimethyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

25 10-chloro-2-cyclopentyl-3,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 120; 25 mg, 0.42 mmol) and), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 112 mg, 0.42 mmol) were combined with p-toluenesulphonic acid monohydrate (202 mg, 1.06 mmol) in 4-methyl-2-pentanol (1 mL) and heated to 150 °C for 2 hr. The cooled reaction mixture was diluted with methanol (approx 50
 30 mL) and loaded onto a 50 g SCX-2 cartridge washing with methanol (100 mL) and eluting

with 7 N methanolic ammonia (100 mL). The concentrated solution was purified by base modified reverse phase HPLC to give the title compound as a white solid (65 mg, 30%)

¹H NMR (399.902 MHz, CDCl₃) δ 1.29 (d, 3H), 1.54 - 1.89 (m, 9H), 1.95 - 2.23 (m, 6H), 2.32 (s, 3H), 2.56 (dd, 1H), 2.72 (dd, 1H), 2.84 (br d, 2H), 3.31 (s, 3H), 3.98 (s, 3H), 4.00 - 4.07 (m, 1H), 4.63 - 4.71 (m, 1H), 5.91 (d, 1H), 7.23 (dd, 1H), 7.42 (d, 1H), 7.67 (s, 1H), 7.97 (s, 1H), 8.47 (d, 1H); MS m/z 522 [M+H]⁺.

Example 235:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

A solution of HATU (221 mg, 0.55 mmol) in DMA (10 mL) was added to a mixture of the 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 242; 220 mg, 0.5 mmol), DIPEA (261 uL, 1.5 mmol) and 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 72 mg, 0.62 mmol) in DMA (10 mL). The resulting mixture was stirred at room temperature for 2 hours, then partially purified by SCX. The compound was retrieved from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave the title compound as a pale yellow amorphous solid. (154 mg, 58%)

¹H NMR (399.9 MHz, CDCl₃) δ 1.22 (6H, s), 1.56 - 1.63 (2H, m), 1.72 - 1.93 (6H, m), 1.99 - 2.03 (2H, m), 2.14 (2H, d), 2.41 - 2.45 (2H, m), 2.48 (3H, s), 3.06 - 3.09 (2H, m), 3.32 (3H, s), 3.40 (2H, s), 4.00 (3H, s), 4.10 - 4.14 (1H, m), 5.29 - 5.38 (1H, m), 6.12 (1H, d), 7.28 (1H, dd), 7.44 (1H, d), 7.65 (1H, s), 7.88 (1H, s), 8.52 (1H, d); MS m/z 536 [M+H]⁺.

Example 236: Example 237:

4-[(4S)-2-cyclopentyl-4-ethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide
and

4-[(4R)-2-cyclopentyl-4-ethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

160

10-chloro-2-cyclopentyl-4-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 123; 186 mg, 0.6 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 159 mg, 0.6 mmol) were combined with p-toluenesulphonic acid monohydrate (286 mg, 1.5 mmol) in 4-methyl-2-pentanol (01 mL) and
 5 at 115°C overnight. The cooled reaction mixture was dissolved in methanol, passed through an SCX-2 column and washed with methanol. The product was eluted off with 7N ammonia/methanol. Product containing fractions were evaporated and the resultant material was purified using base modified reverse phase HPLC to give a mixture of the title compounds as a brown foam (110 mg)

10

The individual enantiomers were separated by chiral column chromatography to as white foams

Enantiomer 1 (26 mg)

¹H NMR (399.9 MHz, DMSO-d₆) : δ_H: 0.89 (tr, 3H), 1.31 (m, 2H), 1.50-1.90 (m, 12H), 2.11
 15 (m, 2H), 2.36 (m, 5H), 2.61 (m, 1H), 3.00 (m, 2H), 3.21 (s, 3H), 3.42 (m, 2H), 3.84 (m, 1H), 3.97 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.77 (m, 1H), 8.12 (m, 2H), 8.39 (d, 1H); MS m/z 536 [M+H]⁺.

Enantiomer 2 (26 mg)

¹H NMR (399.9 MHz, DMSO-d₆) : δ_H: 0.89 (tr, 3H), 1.31 (m, 2H), 1.50-1.90 (m, 12H), 2.11
 20 (m, 2H), 2.36 (m, 5H), 2.61 (m, 1H), 3.00 (m, 2H), 3.21 (s, 3H), 3.42 (m, 2H), 3.84 (m, 1H), 3.97 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.77 (m, 1H), 8.12 (m, 2H), 8.39 (d, 1H).; MS m/z 536 [M+H]⁺.

Example 238: Example 239:

25 **4-[[[(4S)-2-cyclopentyl-6-methyl-5-oxo-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**
and

4-[[[(4R)-2-cyclopentyl-6-methyl-5-oxo-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

30

10-chloro-2-cyclopentyl-6-methyl-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 124; 194 mg, 0.6 mmol), 4-amino-3-methoxy-N-(1-methyl-4-

piperidyl)benzamide (WO06/018220; 159 mg, 0.6 mmol) were combined with *p*-toluenesulphonic acid monohydrate (286 mg, 1.5 mmol) in 4-methyl-2-pentanol (01 mL) and at 115°C overnight. The cooled reaction mixture was dissolved in methanol, passed through an SCX-2 column and washed with methanol. The product was eluted with 7N ammonia/methanol. Product containing fractions were evaporated and the resultant material purified using basic prep HPLC to give a mixture of the title compounds as a light brown foam (65 mg)

The individual enantiomers were separated by chiral column chromatography to as white foams

10 Enantiomer 1 (15 mg)

¹H NMR (399.9 MHz, DMSO-d₆) : δ 0.84 (tr, 3H), 1.29 (m, 3H), 1.50-1.90 (m, 13H), 2.11 (m, 2H), 2.41 (m, 5H), 2.69 (m, 1H), 3.02 (m, 2H), 3.20 (s, 3H), 3.40 (m, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.76 (m, 1H), 8.12 (s, 1H), 8.14 (d, 1H), 8.40 (d, 1H); MS m/z 550 [M+H]⁺.

15 Enantiomer 2 (22 mg)

¹H NMR (399.9 MHz, DMSO-d₆) : δ 0.84 (tr, 3H), 1.29 (m, 3H), 1.50-1.90 (m, 13H), 2.11 (m, 2H), 2.41 (m, 5H), 2.69 (m, 1H), 3.02 (m, 2H), 3.20 (s, 3H), 3.40 (m, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.76 (m, 1H), 8.12 (s, 1H), 8.14 (d, 1H), 8.40 (d, 1H); MS m/z 550 [M+H]⁺.

20

Example 240: Example 241:

4-[[[(4S)-2-cyclopentyl-4,6-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide
 25 and
 4-[[[(4R)-2-cyclopentyl-4,6-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide
 10-chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (**Intermediate 125**; 674 mg, 2.29 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 602 mg, 2.29 mmol) and *p*-toluene sulphonic acid (1.09 g, 0.89 mmol) were dissolved in 4-methyl-2-pentanol (15 mL) and refluxed under a blanket of

nitrogen for 24 hours. The reaction mixture was cooled and passed through an SCX-2 column washed with methanol. The crude product was eluted with 7N ammonia in methanol. Product containing fractions were evaporated and the resultant material purified by column chromatography, eluting with 0-10% ammonia methanol (7N) in DCM. The resultant material was purified by base modified reverse phase HPLC to give a mixture of the title compounds as a white solid (480 mg, 40%).

The individual enantiomers were separated by chiral column chromatography to as white gums which were dissolved separately in DCM then passed through SCX-2 columns and washed with methanol. The products were eluted off the columns using 7N ammonia in methanol and concentrated under reduced pressure to yield the enantiomers as white solids.

Enatiomer 1 (118 mg)

^1H NMR (399.902 MHz, DMSO- d_6) δ 1.04 (d, 3H), 1.51 - 1.84 (m, 12H), 1.99 - 2.13 (m, 3H), 2.81 - 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quintet, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 523

[M+H] $^+$.

Enatiomer 2 (59 mg)

^1H NMR (399.902 MHz, DMSO- d_6) δ 1.04 (d, 3H), 1.51 - 1.84 (m, 12H), 1.99 - 2.13 (m, 3H), 2.81 - 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quintet, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 523

[M+H] $^+$.

Example 242:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid

To a solution of 10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 126; 616 mg, 2.0 mmol) and 4-amino-3-methoxybenzoic acid (378 mg, 2.2 mmol) in ethanol (5 mL) was added water (15 mL) and conc hydrochloric acid (0.335 mL). The mixture was heated under reflux for 36 hours. The reaction was cooled and a brown solid precipitated. This was filtered, dried and

trituated under cold acetonitrile and then dried *in vacuo* to give the product as a pale brown solid (420 mg), 48%)

¹ H NMR (400.13 MHz, DMSO-d₆) δ 1.15 (6H, s), 1.55 - 1.90 (8H, m), 3.19 (3H, s), 3.53 (2H, s), 3.95 (3H, s), 5.07 - 5.16 (1H, m), 7.59 - 7.61 (2H, m), 8.11 (1H, s), 8.13 (1H, d), 9.53 (1H, s); MS m/z 440 [M+H]⁺.

Example 243:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-3-piperidyl)benzamide

10 A solution of HATU (126 mg, 0.33 mmol) in DMA (5 mL) was added to a mixture of the 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 242 132 mg, 0.3 mmol), DIPEA (261 uL, 1.5 mmol) and 3-amino N-methylpiperidine dihydrochloride (71 mg, 0.375 mmol) in DMA (5 mL). The resulting mixture was stirred at room temperature for 2 hours, then partially purified
15 by SCX. The compound was eluted from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave the title compound as a pale yellow amorphous solid (65 mg, 41%)

20 ¹H NMR (400.13 MHz, CDCl₃) δ 1.03 (6H, s), 1.34 - 1.87 (12H, m), 2.17 (5H, s), 2.41 (2H, s), 3.13 (3H, s), 3.20 (2H, s), 3.82 (3H, s), 4.19 (1H, s), 5.10 - 5.20 (1H, m), 7.09 (1H, s), 7.20 (1H, s), 7.34 (1H, s), 7.43 (1H, s), 7.68 (1H, s), 8.31 (1H, d); MS m/z 536 [M+H]⁺.

Example 244:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[1-(2-methoxyethyl)-4-piperidyl]benzamide

A solution of HATU (126 mg, 0.33 mmol) in DMA (5 mL) was added to a mixture of 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 242 132 mg, 0.3 mmol), DIPEA (261 uL, 1.5 mmol) and 4-amino N-(2-methoxyethyl)piperidine (60 mg, 0.375) in DMA (5 mL). The
30 resulting mixture was stirred at room temperature for 2 hours, then partially purified by SCX.

The compound was retrieved from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave a pale yellow
 5 amorphous solid. (55 mg, 32%)

¹H NMR (400.13 MHz, CDCl₃) δ 1.13 (6H, s), 1.43 - 1.56 (2H, m), 1.58 - 1.74 (4H, m), 1.87 - 1.97 (4H, m), 2.04 (2H, d), 2.44 (2H, t), 2.76 (2H, t), 3.10 - 3.12 (2H, m), 3.23 (3H, s), 3.29 - 3.30 (2H, m), 3.30 (3H, s), 3.59 - 3.62 (2H, m), 3.90 (2H, s), 4.03 - 4.07 (1H, m), 5.20 - 5.28 (1H, m), 6.04 (1H, d), 7.17 - 7.20 (2H, m), 7.34 (1H, d), 7.55 (1H, s), 7.79 (1H, s), 8.42 (1H,
 10 d). MS m/z 580 [M+H]⁺.

Example 245:

**4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-
 15 10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide**

A solution of HATU (126 mg, 0.33 mmol) in DMA (5 mL) was added to a mixture of 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzoic acid, (Intermediate 129; 123 mg, 0.3 mmol) DIPEA (261 uL, 1.5 mmol) and 4-amino N-methylpiperidine (43 mg, 0.375) in DMA (5 mL). The resulting mixture was
 20 stirred at room temperature for 2 hours, then partially purified by SCX. The compound was eluted from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave a pale yellow amorphous solid. (100 mg,
 25 66%)

¹H NMR (400.13 MHz, CDCl₃) δ 1.13 (6H, s), 1.43 - 1.53 (2H, m), 1.60 - 1.73 (4H, m), 1.83 - 1.95 (4H, m), 2.01 - 2.09 (2H, m), 2.37 - 2.42 (2H, m), 2.44 (3H, s), 3.06 (2H, d), 3.22 (3H, s), 3.30 (2H, s), 4.01 - 4.07 (1H, m), 5.16 - 5.25 (1H, m), 6.07 (1H, d), 6.99 (1H, s), 7.58 (2H, d), 7.65 (2H, d), 7.77 (1H, s); MS m/z 506 [M+H]⁺.

Example 246:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-methylpiperidin-4-yl)-3-methoxybenzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 153 mg, 0.5 mmol) 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 158 mg, 0.6 mmol) were combined with p-toluenesulphonic acid monohydrate (190 mg, 1.0 mmol) in 4-methyl-2-pentanol (4 mL) mixed and heated by microwave irradiation at 160°C for 1 hour, cleaned up partially by SCX, then purified by column chromatography, eluting with 0-6% methanolic ammonia in DCM, to give the product as a clear oil, which solidified on trituration with ether to give the title compound as a white solid (160 mg, 60%)

¹H NMR (400.13 MHz, CDCl₃) δ 0.61 - 0.64 (2H, m), 1.09 - 1.12 (2H, m), 1.42 - 1.52 (2H, m), 1.61 - 1.76 (6H, m), 1.98 - 2.11 (4H, m), 2.23 (2H, t), 2.35 (3H, s), 2.89 (2H, d), 3.30 (3H, s), 3.47 (2H, s), 3.99 (3H, s), 3.99 - 4.10 (1H, m), 4.93 - 4.99 (1H, m), 5.99 (1H, d), 7.26 (1H, dd), 7.43 (1H, d), 7.65 (1H, s), 7.87 (1H, s), 8.53 (1H, d) MS m/z 534 [M+H]⁺.

Example 247:

3-chloro-N-(2-morpholin-4-ylethyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 104; 104mg, 0.36mmol), 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 52; 100 mg, 0.36 mmol) and p-toluenesulphonic acid monohydrate (174 mg, 0.91mmol) were heated at 140°C in 4-methyl-2-pentanol (2.5ml) for 4.5 hrs. The reaction mixture was cooled and absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. After concentration of the product containing fractions methanol was added to the residue and the suspension filtered to give the title compound as an off-white coloured solid (42 mg, 22%)

¹H NMR (399.9 MHz, DMSO-d₆) δ 2.41 - 2.47 (6H, m), 2.89 (2H, m), 3.36 (2H, t), 3.59 (4H, m), 4.01 - 4.03 (2H, m), 7.19 - 7.22 (1H, m), 7.36 - 7.43 (3H, m), 7.51 - 7.55 (3H, m), 7.69 (1H, s), 7.83 (1H, d), 7.97 (1H, s), 8.27 (1H, t), 9.66 (1H, s); MS m/z 522 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 255 utilising 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide Intermediate 55 to give the title compound as a white solid (31 mg, 17%)

5 **Example 248:**

3-chloro-N-(1-methyl-4-piperidyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.54 - 1.58 (2H, m), 1.74 (2H, d), 1.91 - 1.97 (2H, m), 2.17 (3H, s), 2.74 - 2.79 (2H, m), 2.89 (2H, m), 3.64 - 3.74 (1H, m), 4.00 - 4.03 (2H, m), 7.20
10 - 7.23 (1H, m), 7.35 - 7.41 (3H, m), 7.53 (3H, d), 7.68 (1H, s), 7.87 (1H, d), 7.96 (1H, s), 8.10 (1H, d), 9.65 (1H, s); MS m/z 506 [M+H]⁺.

15

Example 249:

N-(2-morpholin-4-ylethyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 188mg, 0.75mmol) and 10-chloro-
20 2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 160mg, 0.63mmol) were heated together in EtOH:water (8ml, 1:3) in the presence of concentrated hydrochloric acid (126ul) for 24 hours. The mixture was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and the solvent evaporated to give product as a brown gum, which was
25 purified by base, modified reverse phase HPLC to yield the title compound as a white solid. (35 mg, 13%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 2.43 (m, 4H), 2.88 (m, 3H), 3.34 (m, 2H), 3.59 (m, 4H), 3.99 (m, 3H), 7.18 (d, 2H), 7.38 (m, 5H), 7.53 (t, 2H), 7.93 (s, 1H), 8.00 (m, 1H), 9.28 (s, 1H), 9.57 (s, 1H); MS m/z 488 [M+H]⁺.

30

Example 250:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide

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4-amino-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 135 176 mg, 0.75 mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2 168 mg, 0.63mmol) were heated together in EtOH:water (8ml, 1:3) in the presence of concentrated hydrochloric acid (126ul) for 24 hours. The mixture was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and the solvent evaporated to give product as a brown gum, which was purified by base, modified reverse phase HPLC to yield the title compound as a white solid. (154 mg, 54%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.73 (m, 8H), 2.45 (m, 6H), 2.62 (m, 2H), 3.39 (m, 4H), 3.58 (m, 6H), 3.94 (s, 3H), 5.09 (m, 1H), 7.46 (m, 2H), 7.60 (s, 1H), 7.80 (s, 1H), 8.25 (t, 1H), 8.38 (d, 1H), 9.41 (s, 1H); MS m/z 510 [M+H]⁺.

Example 251:

15 3-methoxy-N-(1-methyl-4-piperidyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 173 mg, 0.66 mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 150mg, 0.55mmol) were heated together in EtOH:water (8 mL, 1:3) in the presence of concentrated hydrochloric acid (110 ul) for 24 hours. p-toluenesulphonic acid monohydrate (105 mg, 0.55 mmol) was added and the mixture heated at 150 deg for 3h by microwave irradiation. The mixture was cooled to ambient temperature and loaded onto an SCX-2 (5 g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and solvent evaporated to give a brown gum which was purified by base modified reverse phase HPLC to yield the title compound as a white solid (73 mg, 27%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.57 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.84 (m, 4H), 3.70 (m, 1H), 3.87 (s, 3H), 4.01 (m, 2H), 6.91 (d, 1H), 7.39 (m, 6H), 7.53 (m, 2H), 7.93 (s, 1H), 7.95 (s, 1H), 9.60 (s, 1H); MS m/z 502 [M+H]⁺.

30

Example 252:

N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 183mg, 0.66mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 150 mg, 0.55 mmol) were heated together in EtOH:water (8 mL, 1:3) in the presence of concentrated hydrochloric acid (110ul) for 24 hours. IPA/DMA was added to aid solution followed by p-toluenesulphonic acid monohydrate (52mg, 0.27mmol) and the mixture heated by microwave irradiation for 1 hour at 150°C. The mixture was cooled to ambient temperature and loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and the solvent evaporated to give product as a brown gum which was purified by base modified reverse phase HPLC to yield the title compound as a gum (13 mg, 5%)

ES+518 (M+H), ES- 516 (M-H) Retention Time 2.18 minutes

15

Example 253:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 136; 113mg, 0.45mmol) and 10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 120mg, 0.45mmol) were heated together in EtOH:water (8ml, 1:3) in the presence of 4-toluenesulphonic acid (214mg, 1.13mmol) for 23 hours. The reaction mixture was heated by microwave irradiation at 150°C for 20 minutes cooled to ambient temperature and loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and the solvent evaporated to give product as a gum, which was purified by base modified reverse phase HPLC to yield the title compound as a white solid. (77 mg, 36%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.88 (s, 6H), 1.61 (m, 4H), 1.74 (m, 2H), 1.90 (m, 2H), 2.19 (s, 2H), 2.27 (s, 6H), 2.61 (m, 2H), 3.18 (d, 2H), 3.57 (m, 2H), 5.14 (m, 1H), 7.69 (d, 2H), 7.78 (d, 2H), 7.79 (s, 1H), 8.30 (t, 1H), 9.31 (s, 1H), 9.38 (s, 1H); MS m/z 480 [M+H]⁺.

Example 254:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

4-amino-N-(1-methyl-4-piperidyl)benzamide (Intermediate 4; 131mg, 0.56mmol) and 10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 150mg, 0.56mmol) were heated together in 4-methyl-2-pentanol (4ml) in the presence of p-toluenesulphonic acid (266mg, 1.40mmol) for 24 hours. The mixture was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH₃/MeOH and the solvent evaporated to give crude product, which was purified by base modified reverse phase HPLC to yield the title compound as a white solid.

(56 mg, 22%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.58 (m, 6H), 1.75 (m, 4H), 1.92 (m, 4H), 2.17 (s, 3H), 2.61 (m, 2H), 2.77 (m, 2H), 3.57 (m, 2H), 3.72 (m, 1H), 5.14 (m, 1H), 7.75 (m, 4H), 7.79 (s, 1H), 7.95 (d, 1H), 9.29 (s, 1H), 9.38 (s, 1H); MS m/z 464 [M+H]⁺.

15

Example 255:

3-chloro-4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 107; 118mg, 0.37mmol), 10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 100mg, 0.37mmol) and p-toluenesulphonic acid monohydrate (179mg, 0.94mmol) were heated at 140°C in 4-methyl-2-pentanol for 2h. LC-MS indicated the reaction had not gone to completion with ~50% of product in the mixture. An SCX-3 column was washed with methanol then the solution was loaded onto it. The column was washed with methanol and eluted with 7N ammonia/methanol to give the crude product. The mixture was concentrated the resultant material purified by base modified reverse phase HPLC to yield the title compound as an odd-white solid (24mg, 12.6%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.89 (6H, s), 1.56 (4H, m), 1.71 (2H, s), 1.83 - 1.85 (2H, m), 2.18 (2H, s), 2.27 (6H, s), 2.62 (2H, t), 3.18 - 3.20 (2H, s), 3.57 (2H, t), 5.03 (1H, m), 7.73 - 7.76 (1H, m), 7.80 (1H, s), 7.94 (1H, d), 8.03 (1H, s), 8.28 (1H, d), 8.46 (1H, s), 9.44 (1H, s); MS m/z 514 [M+H]⁺.

30

Example 256:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

- 5 10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 150mg, 0.56mmol), 4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark ; 141mg, 0.56mmol) and p-toluenesulphonic acid monohydrate (268mg, 1.41mmol) were heated in 4-methyl-2-pentanol (4 mL) for 2 hours at 140°C. The reaction mixture was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with
- 10 methanol and 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated, dissolved in DMF and purified by base modified reverse phase HPLC to yield the title compound as a white solid (77 mg, 28.5%)
- ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.62 (2H, m), 1.67 (2H, m), 1.76 (2H, m), 1.91 (2H, m), 2.43 - 2.46 (6H, m), 2.62 (2H, t), 3.38 (2H, q), 3.58 (6H, t), 5.12 - 5.16 (1H, m), 7.74 - 7.77
- 15 (3H, m), 7.77 (2H, d), 8.15 (1H, t), 9.33 (1H, s), 9.40 (1H, s); MS m/z 481 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 256 utilising 4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide Intermediate 50 to give the title compound as a yellow solid (44 mg, 15%)

20

Example 257:

- 3-chloro-4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide**
- 25 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.57 (4H, d), 1.68 - 1.72 (2H, m), 1.85 (2H, s), 2.43 (6H, m), 2.62 (2H, t), 3.39 (2H, q), 3.58 (6H, t), 5.03 (1H, m), 7.78 (2H, t), 7.95 (1H, d), 8.00 (1H, s), 8.30 (1H, d), 8.39 (1H, t), 9.44 (1H, s); MS m/z 515 [M+H]⁺.

30 **Example 258:**

3-methoxy-4-[[6-(1-methoxypropan-2-yl)-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(1-methoxypropan-2-yl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one
(Intermediate 137; 35 mg, 0.13 mmol), 4-amino-3-methoxy-N-(1-methyl-4-
piperidyl)benzamide (WO06/018220; 34 mg, 0.13 mmol) and *p*-toluenesulphonic acid
monohydrate (61 mg, 0.32 mmol) were dissolved in 4-methyl-2-pentanol (2 mL) and heated
5 at 100 °C for 18 hrs. The reaction mixture was cooled to room temperature dissolved in
MeOH and added to a 2g SCX-2 column pre wet with MeOH (2 column volumes). Flushed
with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH. Product
containing fractions were evaporated and the resultant material purified by base modified
reverse phase HPLC to yield the title compound as a cream coloured solid (13 mg, 20%)
10 ¹H NMR (399.902 MHz, CDCl₃) δ 1.29 (d, 3H), 1.61 (m, 2H), 2.06 (m, 2H), 2.18 (m, 2H),
2.31 (s, 3H), 2.77 (m, 2H), 2.84 (m, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.68 (m, 2H), 3.97 (s,
3H), 4.00 (m, 1H), 5.27 (m, 1H), 5.90 (d, 1H), 6.94 (s, 1H), 7.23 (m, 1H), 7.42 (d, 1H), 7.60
(s, 1H), 7.70 (s, 1H), 8.43 (d, 1H); MS m/z 498 [M+H]⁺.

15 **Example 259:**

**4-[(6-cyclopentyl-2-ethyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-
yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide**

10-chloro-2-cyclopentyl-6-ethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one
(Intermediate 139; 221 mg, 0.75 mmol), 4-amino-3-methoxy-N-(1-methyl-4-
20 piperidyl)benzamide (WO06/018220; 198 mg, 0.75 mmol) and *p*-toluenesulphonic acid (357
mg, 1.88 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 18 hours. The
reaction mixture was allowed to cool to room temperature and loaded onto a 10 g SCX-2
cartridge, washing with methanol (10 mL), water (10 mL) and methanol (10 mL) before the
product was eluted off with 7 N methanolic ammonia to provide a brown oil upon evaporation
25 of product containing fractions. The resultant material was purified by flash silica
chromatography, 0-10% methanolic ammonia/DCM to give a pale yellow glass which was
purified by base modified reverse phase HPLC to yield the title compound as a white solid
(192 mg, 0.36 mmol, 49%).

¹H NMR (399.902 MHz, DMSO-d₆) δ 1.00 (t, 3H), 1.55 - 1.82 (m, 12H), 1.91 - 1.98 (m,
30 4H), 2.18 (s, 3H), 2.79 (d, 2H), 3.60 - 3.63 (m, 2H), 3.69 - 3.79 (m, 3H), 3.96 (s, 3H), 4.74

(quintet, 1H), 7.48 - 7.51 (m, 2H), 7.77 (s, 1H), 8.08 (d, 1H), 8.13 (s, 1H), 8.39 (d, 1H); MS m/z 523 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation
5 of Example 259 utilising 10-chloro-2-cyclopentyl-6-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 142 to give the title compound as a white solid (77 mg, 14%)

10

Example 260:

4-[(6-cyclopentyl-3-oxo-2-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

¹H NMR (399.902 MHz, DMSO-d₆) δ 1.14 (d, 6H), 1.54 - 1.81 (m, 12H), 1.92 - 1.98 (m,
15 4H), 2.18 (s, 3H), 2.79 (br d, 2H), 3.56 - 3.59 (m, 2H), 3.70 - 3.80 (m, 1H), 3.96 (s, 3H), 4.40 (septet, 1H), 4.63 (quintet, 1H), 7.48 - 7.51 (m, 2H), 7.80 (s, 1H), 8.03 (s, 1H), 8.08 (d, 1H), 8.40 (d, 1H); MS m/z 536 [M+H]⁺.

Example 261:

20 **2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-thiazole-4-carboxamide**

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 150 mg, 0.53 mmol), 2-amino-N-(1-methyl-4-piperidyl)-1,3-thiazole-4-
25 carboxamide (Intermediate 145; 123 mg, 0.48 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (26 mg, 0.04 mmol) were dissolved in 1,4-dioxane (4.5 mL) Caesium carbonate (315 mg, 0.97 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (27mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled three times with nitrogen and then
30 heated at 100°C overnight. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by reverse phase preparative chromatography to give the title compound as a pale brown solid (80 mg, 34%)

¹H NMR (399.9 MHz, DMSO-d₆) δ1.49 - 1.83 (10H, m), 1.99 - 2.05 (4H, m), 2.18 (3H, s), 2.61 (2H, t), 2.67 - 2.75 (2H, m), 3.19 (3H, s), 3.64 - 3.72 (3H, m), 5.00 (1H, m), 7.48 (1H, d), 7.66 (1H, s), 8.14 (1H, s), 11.28 (1H, s); MS m/z 485 [M+H]⁺.

5 The following example was prepared by an analogous process to that used in the preparation of Example 261 utilising 2-amino-4-methyl-N-(1-methyl-4-piperidyl)-1,3-thiazole-5-carboxamide Intermediate 146. A solid that precipitated from the basic fractions of the SCX column was filtered off. The filtrate was concentrated and methanol added to the residue giving further precipitated material, which was filtered and combined with the original
10 precipitate to give the title compound as a white solid (95mg, 40%)

Example 262:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methyl-N-(1-methyl-4-piperidyl)1,3-thiazole-5-carboxamide

15 ¹H NMR (399.9 MHz, DMSO-d₆) δ1.50 - 1.76 (10H, m), 1.90 - 2.03 (4H, m), 2.16 (3H, s), 2.43 (3H, s), 2.61 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.60 - 3.67 (3H, m), 5.07 (1H, m), 7.60 (1H, d), 8.13 (1H, s), 11.33 (1H, s);

¹H NMR (399.9 MHz, DMSO-d₆) +d4 AcOH δ1.63 - 1.90 (10H, m), 1.86 - 1.92 (2H, m),
20 2.01 (2H, s), 2.44 (3H, s), 2.46 (3H, s), 2.61 (2H, t), 3.08 (2H, m), 3.18 (3H, s), 3.65 (2H, m), 3.78 - 3.85 (1H, m), 5.05 (1H, d), 8.12 (1H, s); MS m/z 499 [M+H]⁺.

Example 263:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-thiazole-5-carboxamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 148 mg, 0.53 mmol), 2-amino-N-(1-methyl-4-piperidyl)-1,3-thiazole-5-
30 carboxamide (Intermediate 147; 115 mg, 0.48 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (25 mg, 0.04 mmol) were dissolved in 1,4-dioxane (5 mL) Caesium carbonate (312 mg, 0.96 mmol) was added and the mixture purged with a stream of

nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (27mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled three times with nitrogen and then heated at 100°C overnight. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol.

5 Product containing fractions were concentrated and purified by normal phase chromatography (5% ammonia in methanol/DCM) to give a yellow solid which was suspended in DCM, filtered and dried on the filter to give the title compound as a white solid (48mg, 21%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.50 – 1.79 (10H, m), 1.90 – 2.04 (4H, m), 2.17 (3H, s), 2.62 (2H, t), 2.77 (2H, d), 3.19 (3H, s), 3.65 – 3.71 (3H, m), 5.09 (1H, m), 8.03 (1H, s), 8.07

10 (1H, d), 8.15 (1H, s), 11.45 (1H, s); MS m/z 485 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 263 utilising 2-amino-N-(1-methyl-4-piperidyl)-1,3-oxazole-5-carboxamide

15 Intermediate 148 the final product being purified by base modified reverse phase HPLC to give the title compound as a pale brown solid (25 mg, 41%)

Example 264:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-oxazole-5-carboxamide

20 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.48 – 1.76 (10H, m), 1.85 – 1.97 (4H, m), 2.17 (3H, s), 2.56 – 2.61 (2H, m), 2.76 (2H, d), 3.18 (3H, s), 3.59 – 3.68 (3H, m), 4.79 (1H, m), 7.63 (1H, s), 8.03 (1H, d), 8.07 (1H, s), 10.64 (1H, s); MS m/z 469 [M+H]⁺.

25 **Example 265:**

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-oxazole-4-carboxamide

2-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-1,3-oxazole-4-carboxylic acid (Intermediate 150; 85 mg, 0.23 mmol), HATU (131

30 mg, 0.34 mmol) and 4-amino-1-methylpiperidine (40 mg, 0.34 mmol) were stirred in DMF (5 mL) and DIPEA (120 µL, 0.68 mmol) added. The mixture was stirred overnight, absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product

containing fractions were concentrated and purified by normal phase chromatography (5% ammonia in methanol/DCM) to give the title compound as a white solid (66 mg, 61%)

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.50 - 1.74 (10H, m), 1.88 - 1.98 (4H, m), 2.16 (3H, s), 2.58 (2H, t), 2.82 (2H, d), 3.18 (3H, s), 3.60 - 3.63 (2H, m), 3.66 - 3.75 (1H, m), 4.71 - 4.80 (1H, m), 7.54 (1H, d), 8.06 (1H, s), 8.26 (1H, s), 10.46 (1H, s); MS m/z 469 [M+H]⁺.

Example 266:

9-[(6-chloropyridin-3-yl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 157 mg, 0.56 mmol), 5-amino-2-chloropyridine (65 mg, 0.51 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (330 mg, 1.01 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) 15 (28 mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled three times with nitrogen and then heated at 100°C for 8h. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase chromatography to give the title compound as a white solid (14mg, 20 7%)

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.56 - 1.74 (6H, m), 1.93 - 1.98 (2H, m), 2.57 - 2.60 (2H, m), 3.18 (3H, s), 3.61 - 3.64 (2H, m), 4.79 (1H, m), 7.40 (1H, d), 8.09 (1H, s), 8.18 - 8.20 (1H, m), 8.75 (1H, d), 9.51 (1H, s); MS m/z 373 [M+H]⁺.

25 Utilising the appropriate commercially available anilines, the following examples were prepared by an analogous process to that used in the preparation of Example 266.

Example 267:

30 **6-cyclopentyl-9-[(6-methoxypyridin-3-yl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one**

176

¹H NMR (399.9 MHz, DMSO-d₆) δ1.52 - 1.73 (6H, m), 1.89 - 2.08 (2H, m), 2.53 - 2.58 (2H, m), 3.16 (3H, s), 3.58 - 3.61 (2H, m), 3.81 (3H, s), 4.69 - 4.77 (1H, m), 6.75 (1H, d), 7.98 - 8.04 (2H, m), 8.39 - 8.40 (1H, m), 9.04 (1H, s); MS m/z 369 [M+H]⁺.

5 **Example 268:**

6-cyclopentyl-2-methyl-9-(pyridin-4-ylamino)-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

¹H NMR (399.9 MHz, DMSO-d₆) δ1.61 - 1.78 (6H, m), 1.97 - 2.08 (2H, m), 2.59 - 2.62 (2H, m), 3.19 (3H, s), 3.63 - 3.66 (2H, m), 4.81 - 4.89 (1H, m), 7.76 - 7.78 (2H, m), 8.13 (1H, s),
10 8.34 (2H, d), 9.81 (1H, s) MS m/z 339 [M+H]⁺.

Example 269:

6-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)pyridine-3-carboxamide

15 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 100 mg, 0.36 mmol), 6-amino-N-(1-methyl-4-piperidyl)pyridine-3-carboxamide (Intermediate 152; 76 mg, 0.32 mmol) and caesium carbonate (211 mg, 0.65 mmol) were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.02 mmol) and 9,9-dimethyl-
20 4,5-bis(diphenylphosphino)xanthene(17 mg, 0.03mmol) were added and the mixture heated at 100 °C overnight. The reaction mixture was cooled to room temperature filtered and the filter cake washed with DCM. The filtrate added to a 5g SCX-2 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated to give a brown
25 gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid (117 mg, 75%)

¹H NMR (399.902 MHz, CDCl₃) δ1.54 - 1.80 (m, 8H), 2.03 (m, 4H), 2.17 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 4.00 (m, 1H), 4.84 (m, 1H), 5.85 (d, 1H), 7.94 (s, 1H), 7.99 (s, 1H), 8.05 (m, 1H), 8.40 (d, 1H), 8.63 (m, 1H); MS m/z 479
30 [M+H]⁺.

The following example was prepared by an analogous process to that used in the preparation of Example 269 utilising 5-amino-N-(1-methyl-4-piperidyl)pyridine-2-carboxamide (Intermediate 153), to give the title compound as a yellow solid (104 mg, 61%)

5 **Example 270:**

5-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)pyridine-2-carboxamide

¹H NMR (399.902 MHz, CDCl₃) δ 1.68 (m, 8H), 2.02 (m, 4H), 2.18 (m, 2H), 2.31 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.69 (m, 2H), 3.98 (m, 1H), 4.85 (m, 1H), 7.11 (s, 1H), 7.78 (d, 1H), 7.94 (s, 1H), 8.13 (d, 1H), 8.31 (m, 1H), 8.59 (d, 1H); MS m/z 479 [M+H]⁺.

Example 271:

3-methoxy-4-[(6-methyl-5-oxo-2-prop-2-ynyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

9-chloro-2-methyl-6-prop-2-ynyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-3-one (Intermediate 154; 53 mg, 0.21 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 66 mg, 0.25 mmol) p-toluenesulphonic acid monohydrate acid (80 mg, 0.42 mmol) and isopropanol (4 mL) were combined in a 10 mL microwave reactor tube and heated in by microwave irradiation at 150 °C for 80 minutes. The sample was transferred to an SCX (10 g) cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as an off white gum (4 mg, 3%).

MS m/z 478 [M+H]⁺. Retention Time 1.03 minutes Monitor Acid

Example 272:

3-methoxy-4-[[6-methyl-2-[(4-methylpentan-2-yloxy)carbonimidoyl)methyl]-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

2-(10-chloro-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-2-

yl)acetonitrile (Intermediate 155; 97 mg, 0.39 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 124mg,0.47mmol) and p-toluenesulphonic acid monohydrate (148 mg, 0.78 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 100 °C for 24 hours. The reaction mixture was diluted with water and methanol and the solution loaded onto an SCX-2 (5 g) column pre-wet with methanol. The column was washed with methanol (x2) and eluted with 2M NH₃/MeOH. Fractions containing product identified as the addition product of the solvent and nitrile group were combined and evaporated. To the residue was added 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220 62 mg, 0.24 mmol) and p-toluenesulphonic acid monohydrate (74 mg, 0.39 mmol) and the mixture heated by microwave irradiation in isopropanol (4 mL) for 20 minutes at 150 °C. The cooled mixture was loaded onto an SCX-2 (5 g) column pre-wet with MeOH. The column was washed with MeOH and eluted with 2M NH₃/MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a light brown solid (21 mg, 9%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.75 (m, 2H), 0.81 (d, 3H), 1.13 (d, 3H), 1.24 (m, 1H), 1.52 (m, 5H), 1.76 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.46 (m, 2H), 2.75 (m, 4H), 3.22 (s, 3H), 3.75 (m, 3H), 3.95 (s, 3H), 4.22 (s, 1H), 4.91 (m, 1H), 7.48 (m, 2H), 7.59 (s, 1H), 7.80 (s, 1H), 8.04 (d, 1H), 8.43 (d, 1H); MS m/z 582 [M+H]⁺.

20

Example 273:

4-[[2-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

9-chloro-6-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-3-one (Intermediate 156; 81 mg, 0.25 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 80 mg, 0.30 mmol) p-toluenesulphonic acid monohydrate acid (96 mg, 0.5 mmol) and isopropanol (4 mL) were combined in a 10 mL microwave reactor tube and heated in by microwave irradiation at 150

⁰C for 80 minutes. The sample was transferred to an SCX (20 g) cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as an off white gum (61 mg, 45%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.58 (2H, m), 1.76 (2H, m), 1.94 (2H, m), 2.08 (3H, s), 2.17 (3H, s), 2.36 (3H, s), 2.61 (2H, m), 2.78 (2H, m), 3.17 (3H, s), 3.53 (2H, m), 3.73 (1H, m), 3.95 (3H, s), 4.61 (2H, s), 7.49 (2H, m), 7.83 (1H, s), 8.05 (1H, d), 8.19 (1H, s), 8.35 (1H, d).

Example 274:

4-[[2-(2-fluoroethyl)-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(2-fluoroethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

(Intermediate 157; 86 mg, 0.33 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 104 mg, 0.40 mmol) and p-toluenesulphonic acid monohydrate (126 mg, 0.66 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 100 °C for 24 hours. The reaction mixture was diluted with water and methanol and the solution loaded onto an SCX-2 (5 g) column pre-wet with methanol. The column was washed with methanol (x2) and the product eluted with 2M NH₃/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a yellow solid (60 mg, 37%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.59 (m, 2H), 1.75 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.73 (m, 4H), 3.13 (s, 3H), 3.57 (m, 2H), 3.72 (s, 3H), 3.72 (m, 1H), 3.83 (t, 2H), 4.05 (t, 2H), 6.91 (d, 1H), 7.32 (m, 2H), 7.89 (s, 1H), 7.91 (d, 1H); MS m/z 466 [M+H]⁺-HF.

Example 275:

N-cyclohexyl-4-[[2-(2-dimethylaminoethyl)-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-3-methoxy-benzamide

10-chloro-2-(2-dimethylaminoethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 158; 84 mg, 0.30 mmol), 4-amino-3-methoxy-N-(1-methyl-4-

piperidyl)benzamide (WO06/018220; 90 mg, 0.36 mmol) and p-toluenesulphonic acid monohydrate (113 mg, 0.60 mmol) were heated together in IPA (4 mL) by microwave irradiation at 150 °C for 20 minutes. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol; the column was washed with methanol and the product eluted
5 with 2M NH₃/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (59 mg, 40%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.24 (m, 5H), 1.72 (m, 6H), 2.19 (s, 6H), 2.54 (t, 2H), 2.62 (m, 2H), 3.17 (s, 3H), 3.70 (t, 3H), 3.75 (m, 2H), 3.95 (s, 3H), 7.48 (m, 2H), 7.70 (s, 1H),
10 8.01 (d, 1H), 8.07 (s, 1H), 8.35 (d, 1H); MS m/z 496 [M+H]⁺.

Example 276:

N-cyclohexyl-3-methoxy-4-[[6-methyl-5-oxo-2-[2-(1-piperidyl)ethyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]benzamide

15 10-chloro-6-methyl-2-[2-(1-piperidyl)ethyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 159; 90 mg, 0.28 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 83 mg, 0.34 mmol) and p-toluenesulphonic acid monohydrate (107 mg, 0.56 mmol) were heated together in IPA (4 mL) by microwave irradiation at 150 °C for 20 minutes. The reaction mixture was loaded onto an SCX-2 (5g)
20 column pre-wet with methanol; the column was washed with methanol and the product eluted with 2M NH₃/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (40 mg, 27%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.15 (m, 1H), 1.34 (m, 6H), 1.47 (m, 4H), 1.72 (m, 6H), 2.35 (m, 4H), 2.54 (t, 2H), 2.62 (m, 2H), 3.17 (s, 3H), 3.69 (t, 2H), 3.74 (m, 2H), 3.94 (s, 3H), 7.49 (m, 2H), 7.69 (s, 1H), 8.01 (d, 1H), 8.06 (s, 1H), 8.33 (d, 1H); MS m/z 536 [M+H]⁺.
25

Example 277:

N-cyclohexyl-3-methoxy-4-[[6-methyl-2-(2-morpholin-4-ylethyl)-5-oxo-2,6,9,11-

30 **tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]benzamide**

10-chloro-6-methyl-2-(2-morpholin-4-ylethyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 160; 95 mg, 0.29 mmol), -amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 86 mg, 0.35 mmol) and p-toluenesulphonic acid monohydrate (110 mg, 0.58 mmol) were heated together in IPA (4 mL) by microwave
 5 irradiation at 150 °C for 20 minutes. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol; the column was washed with methanol and the product eluted with 2M NH₃/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (56 mg, 36%).

10 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.15 (m, 1H), 1.32 (m, 4H), 1.72 (m, 6H), 2.39 (m, 4H), 2.60 (m, 4H), 3.17 (s, 3H), 3.55 (t, 4H), 3.73 (m, 4H), 3.94 (s, 3H), 7.48 (m, 2H), 7.72 (s, 1H), 8.01 (d, 1H), 8.06 (s, 1H), 8.30 (d, 1H); MS m/z 538 [M+H]⁺.

Example 278:

15 **4-[(2-cyclopentyl-4,4-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide**
 10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 127; 62 mg, 0.21 mmol) and 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 161; 63 mg, 0.21 mmol) were taken up
 20 in 4-methyl-2-pentanol (2 mL) and p-toluenesulphonic acid monohydrate (81 mg, 0.42 mmol) added. The reaction mixture was heated at 160 °C by microwave irradiation for 60 minutes. The cooled reaction mixture was treated with a mixture of methanol & water (5:2 v/v, 7 mL). The resultant solution was loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed through with Methanol (~40 mL). Products were then eluted with 2M
 25 ammonia in methanol (~30 mL). The ammoniacal solution was evaporated and the resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (64 mg, 54%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.90 - 0.95 (2H, m), 1.14 (6H, s), 1.41 - 1.50 (3H, m), 1.54 - 1.68 (4H, m), 1.71 - 1.78 (2H, m), 1.83 - 1.96 (4H, m), 2.01 - 2.10 (1H, m), 2.15 - 2.23
 30 (2H, m), 2.42 (3H, s), 2.95 - 3.01 (2H, m), 3.27 - 3.28 (2H, m), 3.95 (3H, s), 4.28 - 4.39 (1H,

m), 5.23 (1H, quintet), 7.45 - 7.49 (2H, m), 7.59 (1H, s), 7.88 - 7.90 (2H, m), 8.35 (1H, d), 9.45 (1H, s); MS m/z 562 $[M+H]^+$.

Example 279:

5 **4-(9'-cyclopentyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide**
2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one (Intermediate 131; 256 mg, 0.875 mmol) and 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 162; 255 mg, 0.875 mmol) and
10 the p-toluenesulphonic acid monohydrate (416 mg, 2.19 mmol) and 4-Methyl-2-pentanol (5 mL) were heated by microwave irradiation for 30 minutes at 160 °C. The cooled reaction mixture was dissolved up in methanol (50 mL) and loaded onto a SCX-2 cartridge (20 g) pre-wet with methanol. The cartridge was washed through with methanol (3 x 35 mL) and the
15 product eluted with 7 N methanolic ammonia (~100 mL). The ammoniacal solution was evaporated and the resultant material purified on a silica column loaded as a solution in DCM (20 mL) and eluted with a linear gradient of 0 to 10% 7N NH₃/MeOH in DCM. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid
20 after trituration under diethyl ether (104 mg, 22%)
¹H NMR (400.13 MHz, CDCl₃) δ 0.77 - 0.80 (2H, m), 0.93 - 1.00 (2H, m), 1.17 - 1.30 (4H, m), 1.34 - 1.37 (2H, m), 1.47 (1H, s), 1.62 - 1.68 (4H, m), 1.88 - 1.93 (5H, m), 2.43 (3H, s), 2.40 - 2.49 (2H, m), 3.02 (2H, d), 3.27 (2H, s), 4.37 - 4.49 (1H, m), 4.98 - 5.07 (1H, m), 5.67 (1H, d), 7.11 (1H, d), 7.20 (1H, s), 7.41 - 7.44 (1H, m), 7.45 - 7.48 (1H, m), 7.63 (1H, s), 8.46
25 (1H, t); MS m/z 548 $[M+H]^+$.

Example 280:

4-(9'-cyclopentyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide
30

2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one (Intermediate 131; 293 mg, 1.0 mmol) and 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 161; 303 mg, 1.0 mmol) and the p-toluenesulphonic acid monohydrate (476 mg, 2.5 mmol) and 4-Methyl-2-pentanol (10 mL) were combined and heated with stirring at 120 °C overnight. The cooled reaction mixture was dissolved up in methanol (60 mL) and loaded onto a SCX-2 cartridge (20 g) pre-wet with methanol. The cartridge was washed through with methanol (3 x 35 mL) and the product eluted with 7 N methanolic ammonia (~100 mL). The ammoniacal solution was evaporated and the resultant material purified on a silica column loaded as a solution in DCM (17 mL) and eluted with a linear gradient of 0 to 10% 2N NH₃/MeOH in DCM. Product containing fractions were combined and evaporated and the resultant material triturated under diethyl ether. The resultant filtered solid was treated with warm DMF (3 mL) and acetonitrile (8 mL) upon cooling in an ice/water bath a solid precipitate formed which was filtered and dried to yield the title compound as a white solid (251 mg, 45%)

¹H NMR (400.13 MHz, CDCl₃) δ 0.77 - 0.79 (2H, m), 0.96 (2H, d), 1.19 - 1.33 (4H, m), 1.35 - 1.37 (2H, m), 1.44 - 1.48 (1H, m), 1.60 - 1.68 (4H, m), 1.85 - 1.98 (5H, m), 2.41 - 2.50 (2H, m), 2.43 (3H, s), 3.02 (2H, d), 3.25 (2H, s), 3.90 (3H, s), 4.41 - 4.46 (1H, m), 5.00 - 5.09 (1H, m), 5.75 (1H, d), 7.16 (1H, dd), 7.36 (1H, d), 7.55 (1H, s), 7.67 (1H, s), 7.75 (1H, s), 8.39 (1H, d); MS m/z 560 [M+H]⁺.

Example 281:

3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

To a stirred solution of 3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzoic acid (Intermediate 163; 80 mg, 0.20 mmol), HATU (115 mg, 0.30 mmol) and 4-amino-1-methylpiperidine (Fluorochem; 35 mg, 0.30 mmol) in DMF (5 mL) was added diisopropylethylamine (105 µl, 0.60 mmol). The mixture was stirred for 2 hours at room temperature and then absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (5% ammonia in methanol/DCM) to yield the title compound as a white foam (87 mg, 88%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.26 (6H, d), 1.44 (3H, t), 1.55 - 1.65 (2H, m), 1.77 (2H, d), 1.92 - 1.98 (2H, m), 2.18 (3H, s), 2.60 (2H, m), 2.79 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.70 - 3.78 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.49 - 7.53 (2H, m), 7.67 (1H, s), 8.05 (2H, m), 8.41 (1H, d); MS m/z 496 [M+H]⁺.

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Example 282:

3-ethoxy-N-(1-ethyl-4-piperidyl)-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of **Example 281**, on a 0.2 mmol scale, utilising 4-amino-1-ethylpiperidine (Fluorochem; 39 mg, 0.3 mmol), as a white foam (67 mg, 66%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.01 (3H, t), 1.26 (6H, d), 1.44 (3H, t), 1.52 - 1.62 (2H, m), 1.77 - 1.80 (2H, m), 1.94 (2H, m), 2.34 (2H, q), 2.60 (2H, m), 2.89 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.72 - 3.80 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.48 - 7.52 (2H, m), 7.67 (1H, s), 8.05 (2H, m), 8.41 (1H, d); MS m/z 510 [M+H]⁺.

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Example 283:

3-ethoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of **Example 281**, on a 0.2 mmol scale, utilising Endo-9-methyl-9-azabicyclo[3,3,1]nonane-3-one (Chempacific; 47 mg, 0.3 mmol), as a white foam (71 mg, 66%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.94 (2H, d), 1.27 (6H, d), 1.41 - 1.49 (6H, m), 1.89 - 1.96 (2H, m), 2.06 (1H, m), 2.15 - 2.23 (2H, m), 2.42 (3H, s), 2.61 (2H, m), 2.99 (2H, d), 3.18 (3H, s), 3.63 (2H, m), 4.22 (2H, q), 4.30 - 4.38 (1H, m), 4.78 - 4.85 (1H, m), 7.49 - 7.53 (2H, m), 7.67 (1H, s), 7.90 (1H, d), 8.07 (1H, s), 8.42 (1H, d); MS m/z 536 [M+H]⁺.

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Example 284:

3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

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10-Chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 10; 100 mg, 0.39 mmol), 4-amino-3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 166; 104 mg, 0.39 mmol) and 4-toluenesulphonic acid monohydrate (187 mg, 0.98 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The cooled reaction mixture was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified preparative reverse phase HPLC to yield the title compound as a white solid (114 mg, 61%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.26 (6H, d), 1.44 (3H, t), 1.73 - 1.81 (1H, m), 2.12 - 2.20 (1H, m), 2.27 (3H, s), 2.37 - 2.46 (2H, m), 2.57 - 2.70 (4H, m), 3.18 (3H, s), 3.62 (2H, m), 4.21 (2H, q), 4.38 - 4.44 (1H, m), 4.78 - 4.85 (1H, m), 7.51 - 7.55 (2H, m), 7.67 (1H, s), 8.07 (1H, s), 8.28 (1H, d), 8.41 (1H, d); MS m/z 482 [M+H]⁺.

Example 285:

15 **N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.26 mmol scale, utilising 4-amino-N-((1s,4s)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 167; 66 mg, 0.36 mmol), as a white solid (39 mg, 29%).

20 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.26 (6H, d), 1.42 - 1.54 (7H, m), 1.72 - 1.80 (2H, m), 1.86 - 1.90 (2H, m), 2.99 - 2.03 (1H, m), 2.19 (6H, s), 2.60 (2H, m), 3.18 (3H, s), 3.62 (2H, m), 3.89 - 3.93 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.51 - 7.56 (2H, m), 7.66 (1H, s), 8.00 (1H, d), 8.07 (1H, s), 8.41 (1H, d); MS m/z 525 [M+H]⁺.

Example 286:

25 **N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.26 mmol scale, utilising 4-amino-N-((1r,4r)-4-(dimethylamino)cyclohexyl)-3-

30 ethoxybenzamide (Intermediate 168; 66 mg, 0.26 mmol), as a white solid (80 mg, 59%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.23 - 1.39 (10H, m), 1.44 (3H, t), 1.83 - 1.91 (4H, m), 2.11 - 2.19 (7H, m), 2.60 (2H, m), 3.18 (3H, s), 3.62 (2H, m), 3.71 - 3.75 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.48 - 7.52 (2H, m), 7.67 (1H, s), 8.01 (1H, d), 8.07 (1H, s), 8.41 (1H, d); MS m/z 525 [M+H]⁺.

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Example 287:

5-ethoxy-2-fluoro-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

10 The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.39 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 169; 116mg, 0.39 mmol), heating at 140 °C for 2 hours, as a white solid (73 mg, 37%).

15 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.27 (6H, d), 1.42 (3H, t), 1.52 - 1.62 (2H, m), 1.78 (2H, d), 1.99 (2H, t), 2.17 (3H, s), 2.62 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.64 (2H, m), 3.69 - 3.79 (1H, m), 4.18 (2H, q), 4.77 - 4.84 (1H, m), 7.20 (1H, d), 7.74 (1H, d), 7.79 - 7.82 (1H, m), 8.10 (1H, s), 8.35 (1H, d); MS m/z 515 [M+H]⁺.

Example 288:

20 **5-ethoxy-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.39 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 170; 132mg, 0.39 mmol), heating at 140
25 °C for 2 hours, as a white solid (92 mg, 43%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.92 (2H, d), 1.28 (6H, d), 1.39 - 1.46 (6H, m), 1.87 - 1.94 (2H, m), 1.99 - 2.10 (1H, m), 2.17 - 2.25 (2H, m), 2.42 (3H, s), 2.62 (2H, m), 2.98 (2H, d), 3.19 (3H, s), 3.64 (2H, m), 4.18 (2H, q), 4.26 - 4.34 (1H, m), 4.78 - 4.85 (1H, m), 7.22 (1H, d), 7.65 - 7.68 (1H, m), 7.75 (1H, d), 8.11 (1H, s), 8.36 (1H, d); MS m/z 555 [M+H]⁺.

Example 289:**5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

4-amino-5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 173; 91 mg, 0.32 mmol), 10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 178; 100 mg, 0.35 mmol) and XANTPHOS (17 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (225 mg, 0.64 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (2.5% 3.5N ammonia in methanol/DCM) to yield the title compound as a white solid (96mg, 56%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.12 (6H, s), 1.21 (6H, d), 1.50 - 1.60 (2H, m), 1.77 - 1.80 (2H, m), 1.93 - 2.00 (2H, m), 2.17 (3H, s), 2.74 (2H, d), 3.21 (3H, s), 3.38 (2H, s), 3.67 - 3.72 (1H, m), 5.07 - 5.14 (1H, m), 7.67 (1H, d), 8.03 - 8.08 (3H, m), 8.31 - 8.36 (1H, m); MS m/z 532 [M+H]⁺.

Example 290:**5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 289, on a 0.39 mmol scale, utilising 4-amino-5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide (Intermediate 174; 96 mg, 0.32 mmol), as a white solid (67 mg, 38%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.00 (3H, t), 1.12 (6H, s), 1.21 (6H, d), 1.48 - 1.58 (2H, m), 1.80 (2H, d), 1.96 (2H, t), 2.32 (2H, q), 2.84 (2H, d), 3.21 (3H, s), 3.38 (2H, s), 3.68 - 3.76 (1H, m), 5.07 - 5.14 (1H, m), 7.67 (1H, d), 8.03 - 8.07 (3H, m), 8.32 - 8.36 (1H, m); MS m/z 546 [M+H]⁺.

Example 291:

5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 289, on a 0.39 mmol scale, utilising 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 100 mg, 0.32 mmol), as a white solid (109 mg, 61%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.12 (6H, s), 1.17 - 1.37 (8H, m), 1.46 - 1.58 (2H, m), 1.68 - 1.94 (4H, m), 2.13 - 2.18 (7H, m), 3.20 (3H, s), 3.38 (2H, s), 3.64 - 3.71 and 3.91 - 4.95 (each 0.5H, m), 5.08 - 5.15 (1H, m), 7.62 - 7.67 (1H, m), 7.98 - 8.04 (3H, m), 8.29 - 8.34 (1H, m); MS m/z 560 [M+H]⁺.

Example 292:

2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 178; 100 mg, 0.35 mmol), 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 95 mg, 0.35 mmol) and p-toluenesulphonic acid monohydrate (169 mg, 0.88 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified preparative reverse phase HPLC to yield the title compound as a white solid (60 mg, 33%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.12 (6H, s), 1.23 (6H, d), 1.68 - 1.76 (1H, m), 2.13 - 2.22 (1H, m), 2.27 (3H, s), 2.36 - 2.45 (2H, m), 2.59 - 2.64 (1H, m), 2.67 - 2.71 (1H, m), 3.20 (3H, s), 3.39 (2H, s), 3.93 (3H, s), 4.35 - 4.43 (1H, m), 5.09 - 5.16 (1H, m), 7.22 (1H, d), 7.75 (1H, d), 7.96 - 7.99 (1H, m), 8.03 (1H, s), 8.34 (1H, d); MS m/z 516 [M+H]⁺.

Example 293:

3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.35 mmol scale, utilising 4-amino-3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-

5 yl]benzamide (Intermediate 166; 94 mg, 0.35 mmol), as a white solid (106 mg, 59%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.23 (6H, d), 1.44 (3H, t), 1.74 - 1.80 (1H, m), 2.15 - 2.19 (1H, m), 2.27 (3H, s), 2.38 - 2.47 (2H, m), 2.61 - 2.71 (2H, m), 3.20 (3H, s), 3.38 (2H, s), 4.21 (2H, q), 4.39 - 4.43 (1H, m), 5.09 - 5.16 (1H, m), 7.51 - 7.54 (2H, m), 7.63 (1H, s), 7.98 (1H, s), 8.28 (1H, d), 8.38 (1H, d); MS m/z 511 [M+H]⁺.

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Example 294:

N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

15 The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.26 mmol scale, utilising 4-amino-N-((1s,4s)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 167; 80 mg, 0.26 mmol), as a white solid (91 mg, 59%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.23 (6H, d), 1.40 - 1.55 (7H, m), 1.72 - 1.81 (2H, m), 1.86 - 1.90 (2H, m), 2.01 - 2.05 (1H, m), 2.19 (6H, s), 3.20 (3H, s), 3.38 (2H, 20 s), 3.88 - 3.95 (1H, m), 4.21 (2H, q), 5.09 - 5.16 (1H, m), 7.51 - 7.55 (2H, m), 7.62 (1H, s), 7.97 - 8.01 (2H, m), 8.37 (1H, d); MS m/z 553 [M+H]⁺.

Example 295:

25 **N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.26 mmol scale, utilising 4-amino-N-((1r,4r)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 168; 80 mg, 0.26 mmol), as a white solid (77 mg, 54%).

30 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.23 (6H, d), 1.27 - 1.39 (4H, m), 1.44 (3H, t), 1.83 - 1.92 (4H, m), 2.15 - 2.21 (7H, m), 3.20 (3H, s), 3.38 (2H, s), 3.71 - 3.75 (1H, m),

4.21 (2H, q), 5.09 - 5.15 (1H, m), 7.48 - 7.51 (2H, m), 7.63 (1H, s), 7.98 - 8.02 (2H, m), 8.37 (1H, d); MS m/z 553 [M+H]⁺.

Example 296:

5 **5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.39 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 169; 116 mg, 0.39 mmol), as a white solid (92 mg, 48%).

10 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.12 (6H, s), 1.21 - 1.24 (6H, d), 1.42 (3H, t), 1.52 - 1.62 (2H, m), 1.77 - 1.80 (2H, m), 1.94 - 2.00 (2H, m), 2.17 (3H, s), 2.69 - 2.75 (2H, m), 3.20 (3H, s), 3.39 (2H, s), 3.69 - 3.76 (1H, m), 4.18 (2H, q), 5.07 - 5.14 (1H, m), 7.20 (1H, d), 7.71 (1H, d), 7.77 - 7.80 (1H, m), 8.02 (1H, s), 8.31 (1H, d); MS m/z 543 [M+H]⁺.

15 **Example 297:**

5-ethoxy-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.32 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-

20 yl]benzamide (Intermediate 186; 90 mg, 0.32 mmol), as a white foam (61 mg, 36%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.12 (6H, s), 1.24 (6H, d), 1.42 (3H, t), 1.67 - 1.75 (1H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.34 - 2.47 (2H, m), 2.58 - 2.63 (1H, m), 2.66 - 2.70 (1H, m), 3.20 (3H, s), 3.39 (2H, s), 4.18 (2H, q), 4.34 - 4.43 (1H, m), 5.07 - 5.14 (1H, m), 7.21 (1H, d), 7.71 (1H, s), 7.95 - 7.98 (1H, m), 8.02 (1H, s), 8.31 (1H, d); MS m/z 529

25 [M+H]⁺.

Example 298:

3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]benzamide

30 **10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one** (Intermediate 178; 43 mg, 0.15 mmol) and 4-amino-3-fluoro-N-(9-methyl-9-

azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 162; 44 mg, 0.15 mmol) were combined with p-toluenesulphonic acid monohydrate (72 mg, 0.38 mmol) in 4-methyl-2-pentanol (1 mL) and heated by microwave irradiation for 50 minutes at 160 °C. The cooled reaction mixture was diluted with methanol (5 mL) and loaded onto an SCX-3 cartridge (2 g) pre-wet with Methanol. The cartridge was washed with methanol (2 x 3 mL) and product eluted with 7 N methanolic ammonia (10 mL). The basic fraction was evaporated to give a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid (46 mg, 57 %).

¹H NMR (400 MHz, DMSO-d₆) δ 0.9 (2H, d), 1.1 (6H, s), 1.15 (6H, d), 1.45 (4H, t), 1.9 (2H, m), 2.05 (1H, m), 2.2 (3H, m), 2.4 (3H, s), 2.95 (2H, d), 3.20 (3H, s), 3.3 (2H, s), 4.3 (1H, m), 5.1 (1H, m), 7.65 (2H, m), 7.95 (2H, m), 8.15 (2H, m), 8.15 (1H, t), 8.55 (1H, s); MS m/z 539 [M+H]⁺.

Example 299:

15 **3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide**
10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 178; 75 mg, 0.27 mmol), 4-amino-3-methoxy-N-(1-methylpyrrolidin-3-yl)benzamide (Intermediate 187; 67 mg, 0.27 mmol) and p-toluenesulphonic acid monohydrate (127 mg, 0.66 mmol) were heated at 140 °C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction mixture was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with methanol and eluted with 2% 7N ammonia/methanol to. Product containing fractions were evaporated and the residue dissolved in DMF and purified by base modified reverse phase HPLC to give the title compound as a white solid (23 mg, 17.5%).
25 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.08 (6H, s), 1.22 (6H, d), 1.78 (1H, m), 2.18 (1H, m), 2.23 (3H, s), 2.38 (1H, m), 2.41 (1H, m), 2.61 (1H, m), 2.64 (1H, m), 3.18 (3H, s), 3.37 (2H, s), 3.95 (3H, s), 4.41 (1H, m), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 496 [M+H]⁺.

30 **Example 300:**

N-(1-ethyl-4-piperidyl)-3-methoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299, on a 0.27 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

5 (Intermediate 190; 74 mg, 0.27 mmol), as a white solid (31 mg, 22%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.00 (3H, t), 1.10 (6H, s), 1.22 (6H, d), 1.55 (2H, q), 1.78 (2H, d), 1.95 (2H, t), 2.31 (2H, q), 2.89 (2H, d), 3.17 (3H, s), 3.37 (2H, s), 3.75 (1H, m), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 524 [M+H]⁺.

10

Example 301:

3-methoxy-N-(2-pyrrolidin-1-ylethyl)-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299,

15 on a 0.27 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

(Intermediate 192; 70 mg, 0.27 mmol), as a white solid (52 mg, 38%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.10 (6H, s), 1.22 (6H, d), 1.68 (4H, m), 2.49 (4H, m), 2.60 (2H, t), 3.18 (3H, s), 3.38 (2H, s), 3.40 (2H, m), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 510 [M+H]⁺.

20

Example 302:

N-(2-dimethylaminoethyl)-3-methoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299,

25 on a 0.27 mmol scale, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

(Intermediate 194; 63 mg, 0.27 mmol), as a white solid (38 mg, 30%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.10 (6H, s), 1.22 (6H, d), 2.18 (6H, s), 2.39 (2H, t), 3.18 (3H, s), 3.35 (2H, t), 3.37 (2H, s), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 510 [M+H]⁺.

30

Example 303:

N-(3-dimethylaminopropyl)-3-methoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299, on a 0.27 mmol scale, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

5 (Intermediate 196; 67 mg, 0.27 mmol), as a white solid (8 mg, 6%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.10 (6H, s), 1.22 (6H, d), 1.68 (2H, m), 2.18 (3H, s), 2.28 (2H, t), 3.17 (3H, s), 3.29 (2H, t), 3.37 (2H, s), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 498 [M+H]⁺.

10 **Example 304:**

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-4,4-diethyl-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 198; 100 mg, 0.322 mmol), p-toluene sulphonic acid monohydrate

15 (153 mg, 0.81 mmol) and 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

(WO06/018220; 84 mg, 0.322 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The reaction mixture was loaded on to an SCX column (10 g), pre-wet with methanol, washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the resultant

20 material purified by base modified reverse phase preparative HPLC to yield the title

compound, after drying under vacuum at 70 °C, as a white solid (97 mg, 56%)

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.25 (d, 6H), 1.63 - 1.49 (m, 4H), 1.70 (sextet, 2H), 2.07 - 2.04 (m, 2H), 2.19 - 2.13 (m, 2H), 2.30 (s, 3H), 2.84 - 2.81 (m, 2H), 3.28 (s, 3H), 3.40 (s, 2H), 4.04 - 3.92 (m, 4H), 5.32 (sextet, 1H), 5.93 (d, 1H), 7.24 (dd, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.83 (s, 1H), 8.48 (d, 1H); MS m/z 538 [M+H]⁺.

Example 305:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 89 mg, 0.322 mmol), as a white solid (89 mg, 30%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.10 (t, 3H), 1.25 (d, 6H), 1.63 - 1.49 (m, 4H), 1.75 - 1.66 (m, 2H), 2.17 - 2.06 (m, 4H), 2.44 (q, 2H), 2.93 - 2.90 (m, 2H), 3.28 (s, 3H), 3.40 (s, 2H), 4.05 - 3.97 (m, 4H), 5.32 (septet, 1H), 5.91 (d, 1H), 7.23 (dd, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.83 (s, 1H), 8.47 (d, 1H); MS m/z 552 [M+H]⁺.

10 **Example 306:**

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 97 mg, 0.322 mmol), as a white solid (83 mg, 45%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.78 (t, 6H), 1.22 (d, 6H), 1.60 - 1.40 (m, 6H), 1.89 - 1.77 (m, 2H), 2.16 - 2.03 (m, 2H), 2.42 - 2.33 (m, 2H), 3.18 (s, 3H), 3.29 (s, 4H), 3.41 (s, 2H), 3.69 - 3.57 (m, 2H), 3.97 (s, 3H), 4.70 - 4.52 (m, 1H), 5.24 - 5.18 (m, 1H), 7.53 - 7.51 (m, 2H), 7.67 (s, 1H), 7.98 (s, 1H), 8.31 - 8.22 (m, 1H), 8.41 (d, 1H), 9.27 - 9.18 (m, 1H); MS m/z 578 [M+H]⁺.

25

Example 307:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-

azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 204; 103 mg, 0.322 mmol), as a white solid (100 mg, 52%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.85 (t, 6H), 1.05 - 1.03 (m, 2H), 1.34 - 1.26 (m, 8H), 1.59 - 1.49 (m, 3H), 1.70 (sextet, 2H), 2.02 - 1.91 (m, 3H), 2.57 - 2.50 (m, 5H), 3.10 - 3.07 (m, 2H), 3.29 (s, 3H), 3.42 (s, 2H), 3.95 (s, 3H), 4.57 - 4.46 (m, 1H), 5.30 (septet, 1H), 6.55 (dd, 1H), 7.57 (d, 1H), 7.64 (s, 1H), 7.85 (s, 1H), 8.38 (d, 1H); MS m/z 596 [M+H]⁺.

Example 308:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 95 mg, 0.322 mmol), as a white solid (87 mg, 48%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.85 (t, 6H), 1.10 (t, 3H), 1.27 (d, 6H), 1.75 - 1.49 (m, 6H), 2.08 - 2.06 (m, 2H), 2.20 - 2.14 (m, 2H), 2.44 (q, 2H), 2.88 - 2.85 (m, 2H), 3.29 (s, 3H), 3.42 (s, 2H), 3.95 (s, 3H), 4.10 - 4.00 (m, 1H), 5.33 - 5.26 (m, 1H), 6.68 (dd, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.85 (s, 1H), 8.38 (d, 1H); MS m/z 570 [M+H]⁺.

Example 309:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.33 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-

methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol), as a white solid (76 mg, 40%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.01 (s, 6H), 1.24 (d, 6H), 1.53 (sextet, 2H), 1.71 (sextet, 2H), 1.86 - 1.81 (m, 4H), 2.57 (s, 2H), 2.72 - 2.68 (m, 4H), 3.28 (s, 3H), 3.40 - 3.39 (m, 4H), 3.97 (s, 3H), 5.34 (septet, 1H), 7.20 (dd, 1H), 7.58 (d, 1H), 7.62 (s, 1H), 7.84 (s, 1H), 8.44 (d, 1H), 9.28 (s, 1H); MS m/z 5780 [M+H]⁺.

Example 310:

(R)-5-chloro-2-fluoro-4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-methylpyrrolidin-3-yl)benzamide

2'-chloro-9'-isopropyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 208; 88 mg, 0.32mmol), 4-amino-5-chloro-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 207; 101 mg, 0.36 mmol) and XANTPHOS (17 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (229 mg, 0.65 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (2.5% 7N ammonia in MeOH/DCM) to yield the title compound as a pale yellow foam (148 mg, 90%).
¹H NMR (399.9 MHz, DMSO-d₆) δ 0.70 - 0.73 (2H, m), 0.94 - 0.96 (2H, m), 1.15 (6H, d), 1.67 - 1.75 (1H, m), 2.12 - 2.21 (1H, m), 2.26 (3H, s), 2.33 - 2.43 (2H, m), 2.56 - 2.62 (1H, m), 2.67 - 2.71 (1H, m), 3.19 (3H, s), 3.49 (2H, s), 4.31 - 4.40 (1H, m), 4.79 - 4.86 (1H, m), 7.69 (1H, d), 8.04 (2H, m), 8.23 - 8.25 (1H, m), 8.36 - 8.41 (1H, m); MS m/z 516 [M+H]⁺.

Example 311:

5-chloro-N-(1-ethylpiperidin-4-yl)-2-fluoro-4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)benzamide

The title compound was prepared by an analogous method to the preparation of Example 310, on a 0.29 mmol scale, utilising 4-amino-5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide (Intermediate 174; 87 mg, 0.29 mmol), after purification by base modified reverse phase preparative HPLC, as a white solid (98 mg, 62%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.72 (2H, m), 0.94 (2H, m), 1.00 (3H, t), 1.17 (6H, d), 1.51 - 1.57 (2H, m), 1.80 (2H, d), 1.96 (2H, t), 2.32 (2H, q), 2.84 (2H, d), 3.18 (3H, s), 3.49 (2H, s), 3.67 - 3.78 (1H, m), 4.79 - 4.86 (1H, m), 7.67 (1H, d), 8.02 - 8.07 (3H, m), 8.38 (1H, d); MS m/z 544 [M+H]⁺.

Example 312:

4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(2-(pyrrolidin-1-yl)ethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.36 mmol scale, utilising 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 94 mg, 0.36 mmol), heating at 140 °C for 2 hours, as a white solid (65 mg, 36%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 (2H, t), 0.93 (2H, t), 1.19 (6H, d), 1.69 – 1.72 (4H, s), 2.71 (4H, s), 2.80 (2H, s), 3.17 (3H, s), 3.39 – 3.41 (2H, t), 3.48 (2H, s), 3.95 (3H, s), 4.82 – 4.86 (1H, m), 7.49 (1H, d), 7.50 (1H, s), 7.63 (1H, s), 7.99 (1H, s), 8.32 (1H, t), 8.43 (1H, d); MS m/z 509 [M+H]⁺.

Example 313:

N-(3-(dimethylamino)-2,2-dimethylpropyl)-4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxybenzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.36 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide (Intermediate 206; 100 mg, 0.36 mmol), heating at 140 °C for 2 hours, as a white solid (78 mg, 42%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 (2H, t), 0.89 (6H, s), 0.93 (2H, t), 1.18 (6H, d), 2.21 (2H, s), 2.25 (6H, s), 3.17 (3H, s), 3.21 (2H, d), 3.48 (2H, s), 3.95 (3H, s), 4.82 – 4.86 (1H, m), 7.49 (1H, d), 7.50 (1H, s), 7.63 (1H, s), 7.99 (1H, s), 8.32 (1H, t), 8.43 (1H, d); MS m/z 525 [M+H]⁺.

Example 314:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-propyl-4-piperidyl)benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 231 mg, 0.56 mmol), DIPEA (0.3 mL, 1.68 mmol) and HATU (283 mg, 0.75 mmol) were stirred together in DMA (4 mL) at ambient temperature for 10 minutes. 4-amino-1-propylpiperidine (Fluorochem; 100 mg, 0.70 mmol) was added and the mixture stirred at room temperature for 4 hours. The reaction mixture was loaded onto an SCX-2 (10g) column pre-wet with MeOH. The column was washed with MeOH (x2) and the product eluted with 2M NH₃/MeOH. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC. Product containing fractions were combined and evaporated to yield the title compound as a gum (194 mg, 65%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.86 (t, 3H), 1.44 (m, 2H), 1.66 (m, 10H), 1.94 (m, 4H), 2.24 (t, 2H), 2.59 (m, 2H), 2.87 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.76 (m, 1H), 3.95 (s, 3H), 4.82 (m, 1H), 7.48 (m, 2H), 7.72 (s, 1H), 8.05 (d, 1H), 8.08 (s, 1H), 8.38 (d, 1H); MS m/z 536 [M+H]⁺.

Example 315:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-dimethylaminoethyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 80 mg, 0.285 mmol) and 4-amino-3-chloro-N-(2-dimethylaminoethyl)benzamide (Intermediate 213; 69 mg, 0.285 mmol), p-toluenesulphonic acid monohydrate (136 mg, 0.713 mmol) were combined in 4-Methyl-2-pentanol (2 mL) and heated at 100 °C overnight. Methanol was added to the cooled reaction mixture and the solution loaded onto an SCX-3 column (5 g) pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were evaporated and the residue dissolved in DCM with a little MeOH. The resultant solution was purified on a silica column, eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (21 mg, 15%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.56 - 1.79 (m, 6H), 2.02 (m, 2H), 2.29 (s, 6H), 2.53 (m, 2H), 2.68 (m, 2H), 3.30 (s, 3H), 3.51 (m, 2H), 3.70 (m, 2H), 4.87 (m, 1H), 6.71 (s, 1H), 7.53 (s, 1H), 7.68 (m, 1H), 7.83 (m, 1H), 7.95 (s, 1H), 8.63 (d, 1H); MS m/z 486 [M+H]⁺.

5 **Example 316:**

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 80 mg, 0.285 mmol) and 4-amino-3-chloro-N-(1-ethyl-4-piperidyl)benzamide (Intermediate 212; 76 mg, 0.285 mmol), p-toluenesulphonic acid monohydrate (136 mg, 0.713 mmol) were combined in 4-Methyl-2-pentanol (2 mL) and heated at 100 °C overnight. Methanol was added to the cooled reaction mixture and the solution loaded onto an SCX-3 column (5 g) pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were evaporated and the residue dissolved in DCM with a little MeOH. The resultant solution was purified on a silica column, eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (22 mg, 15%).
20 ¹H NMR (399.902 MHz, CDCl₃) δ 1.11 (t, 3H), 1.54 - 1.79 (m, 8H), 2.08 (m, 6H), 2.44 (q, 2H), 2.68 (m, 2H), 2.92 (m, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 3.99 (m, 1H), 4.87 (m, 1H), 5.84 (d, 1H), 7.54 (s, 1H), 7.62 (m, 1H), 7.80 (m, 1H), 7.96 (s, 1H), 8.64 (d, 1H); MS m/z 526 [M+H]⁺.

Example 317:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.356 mmol scale, utilising 4-amino-3-chloro-N-(3-dimethylaminopropyl)benzamide (Intermediate 214; 91 mg, 0.356 mmol), as a white solid (31 mg, 17%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.55 - 1.80 (m, 8H), 2.03 (m, 2H), 2.33 (s, 6H), 2.53 (m, 2H), 2.68 (m, 2H), 3.30 (s, 3H), 3.56 (m, 2H), 3.70 (m, 2H), 4.88 (m, 1H), 7.54 (s, 1H), 7.65 (d, 1H), 7.84 (s, 1H), 7.96 (s, 1H), 8.57 (s, 1H), 8.63 (d, 1H); MS m/z 500 [M+H]⁺.

Example 318:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.356 mmol scale, utilising 4-amino-3-chloro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 215; 95 mg, 0.356 mmol), as a white solid (39 mg, 21%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.56 - 1.82 (m, 10H), 2.02 (m, 2H), 2.58 (m, 4H), 2.70 (m, 4H), 3.30 (s, 3H), 3.55 (m, 2H), 3.70 (m, 2H), 4.87 (m, 1H), 6.74 (s, 1H), 7.53 (s, 1H), 7.67 (m, 1H), 7.84 (m, 1H), 7.95 (s, 1H), 8.63 (d, 1H); MS m/z 512 [M+H]⁺.

Example 319:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[1-(cyclopropylmethyl)-4-piperidyl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.24 mmol scale, utilising 1-(cyclopropylmethyl)-4-piperidinamine di hydrochloride (Aldrich; 95 mg, 0.356 mmol) and DIPEA (210 μL, 1.3 mmol) and stirring at ambient temperature for 24 hours, as a white solid (85 mg, 64%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.00 (m, 2H), 0.38 (m, 2H), 0.75 (m, 1H), 1.60 (m, 10H), 1.90 (m, 4H), 2.11 (d, 2H), 2.51 (m, 2H), 2.91 (m, 2H), 3.10 (s, 3H), 3.55 (m, 2H), 3.68 (m, 1H), 3.87 (s, 3H), 4.74 (m, 1H), 7.40 (m, 2H), 7.64 (s, 1H), 7.98 (d, 1H), 8.00 (s, 1H), 8.30 (d, 1H); MS m/z 548 [M+H]⁺.

Example 320:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.285 mmol scale, utilising 4-amino-2-chloro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide (Intermediate 216; 85 mg, 0.285 mmol), as a white solid (108 mg, 70%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.61 (m, 4H), 1.76 (m, 4H), 2.09 (m, 4H), 2.20 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.78 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.03 (m, 1H), 4.97 (m, 1H), 6.56 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.62 (s, 1H); MS m/z 542 [M+H]⁺.

Example 321:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-[(3R)-pyrrolidin-3-yl]benzamide

tert-butyl (3R)-3-[[5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoyl]amino]pyrrolidine-1-carboxylate (Example 324; 175 mg, 0.29 mmol) was dissolved in 1,4-dioxane (5 mL) and 4M HCl_(aq) in 1,4-dioxane (10 mL) added. The mixture was stirred at room temperature for 2 hours. TFA (2 mL) was added and the reaction stirred for a further 1 hour. The reaction was concentrated, dissolved in DCM (10 mL) and TFA (3 mL) added. The reaction was stirred at room temperature for 1 hour, concentrated and the residue dissolved in methanol, absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the residue purified by column chromatography (7.5% ammonia in methanol/DCM) to yield the title compound as a white foam (112 mg, 77%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.58 - 1.77 (8H, m), 1.92 - 2.02 (3H, m), 2.60 - 2.77 (5H, m), 2.87 - 3.01 (2H, m), 3.19 (3H, s), 3.65 (2H, m), 4.23 - 4.31 (1H, m), 4.76 - 4.84 (1H, m), 7.70 (1H, d), 8.07 - 8.17 (3H, m), 8.33 (1H, d); MS m/z 502 [M+H]⁺.

Example 322:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoic acid (Intermediate 219; 100 mg, 0.23 mmol), 4-amino-1-methylpiperidine (Fluorochem; 40 mg, 0.35 mmol) and HATU (132 mg, 0.35 mmol) were stirred in DMF (3 mL). *N,N*-diisopropylethylamine (121 μ l, 0.69 mmol) was added and the mixture heated at 50 °C for 2 hours. The mixture was cooled and absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the residue purified by base modified reverse phase preparative chromatography to yield the title compound as a white solid (58 mg, 48%)

^1H NMR (399.9 MHz, DMSO- d_6) δ 1.50 - 1.80 (10H, m), 1.92 - 1.99 (4H, m), 2.17 (3H, s), 2.61 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.63 - 3.74 (3H, m), 4.76 - 4.84 (1H, m), 7.67 (1H, d), 8.07 (1H, d) 8.14 (1H, m), 8.31 - 8.36 (1H, m); MS m/z 530 $M+H]^+$.

Example 323:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 322, on a 0.23 mmol scale, utilising 4-amino-1-ethylpiperidine (Fluorochem; 45 mg, 0.35 mmol), as a white solid (60 mg, 48%).

^1H NMR (399.9 MHz, DMSO- d_6) δ 1.00 (3H, t), 1.59 (8H, d), 1.80 (2H, d), 1.93 - 1.98 (4H, m), 2.32 (2H, q), 2.61 (2H, m), 2.84 (2H, d), 3.19 (3H, s), 3.63 - 3.76 (3H, m), 4.76 - 4.84 (1H, m), 7.67 (1H, d), 8.08 (1H, d), 8.14 (2H, d), 8.31 - 8.36 (1H, m); MS m/z 544 $[M+H]^+$.

Example 324:

tert-butyl (3R)-3-[[5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoyl]amino]pyrrolidine-1-carboxylate

The title compound was prepared by an analogous method to the preparation of Example 322, on a 0.46 mmol scale, utilising boc-R-(3R)-aminopyrrolidine (Aldrich; 130 mg, 0.75 mmol)

and purification by normal phase chromatography (5% MeOH/DCM), as a white foam (179 mg, 65%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.42 (9H, s), 1.56 – 1.74 (7H, m), 1.87 – 1.97 (3H, m), 2.09 – 2.13 (1H, m), 2.60 – 2.64 (2H, m), 3.19 (4H, m), 3.37 – 3.44 (1H, m), 3.49 – 3.57 (1H, m), 3.63 – 3.67 (2H, m), 4.38 (1H, m), 4.80 (1H, m), 7.70 (1H, d), 8.09 – 8.25 (2H, m), 8.32 – 8.37 (1H, m), 8.44 (1H, d); MS m/z 602 [M+H]⁺.

Example 325:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide
 5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-[(3R)-pyrrolidin-3-yl]benzamide (Example 321; 95 mg, 0.19 mmol) was dissolved in 37% aqueous formaldehyde solution (1.1 mL) and acetic acid (120 μl, 1.89 mmol). Sodium acetate (156 mg, 1.89 mmol) was added and the mixture cooled in an ice/water bath. Sodium cyanoborohydride (12 mg, 0.19 mmol) was added and the mixture allowed to warm to room temperature. After stirring for 1 hour, the mixture was absorbed on to an SCX column, and subsequently washed with methanol and eluted with ammonia in methanol. The product containing fractions were concentrated and purified by column chromatography (2% 7N ammonia in methanol/DCM) to yield the title compound as a white foam (69mg, 70%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.58 – 1.73 (7H, m), 1.90 – 1.96 (2H, m), 2.12 – 2.21 (1H, m), 2.26 (3H, s), 2.38 – 2.43 (3H, m), 2.56 – 2.64 (3H, m), 2.67 – 2.71 (1H, m), 3.19 (3H, s), 3.63 – 3.67 (2H, m), 4.34 – 4.36 (1H, m), 4.80 (1H, m), 7.69 (1H, d), 8.14 (2H, m), 8.27 (1H, d), 8.33 (1H, d); MS m/z 516 [M+H]⁺.

Example 326:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-yl]benzamide (Example 55; 100 mg, 0.21 mmol) in DMF (3 mL) was added triethylamine (59 μl, 0.42 mmol) and ethyl bromide (Acros; 24 μl,

0.31 mmol). The reaction mixture was heated to 90 °C by microwave irradiation for 1 hour. The cooled reaction mixture was poured onto an SCX-3 cartridge (5 g) and the cartridge washed through with methanol (40 mL) and then eluted with 2M ammonia in methanol. Ammoniacal fractions were combined and evaporated. The residue was purified by base
5 modified reverse phase preparative HPLC and product containing fractions combined and evaporated to yield the title compound as a white solid (27 mg, 25%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.97 (t, 3H), 1.51 - 1.75 (m, 7H), 1.87 (m, 2H), 2.08 (m, 1H), 2.32 - 2.68 (m, 8H), 3.10 (s, 3H), 3.56 (m, 2H), 3.88 (s, 3H), 4.32 (m, 1H), 4.75 (m, 1H), 7.44 (m, 2H), 7.65 (s, 1H), 8.01 (s, 1H), 8.22 (d, 1H), 8.31 (d, 1H); MS m/z 508 [M+H]⁺.

10

Example 327:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(3R)-1-propylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 326,
15 on a 0.21 mmol scale, utilising n-propyl bromide (Aldrich; 29 µL, 0.31 mmol) and heating for 45 minutes at 90 °C, as an off-white gum (63 mg, 58%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.88 (t, 3H), 1.45 (m, 2H), 1.56 - 1.82 (m, 7H), 1.95 (m, 2H), 2.14 (m, 1H), 2.35 (m, 2H), 2.44 (m, 2H), 2.61 (m, 3H), 2.74 (m, 1H), 3.17 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.39 (m, 1H), 4.82 (m, 1H), 7.50 (m, 2H), 7.72 (s, 1H), 8.08 (s,
20 1H), 8.27 (d, 1H), 8.38 (d, 1H); MS m/z 522 [M+H]⁺.

Example 328:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(3R)-1-(2-methoxyethyl)pyrrolidin-3-yl]benzamide

25 The title compound was prepared by an analogous method to the preparation of Example 326, on a 0.21 mmol scale, utilising 2-bromoethyl methylether (Aldrich; 30 µL, 0.31 mmol) and heating for 45 minutes at 90 °C, as an off-white gum (57 mg, 50%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.57 - 1.82 (m, 7H), 1.95 (m, 2H), 2.13 (m, 1H), 2.52 (d, 2H)[obscured by DMSO], 2.59 (m, 4H), 2.69 (m, 1H), 2.79 (m, 1H), 3.17 (s, 3H), 3.24 (s,
30 3H), 3.43 (t, 2H), 3.63 (m, 2H), 3.95 (s, 3H), 4.39 (m, 1H), 4.82 (m, 1H), 7.51 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.29 (d, 1H), 8.38 (d, 1H); MS m/z 538 [M+H]⁺.

Example 329:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

- 5 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 162; 1.0 g, 3.43 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 0.96 g, 3.43 mmol) and p-toluenesulphonic acid monohydrate (1.63 g, 8.56 mmol) were stirred and heated together at 110 °C in 4-methyl-2-pentanol (30 mL) for 18 hours. The cooled reaction mixture was diluted
10 with water and methanol and the solution loaded onto an SCX-2 (20g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and the product eluted with 2M NH₃/MeOH (2 column volumes). Product containing fractions were combined and evaporated and the residue purified by chromatography on a silica column eluting with a 0-100% gradient of 10% 2M NH₃-MeOH in DCM. Product containing fractions were combined
15 and evaporated to give a foam which on trituration with ethyl acetate yielded, on filtration, the title compound as a white solid (473 mg, 26%) 536 (M+H), ES- 534 (M-H)
¹H NMR (400.132 MHz, DMSO-d₆) δ 0.94 (m, 2H), 1.55 (m, 9H), 1.90 (m, 4H), 2.03 (m, 1H), 2.19 (m, 3H), 2.42 (s, 3H), 2.58 (m, 2H), 2.98 (m, 2H), 3.17 (s, 3H), 3.60 (m, 2H), 4.32 (m, 1H), 4.74 (m, 1H), 7.69 (m, 2H), 8.00 (d, 1H), 8.06 (s, 1H), 8.12 (m, 1H), 8.72 (s, 1H);
20 MS m/z 536 [M+H]⁺.

Example 330:

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

- 25 3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoic acid (Intermediate 221; 85 mg, 0.18 mmol), HATU (104 mg, 0.27 mmol) and 4-amino-1-methylpiperidine (32 mg, 0.27 mmol) were stirred in DMF (3 mL) and diisopropylethylamine (95 µl, 0.54 mmol) added. The mixture was stirred for 2 hours and absorbed on to an SCX column, which was subsequently washed with methanol
30 and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the residue purified by column chromatography (4% ammonia in methanol/DCM) to yield the title compound as a white solid (67 mg, 66%).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.26 - 1.65 (10H, m), 1.79 (2H, d), 1.98 (2H, t), 2.17 (3H, s), 2.55 (2H + DMSO, m), 2.73 (2H, d), 3.15 (3H, s), 3.53 - 3.55 (2H, m), 3.67 - 3.74 (1H, m), 4.37 (1H, t), 7.65 (1H, d), 7.96 (1H, s), 8.43 (1H, d), 9.01 (1H, s); MS m/z 564 [M+H]⁺.

5 **Example 331:**

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 330, on a 0.21 mmol scale, utilising utilising 1-amino-4-dimethylaminocyclohexane (ABChem
10 Inc.; 30 µL, 0.31 mmol) and separation of the cis-isomer by column chromatography, as a white solid (21 mg, 19%).

¹H NMR (500.13 MHz, DMSO-d₆) δ1.38 - 1.92 (16H, m), 2.04 - 2.08 (1H, m), 2.18 (6H, s), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.53 - 3.55 (2H, m), 3.91 - 3.95 (1H, m), 4.39 (1H, m), 7.63 (1H, d), 7.95 (1H, s), 8.39 (1H, d), 9.00 (1H, s); MS m/z 592 [M+H]⁺.

15

Example 332:

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 330, on a 0.21 mmol scale, utilising utilising 1-amino-4-dimethylaminocyclohexane (ABChem
20 Inc.; 30 µL, 0.31 mmol) and separation of the trans-isomer by column chromatography, as a white solid (42 mg, 39%).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.22 - 1.68 (12H, m), 1.80 - 1.85 (2H, m), 1.90 - 1.95 (2H, m), 2.10 - 2.14 (1H, m), 2.18 (6H, s), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.53 - 3.56 (2H, m), 3.63 - 3.71 (1H, m), 4.33 - 4.42 (1H, m), 7.64 (1H, d), 7.95 (1H, s), 8.39 (1H, d),
25 9.01 (1H, s); MS m/z 592 [M+H]⁺.

Example 333:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide
30

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 80 mg, 0.285 mmol), 4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 228; 80 mg, 0.285 mmol), p-toluenesulphonic acid monohydrate (136 mg, 0.732 mmol) and 4-Methyl-2-pentanol (3 mL) were combined and
5 heated at 100 °C overnight. The cooled reaction mixture was added to an SCX-2 column (5 g), pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC and product containing fractions combined and evaporated to yield the title
10 compound as a cream solid (94 mg, 36%)

¹H NMR (399.902 MHz, CDCl₃) δ1.63 (m, 2H), 1.77 (m, 8H), 2.06 (m, 2H), 2.58 (m, 4H), 2.68 (m, 2H), 2.72 (m, 2H), 3.30 (s, 3H), 3.60 (m, 2H), 3.71 (m, 2H), 3.95 (s, 3H), 4.91 (m, 1H), 7.31 (m, 1H), 7.57 (d, 1H), 7.72 (s, 1H), 7.95 (s, 1H), 8.40 (d, 1H); MS m/z 526 [M+H]⁺.

15

Example 334:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one
20 (Intermediate 1; 100 mg, 0.356 mmol), 4-amino-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 229; 83 mg, 0.324 mmol) and caesium carbonate (211 mg, 0.648 mmol) was added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone) palladium (II) (11 mg, 0.019 mmol) and XANTPHOS (17 mg, 0.029 mmol) were added and the mixture heated to 100 °C overnight. The cooled
25 reaction mixture was filtered and the filter cake washed with DCM and the filtrate evaporated. The residue was dissolved in DCM and purified on a silica column eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM over 30 column volumes. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a yellow solid (91 mg, 56%)
30 ¹H NMR (399.902 MHz, CDCl₃) δ1.64 (m, 2H), 1.75 (m, 5H), 2.05 (m, 2H), 2.30 (m, 1H), 2.41 (m, 4H), 2.67 (m, 4H), 2.89 (m, 1H), 3.30 (s, 3H), 3.71 (m, 2H), 4.65 (m, 1H), 4.88 (m,

1H), 6.95 (m, 1H), 7.30 (m, 1H), 7.81 (m, 1H), 7.96 (s, 1H), 8.45 (m, 1H); MS m/z 500 [M+H]⁺.

Example 335:

5 **4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide**

The title compound was prepared by an analogous method to the preparation of Example 334, on a 0.324 mmol scale, utilising 4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 230; 87 mg, 0.324 mmol), as a white solid (117 mg, 70%).

10 ¹H NMR (399.902 MHz, CDCl₃) δ1.63 (m, 2H), 1.77 (m, 8H), 2.05 (m, 2H), 2.57 (m, 4H), 2.70 (m, 4H), 3.30 (s, 3H), 3.58 (m, 2H), 3.71 (m, 2H), 4.88 (m, 1H), 7.28 (m, 2H), 7.82 (m, 1H), 7.96 (s, 1H), 8.46 (m, 1H); MS m/z 514 [M+H]⁺.

Example 336:

15 **2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide**

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-benzoic acid (Intermediate 231; 100mg, 0.224 mmol), (3R)-1-methylpyrrolidin-3-amine di Hydrochloride (Intermediate 184; 40 mg, 0.235 mmol), HATU
20 (94 mg, 0.246 mmol) and DIPEA (195 µL, 1.12 mmol) were combined in DMF (3 mL) and stirred at room temperature overnight. The reaction mixture was added to an SCX-2 column (5 g) pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase
25 preparative HPLC to yield the title compound as a white solid (76 mg, 64%).

¹H NMR (399.902 MHz, CDCl₃) δ1.62 (m, 2H), 1.78 (m, 5H), 2.11 (m, 2H), 2.31 (m, 1H), 2.42 (m, 4H), 2.69 (m, 4H), 2.90 (m, 1H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.68 (m, 1H), 4.97 (m, 1H), 6.97 (m, 1H), 7.38 (s, 1H), 7.63 (s, 1H), 7.93 (s, 1H), 8.61 (s, 1H); MS m/z 528 [M+H]⁺.

Example 337:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 336, on a 0.224 mmol scale, utilising 4-amino-1-ethyl piperidine (Fluorochem; 32 mg, 0.246

5 mmol), as a white solid (97 mg, 79%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.11 (t, 3H), 1.60 (m, 4H), 1.75 (m, 4H), 2.09 (m, 4H), 2.19 (m, 2H), 2.44 (m, 2H), 2.68 (m, 2H), 2.88 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.06 (m, 1H), 4.97 (m, 1H), 6.58 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.61 (s, 1H); MS m/z 556 [M+H]⁺.

10

Example 338:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 336,

15 on a 0.224 mmol scale, utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 35 mg, 0.246 mmol), as a white solid (84 mg, 66%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.26 - 1.76 (m, 11H), 1.94 (m, 2H), 2.10 (m, 2H), 2.21 (m, 2H), 2.30 (m, 6H), 2.68 (m, 2H), 3.29 (m, 3H), 3.71 (m, 2H), 3.94 (m, 3.5H), 4.25 (m, 0.5H), 4.97 (m, 1H), 6.46 (d, 0.5H), 6.85 (d, 0.5H), 7.39 (s, 0.5H), 7.45 (s, 0.5H), 7.63 (m, 1H), 7.94

20 (m, 1H), 8.62 (m, 1H); MS m/z 570 [M+H]⁺.

Example 339:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 336, on a 0.224 mmol scale, utilising Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 38 mg, 0.246 mmol), as a white solid (84 mg, 64%).

30 ¹H NMR (399.902 MHz, CDCl₃) δ 1.05 (m, 2H), 1.30 (m, 2H), 1.52 - 1.66 (m, 4H), 1.76 (m, 4H), 1.97 (m, 2H), 2.11 (m, 2H), 2.55 (m, 5H), 2.68 (m, 2H), 3.10 (m, 2H), 3.29 (s, 3H), 3.71

(m, 2H), 3.94 (s, 3H), 4.52 (m, 1H), 4.98 (m, 1H), 6.42 (d, 1H), 7.41 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.61 (s, 1H); MS m/z 582 [M+H]⁺.

Example 340:

5 **4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[1-(2-methylpropyl)-4-piperidyl]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.49 mmol scale, utilising 1-isobutylpiperidin-4-amine hydrochloride (Ambinter; 96 mg, 0.61 mmol) and DIPEA (340 µL, 1.6 mmol) and stirring at ambient temperature for 24 hours,
10 as a white solid (159 mg, 59%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.87 (d, 6H), 1.68 (m, 11H), 1.94 (m, 4H), 2.04 (d, 2H), 2.59 (m, 2H), 2.84 (m, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.77 (m, 1H), 3.95 (s, 3H), 4.81 (m, 1H), 7.47 (s, 1H), 7.50 (s, 1H), 7.72 (s, 1H), 8.04 (d, 2H), 8.08 (s, 1H), 8.38 (d, 1H); MS m/z 550 [M+H]⁺.

15

Example 341:

7-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide

7-amino-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide (Intermediate 223; 60mg, 0.21mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 60 mg, 0.21 mmol) and p-toluenesulphonic acid monohydrate (102 mg, 0.53 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 2 hours. The cooled reaction mixture was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were
25 evaporated and the residue purified by normal phase chromatography (2.5% 7N NH₃ in methanol/DCM) and then base modified reverse phase preparative HPLC to yield the title compound as a white solid (35 mg, 32%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.48 – 1.60 (6H, m), 1.63 – 1.69 (2H, m), 1.79 – 1.83 (4H, m), 2.00 - 2.05 (2H, m), 2.17 (3H, s), 2.55 - 2.58 (2H, m), 2.67 - 2.70 (2H, m), 3.17 (3H, s), 3.59 (2H, m), 3.74 - 3.78 (1H, m), 4.69 – 1.77 (1H, m), 6.14 (2H, s), 7.23 (1H, d), 7.27 (1H, d), 7.48 - 7.51 (1H, m), 8.04 (1H, s), 8.60 (1H, s); MS m/z 522 [M+H]⁺.

30

Example 342:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-yl)benzamide

5 The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.49 mmol scale, utilising 1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-amine (CBI Building Blocks; 103 mg, 0.61 mmol) and DIPEA (260 μ L, 1.47 mmol) and stirring at ambient temperature for 2 hours, as a single isomer of unspecified stereochemistry, as a white solid (52 mg, 19%).

10 ^1H NMR (400.132 MHz, DMSO- d_6) δ 1.09 (6H, m), 1.66 (11H, m), 1.94 (2H, m), 2.07 (2H, m), 2.16 (3H, s), 2.59 (2H, m), 2.81 (1H, m), 3.18 (3H, s), 3.63 (3H, m), 3.95 (3H, s), 4.81 (1H, m), 7.49 (2H, m), 7.73 (1H, s), 7.97 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 562 $[\text{M}+\text{H}]^+$.

15 **Example 343:**

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 314,
20 on a 0.49 mmol scale, utilising 1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-amine (CBI Building Blocks; 103 mg, 0.61 mmol) and DIPEA (260 μ L, 1.47 mmol) and stirring at ambient temperature for 2 hours, as a single isomer of unspecified stereochemistry, as a white solid (102 mg, 37%).

^1H NMR (400.132 MHz, DMSO- d_6) δ 0.94 (1H, m), 1.21 (3H, m), 1.44 (2H, m), 1.66 (10H, m), 1.88 (3H, m), 2.10 (2H, m), 2.19 (3H, s), 2.59 (2H, m), 3.18 (3H, s), 3.63 (2H, m), 3.96 (3H, s), 4.17 (1H, m), 4.81 (1H, m), 7.40 (1H, s), 7.45 (2H, d), 7.56 (1H, d), 7.75 (1H, s), 8.08 (1H, s), 8.37 (1H, d); MS m/z 562 $[\text{M}+\text{H}]^+$.

Example 344:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

4-amino-2-fluoro-5-methoxy-N-(9-methyl-9-azabicyclo[3.3.1]non-7-yl)benzamide

5 (Intermediate 204; 50 mg, 0.16 mmol), 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 1; 45 mg, 0.16 mmol) and p-toluenesulphonic acid monohydrate (76 mg, 0.40 mmol) were stirred and heated together in 4-methyl-2-pentanol (3 mL) at 110 °C for 18 hours.

A further portion of 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-10 7,9,11-trien-5-one (Intermediate 1; 20 mg, 0.07 mmol) was added and the mixture heated by microwave irradiation at 150 °C for 1 hour and 30 minutes.

The cooled reaction mixture was loaded onto an SCX-3 (5 g) column pre-wet with MeOH.

The column was washed with MeOH (2 column volumes) and eluted with 2M NH₃/MeOH.

Product containing fractions were evaporated and the residue purified by base modified 15 reverse phase preparative HPLC to yield the title compound as a white solid (48 mg, 53%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.90 (m, 2H), 1.42 (m, 3H), 1.69 (m, 6H), 1.96 (m, 5H), 2.21 (m, 2H), 2.41 (s, 3H), 2.61 (m, 2H), 2.97 (m, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 3.93 (s, 3H), 4.30 (m, 1H), 4.84 (m, 1H), 7.22 (d, 1H), 7.67 (m, 1H), 7.81 (s, 1H), 8.12 (s, 1H), 8.34 (d, 1H); MS m/z 566 [M+H]⁺.

20

Example 345:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-fluoro-benzamide

10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

25 (Intermediate 1; 212 mg, 0.75 mmol), 4-amino-N-(1-ethylpiperidin-4-yl)-3-fluorobenzamide (Intermediate 225; 200 mg, 0.75 mmol) and p-toluenesulphonic acid monohydrate (0.335 mL, 1.88 mmol) were suspended in 4-Methyl-2-pentanol (5 mL) and sealed in a microwave tube. The reaction was heated to 160 °C for 30 minutes in the microwave reactor and allowed to cool to room temperature.

30 The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were

evaporated to dryness to afford the crude product as an orange oil which was purified by base modified reverse phase preparative HPLC. Fractions containing the desired compound were evaporated to dryness to afford the title compound as a white solid (35 mg, 9%).

¹H NMR DMSO-d₆ δ 0.65 (t, 2H), 0.9 (t, 2H), 1.0 (t, 3H), 1.5 (m, 7H), 1.6 (m, 2H), 1.9 (t, 2H), 2.3 (q, 2H), 2.9 (d, 2H), 3.2 (s, 3H), 3.4 (s, 2H), 3.6 (m, 1H), 4.75 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.6 (s, 1H); MS m/z 510 [M+H]⁺.

Example 346:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

To a solution of 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 1; 70 mg, 0.17 mmol) in DMF (3 mL) was added a solution of 4-(azetidin-1-yl)cyclohexan-1-amine (Intermediate 226; 39 mg, 0.25 mmol) in DMF (1 mL). DIPEA (90 uL, 0.51 mmol) was added, followed by HATU (98 mg, 0.26 mmol). The resultant mixture was stirred at ambient temperature for 4 hours.

The reaction mixture was evaporated and the residue partitioned between DCM (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was separated by gravity elution through a PTFE filter cup and evaporated to an amber gum which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (29 mg, 31%) assigned as the trans isomer.

The cis isomer (Example 347) was isolated as a tan coloured solid (32 mg, 34%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.92 - 1.00 (2H, m), 1.29 - 1.38 (2H, m), 1.57 - 1.99 (15H, m), 2.58 - 2.60 (2H, m), 3.07 (4H, t), 3.17 (3H, s), 3.61 - 3.65 (2H, m), 3.66 - 3.76 (1H, m), 3.95 (3H, s), 4.82 (1H, quintet), 7.45 - 7.48 (2H, m), 7.72 (1H, s), 8.01 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 548 [M+H]⁺.

Example 347:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

The title compound was isolated from the reaction above to produce Example 346 as a tan coloured solid (32 mg, 34%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.30 - 1.40 (2H, m), 1.43 - 1.50 (2H, m), 1.56 - 1.77 (10H, m), 1.86 - 1.98 (4H, m), 2.18 - 2.23 (1H, m), 2.58 - 2.60 (2H, m), 3.07 (4H, t), 3.18 (3H, s), 3.62 - 3.65 (2H, m), 3.77 - 3.87 (1H, m), 3.95 (3H, s), 4.82 (1H, quintet), 7.50 - 7.54 (2H, m), 7.71 (1H, s), 8.04 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 548 [M+H]⁺.

Example 348:

tert-butyl 3-[[4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoyl]amino]azepane-1-carboxylate

The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.30 mmol scale, utilising tert-butyl 3-aminoazepane-1-carboxylate (Anichem; 78 mg, 0.36 mmol) and DIPEA (151 µL, 0.91 mmol) and stirring at ambient temperature for 19 hours, as an amber gum (153 mg, 83%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.24 - 1.46 (11H, m), 1.50 - 2.00 (14H, m), 2.57 - 2.61 (2H, m), 3.06 - 3.19 & 3.30 - 3.37 (1H, m), 3.18 (3H, s), 3.54 - 3.70 (3H, m), 3.95 (3H, s), 4.08 - 4.22 (1H, m), 4.75 - 4.87 (1H, m), 7.36 - 7.49 (2H, m), 7.74 (1H, s), 8.01 & 8.16 (2 x d, 1H), 8.09 (1H, s), 8.39 (1H, d); MS m/z 608 (M+H)⁺

Example 349:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(4-piperidyl)benzamide

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 50 mg, 0.16 mmol) and tert-butyl 4-[(4-amino-3-methoxy-benzoyl)amino]piperidine-1-carboxylate (Intermediate 234; 85 mg, 0.24 mmol) were dissolved in 4-methyl-2-pentanol (1 mL) and p-toluenesulphonic acid monohydrate (44 mg, 0.32 mmol) added. The reaction mixture was heated at 90°C by microwave irradiation for 20 minutes and then at 150°C for a further 45 minutes.

The reaction mixture was diluted with water (3 mL) and methanol (3 mL) and the solution poured directly onto an SCX-3 (2 g) cartridge. The cartridge was washed with methanol (30 mL) and then eluted with 2M ammonia in methanol. Evaporation to dryness of the

ammoniacal fractions afforded an amber gum, which was purified by base modified reverse phase, preparative HPLC to yield the title compound as a white solid (32 mg, 38%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.10 (s, 6H), 1.43 (m, 2H), 1.55 - 1.79 (m, 10H), 1.89 (m, 2H), 2.96 (m, 2H), 3.19 (s, 3H), 3.38 (s, 2H), 3.83 (m, 1H), 3.95 (s, 3H), 5.19 (m, 1H),
5 7.48 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.05 (d, 1H), 8.36 (d, 1H); MS m/z 522 [M+H]⁺.

Example 350:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

10 10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 115 mg, 0.37 mmol) and 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 104 mg, 0.37 mmol) were dissolved 4-methyl-2-pentanol (3 mL). p-Toluenesulphonic acid monohydrate (142 mg, 0.74 mmol) was added and mixture heated by microwave irradiation at 160 °C for 1 hour.
15 After cooling, the reaction mixture was diluted with MeOH (5 mL) and poured directly onto an SCX-3 (5 g) cartridge. The cartridge was washed with methanol (40 mL) and eluted with 2M ammonia in methanol (40 mL). Evaporation to dryness of the ammoniacal fractions afforded a yellow gum which was purified by base modified reverse phase, preparative HPLC to yield the title compound as a white solid (125 mg, 61%).

20 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.01 (t, 3H), 1.11 (s, 6H), 1.53 - 1.97 (m, 14H), 2.34 (q, 2H), 2.90 (m, 2H), 3.20 (s, 3H), 3.39 (s, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 5.20 (m, 1H), 7.48 (m, 2H), 7.68 (s, 1H), 8.00 (s, 1H), 8.07 (d, 1H), 8.37 (d, 1H); MS m/z 550 [M+H]⁺.

25 **Example 351:**

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.24 mmol scale, utilising 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 68 mg, 0.24 mmol), as a white foam (47 mg, 53%).
30

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.90 (s, 6H), 1.11 (s, 6H), 1.62 (m, 4H), 1.75 (m, 2H), 1.90 (m, 2H), 2.21 (s, 2H), 2.29 (s, 6H), 3.21 (m, 5H), 3.40 (s, 2H), 3.96 (s, 3H), 5.20 (m, 1H), 7.42 (m, 1H), 7.47 (d, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.39 (d, 1H), 8.44 (t, 1H); MS m/z 552 [M+H]⁺.

5

Example 352:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

10 The title compound was prepared by an analogous method to the preparation of **Example 350**, on a 0.31 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (**Intermediate 204**; 96 mg, 0.31 mmol) heating by microwave irradiation at 150 °C for 1 hour, as a white foam (47 mg, 53%).

15 ¹H NMR (400.132 MHz, CDCl₃) δ 1.16 - 1.23 (8H, m), 1.52 - 1.65 (4H, m), 1.73 - 1.83 (5H, m), 1.97 - 2.11 (5H, m), 2.54 - 2.65 (5H, m), 3.17 - 3.26 (2H, m), 3.31 (3H, s), 3.40 (2H, s), 3.96 (3H, s), 4.51 - 4.62 (1H, m), 5.29 (1H, quintet), 6.60 - 6.74 (1H, m), 7.57 (1H, d), 7.70 (1H, s), 7.88 (1H, s), 8.39 (1H, d); MS m/z 594 [M+H]⁺.

Example 353:

20 **4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide**

The title compound was prepared by an analogous method to the preparation of **Example 350**, on a 0.34 mmol scale, utilising 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (**Intermediate 162**; 100 mg, 0.34 mmol) heating by
25 microwave irradiation at 150 °C for 40 minutes, as a white foam (52 mg, 27%).

¹H NMR (399.902 MHz, DMSO-d₆) δ 0.9 (2H, d), 1.1 (6H, s), 1.45 (3H, m), 1.55 (4H, m), 1.7 (2H, m), 1.8 (2H, m), 1.9 (2H, m), 2.05 (1H, m), 2.2 (2H, m), 2.40 (2H, s), 3.0 (2H, d), 3.2 (3H, s), 3.35 (2H, s), 4.3 (1H, m), 5.2 (1H, m), 7.65 (1H, d), 7.70 (1H, d), 8.0 (2H, m), 8.15 (1H, t), 8.65 (1H, s); MS m/z 564 [M+H]⁺.

30

Example 354:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 99 mg, 0.32 mmol) heating thermally at 140 °C for 2 hours, as a white solid (104 mg, 56%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.94 (2H, d), 1.10 (6H, s), 1.42 - 1.49 (3H, m), 1.63 (4H, s), 1.75 (2H, s), 1.89 - 1.96 (3H, m), 1.92 - 1.95 (2H, m), 2.16 - 2.21 (2H, m), 2.42 (3H, s), 2.99 (2H, d), 3.20 (3H, s), 3.39 (2H, s), 3.96 (3H, s), 4.32 - 4.38 (1H, m), 5.21 (1H, m), 7.47 (1H, d), 7.50 (1H, s), 7.68 (1H, s), 7.92 (1H, d), 8.00 (1H, s), 8.38 (1H, d); MS m/z 576 [M+H]⁺.

Example 355:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 100mg, 0.32mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 101 mg, 0.36 mmol) and caesium carbonate (22 mg, 0.65 mmol) added to dioxane (5 mL) and the suspension bubbled with nitrogen for 10 minutes. tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol) were added and the mixture heated at 110 °C overnight. The mixture was filtered and the filtrate loaded onto an SCX (10 g) cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white crystalline solid (97mg, 54%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.00 (3H, t), 1.11 (6H, s), 1.48 - 1.55 (2H, m), 1.60 (4H, d), 1.73 (2H, s), 1.77 - 1.82 (2H, m), 1.88 (2H, d), 1.93 - 1.99 (2H, m), 2.32 (2H, q), 2.83 (2H, d), 3.20 (3H, s), 3.39 (2H, s), 3.70 - 3.74 (1H, m), 5.21 (1H, m), 7.40 - 7.45 (1H, m), 7.95 - 7.98 (1H, m), 8.02 (1H, s), 8.20 - 8.25 (1H, m), 8.88 (1H, s); MS m/z 556 [M+H]⁺.

Example 356:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.32 mmol scale, utilising 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 96 mg, 0.32 mmol), as a white solid (38 mg, 22%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.54 - 1.58 (2H, m), 1.59 (3H, s), 1.74 (3H, d), 1.79 (2H, s), 1.87 (2H, s), 1.95 (1H, d), 1.99 (1H, s), 2.17 (3H, s), 2.75 (2H, d), 3.20 (3H, s), 3.37 (2H, s), 3.70 (1H, m), 5.22 (1H, m), 7.40 - 7.45 (1H, m), 7.95 - 7.98 (1H, m), 8.02 (1H, s), 8.20 - 8.25 (1H, m), 8.88 (1H, s); MS m/z 540 [M+H]⁺.

Example 357:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide (Intermediate 196; 82 mg, 0.32 mmol) heating thermally at 140 °C for 2 hours, as a white solid (84 mg, 50%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.63 (2H, m), 1.65 - 1.71 (4H, m), 1.75 (2H, s), 1.86 - 1.89 (2H, t), 2.16 (6H, s), 2.28 - 2.34 (2H, t), 3.15 - 3.20 (3H, s), 3.28 - 3.31 (2H, m), 3.36 - 3.39 (2H, s), 3.95 (3H, s), 5.18 - 5.22 (1H, m), 7.47 - 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s), 8.37 (1H, s), 8.39 (1H, t); MS m/z 524 [M+H]⁺.

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Example 358:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 86 mg, 0.32 mmol) heating thermally at 140 °C for 2 hours, as a white solid (56 mg, 32%).

5 ¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.63 (3H, m), 1.68 - 1.71 (3H, m), 1.74 (3H, d), 1.86 - 1.89 (3H, m), 2.48 (4H, m), 2.58 (2H, t), 3.18 (3H, s), 3.39 (4H, t), 3.92 - 3.98 (3H, s), 5.18 (1H, m), 7.47 - 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.29 (1H, 4), 8.39 (1H, d); MS m/z 536 [M+H]⁺.

10 **Example 359:**

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide
15 (Intermediate 194; 77 mg, 0.32 mmol) heating thermally at 140 °C for 2 hours, as a white solid (37 mg, 22%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.63 - 1.68 (4H, m), 1.75 (2H, m), 1.92 (2H, m), 2.15 (6H, s), 2.40 (2H, t), 3.19 (3H, s), 3.33 - 3.37 (4H, m), 3.95 (3H, s), 5.18 (1H, m), 7.47 - 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.29 (1H, 4), 8.39 (1H, d); MS
20 m/z 510 [M+H]⁺.

Example 360:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(4-pyrrolidin-1-ylcyclohexyl)benzamide

25 To a solution of 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Intermediate 236; 83 mg, 0.19 mmol) in DMF (3 mL) was added a solution of 4-pyrrolidin-1-ylcyclohexan-1-amine (Intermediate 237; 78 mg, 0.46 mmol). DIPEA (100 uL, 0.57 mmol) was added, followed by HATU (107 mg, 0.28 mmol). The resultant mixture was stirred at
30 ambient temperature for 2 hours. The reaction mixture was evaporated to a gum, which was partitioned between DCM (20 mL) and saturated aqueous sodium bicarbonate solution (20

mL). The organic phase was separated by gravity elution through a PTFE filter cup and evaporated to an amber gum which was purified by base modified reverse phase preparative HPLC to yield the title compound as an off white solid (34 mg, 30%).

¹H NMR (400.132 MHz, CDCl₃) δ 1.20 (s, 6H), 1.29 (m, 2H), 1.41 - 1.83 (m, 12H), 1.95 - 2.20 (m, 7H), 2.60 (m, 4H), 3.30 (s, 3H), 3.37 (s, 2H), 3.94 (m, 1H), 3.97 (s, 3H), 5.31 (m, 1H), 5.83 (d, 1H), 7.20 (m, 1H), 7.42 (d, 1H), 7.60 (s, 1H), 7.85 (s, 1H), 8.47 (d, 1H); MS m/z 590 [M+H]⁺.

Example 361:

10 **4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide**

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.49 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide (Intermediate 27; 144 mg, 0.51 mmol), as a white foam (66 mg, 24%).

15 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.11 (s, 6H), 1.52 - 1.68 (m, 6H), 1.76 (m, 4H), 1.95 (m, 4H), 2.16 (s, 3H), 2.73 (m, 2H), 3.20 (s, 3H), 3.40 (s, 2H), 3.73 (m, 1H), 3.92 (s, 3H), 5.19 (m, 1H), 7.19 (d, 1H), 7.79 (m, 2H), 8.02 (s, 1H), 8.31 (d, 1H); MS m/z 554 [M+H]⁺.

Example 362:

20 **3-chloro-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)benzamide**

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.34 mmol scale, utilising 4-amino-3-chloro-N-(3-dimethylaminopropyl)benzamide (Intermediate 214; 98 mg, 0.38 mmol), as an off-white solid (27 mg, 15%).

25 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.10 (s, 6H), 1.50 - 1.74 (m, 8H), 1.83 (m, 2H), 2.15 (s, 6H), 2.27 (t, 2H), 3.19 (s, 3H), 3.28 (m, 2H), 3.37 (s, 2H), 5.11 (m, 1H), 7.77 (m, 1H), 7.96 (d, 1H), 7.99 (s, 1H), 8.11 (s, 1H), 8.27 (d, 1H), 8.48 (t, 1H); MS m/z 528 [M+H]⁺.

Example 363:

30 **4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide**

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.49 mmol scale, utilising 4-amino-N-(4-dimethylaminocyclohexyl)-3-methoxybenzamide (Intermediate 239; 144 mg, 0.51 mmol), as a white foam (39 mg, 14%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.10 (s, 6H), 1.21 - 2.04 (m, 16H), 2.10 - 2.21 (m, 7H), 3.19 (s, 3H), 3.38 (s, 2H), 3.72 & 3.92 (m, 1H), 3.95 (s, 3H), 5.19 (m, 1H), 7.49 (m, 2H), 7.66 (d, 1H), 7.99 (s, 1H), 8.01 (d, 1H), 8.36 (d, 1H); MS m/z 564 [M+H]⁺.

Example 364:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 77 mg, 0.32 mmol) heating thermally at 140 °C for 3 hours, as a white solid (84 mg, 49%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.64 - 1.76 (7H, m), 1.87 - 1.94 (2H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.34 - 2.45 (2H, m), 2.58 - 2.64 (1H, m), 2.66 - 2.71 (1H, m), 3.20 (3H, s), 3.41 (2H, s), 3.93 (3H, s), 4.36 - 4.41 (1H, m), 5.15 - 5.24 (1H, m), 7.22 (1H, d), 7.78 (1H, d), 7.97 - 8.00 (1H, m), 8.03 (1H, s), 8.32 (1H, d); MS m/z 540 [M+H]⁺.

Example 365:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.32 mmol scale, utilising 4-amino-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 241; 93 mg, 0.34 mmol), as an off-white solid (113 mg, 62%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.91 (2H, d), 1.11 (6H, s), 1.38 (1H, m), 1.42 (2H, m), 1.61 (2H, s), 1.64 (2H, t), 1.75 (1H, s), 1.84 (2H, m), 1.89 (2H, m), 2.03 (1H, m), 2.20 (2H, m), 2.39 (3H, s), 2.98 (2H, d), 3.17 (3H, s), 3.40 (2H, s), 4.28 (1H, m), 5.23 (1H, m), 7.38 (1H, d), 7.52 (1H, t), 7.64 (1H, m), 7.89 (1H, d), 8.01 (1H, s), 9.62 (1H, s); MS m/z 565 [M+H]⁺.

Example 366:

5-chloro-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

5 The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.29 mmol scale, utilising 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 92 mg, 0.29 mmol) heating at 110 °C for 3 hours, as an off-white solid (55 mg, 32%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.25 - 1.37 (3H, m), 1.47 - 2.01 (13.5H, m),
10 2.13 (6.5H, d), 3.20 (3H, s), 3.40 (2H, s), 3.62 - 3.71 and 3.88 - 3.95 (each 0.5H, m), 5.12 - 5.20 (1H, m), 7.65 - 7.68 (1H, m), 7.99 - 8.04 (2H, m), 8.10 (1H, d), 8.30 - 8.35 (1H, m); MS m/z 587 [M+H]⁺.

Example 367:

15 **3-chloro-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)benzamide**

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.34 mmol scale, utilising 4-amino-3-chloro-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)benzamide (Intermediate 244; 123 mg, 0.39 mmol) heating at 110 °C for 3 hours, as an
20 off-white solid (35 mg, 18%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.90 (s, 6H), 1.10 (s, 6H), 1.49 - 1.85 (m, 12H), 2.42 (s, 2H), 2.60 (m, 4H), 3.19 (s, 3H), 3.21 (d, 2H), 3.36 (s, 2H), 5.09 (m, 1H), 7.73 (m, 1H), 7.88 (d, 1H), 7.98 (s, 1H), 8.15 (s, 1H), 8.25 (d, 1H), 8.69 (t, 1H); MS m/z 582 [M+H]⁺.

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Example 368:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

30 The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.33 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-

methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) heating thermally at 120 °C for 3 days, as a white solid (55 mg, 29%).

¹H NMR (400.132 MHz, CDCl₃) δ 1.01 (s, 3H), 1.20 (s, 3H), 1.54 – 1.60 (m, 8H), 1.80 - 1.63 (m, 8H), 2.03 - 1.95 (m, 2H), 2.56 (s, 2H), 2.72 - 2.65 (m, 4H), 3.29 (s, 3H), 3.37 (s, 2H), 3.39 (d, 2H), 3.98 (s, 3H), 5.34 (quintet, 1H), 7.20 (d, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.86 (s, 1H), 8.43 (d, 1H), 9.16 - 9.10 (m, 1H); MS m/z 578 [M+H]⁺.

Example 369:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.22 mmol scale, utilising 4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide (Intermediate 245; 70 mg, 0.26 mmol) heating by microwave irradiation at 160 °C for 1 hour, as a white solid (50 mg, 42%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.04 (t, 3H), 1.10 (s, 6H), 1.55 - 1.93 (m, 9H), 2.15 (m, 1H), 2.43 (m, 4H), 2.65 (m, 1H), 2.73 (m, 1H), 3.19 (s, 3H), 3.38 (s, 2H), 3.95 (s, 3H), 4.40 (m, 1H), 5.19 (m, 1H), 7.51 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.28 (d, 1H), 8.37 (d, 1H); MS m/z 536 [M+H]⁺.

Example 370:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 127; 52 mg, 0.17 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 50 mg, 0.17mmol) and p-toluenesulphonic acid monohydrate (81 mg, 0.43 mmol) were stirred and heated together in 4-methyl-2-pentanol (2 mL) by microwave irradiation at 150 °C for 1 hour. A further portion of 10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (10mg) was added and reaction continued for a further 1 hour. The cooled solution was loaded onto an SCX-3 (5g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and eluted with 2M NH₃/MeOH. Product containing fractions were combined and

evaporated and the residue purified by base modified reverse phase preparative HPL to yield the title compound as a white solid (49 mg, 51%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.00 (t, 3H), 1.11 (s, 6H), 1.74 (m, 12H), 2.32 (q, 2H), 2.83 (m, 2H), 3.17 (s, 3H), 3.40 (s, 2H), 3.73 (m, 1H), 3.92 (s, 3H), 5.19 (m, 1H), 7.19 (d, 1H), 7.77 (s, 1H), 7.80 (m, 1H), 8.02 (s, 1H), 8.31 (d, 1H); MS m/z 568 [M+H]⁺.

Example 371:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.45 mmol scale, utilising 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 65; 114 mg, 0.45 mmol) heating by microwave irradiation at 160 °C for 30 minutes, as a white solid (96 mg, 41%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.1 (s, 6H), 1.55 (m, 6H), 1.7 – 1.85 (m, 6H), 1.95 (t, 2H), 2.8 (d, 2H), 3.2 (s, 3H), 3.35 (s, 2H), 3.75 (m, 1H), 5.15 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.85 (s, 1H); MS m/z 525 [M+H]⁺.

Example 372:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.16 mmol scale, utilising 4-amino-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide (single undefined isomer) (Intermediate 248; 50 mg, 0.16 mmol) heating by microwave irradiation at 150 °C for 1 hour, as a white solid (30 mg, 32%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.63 (14H, m), 1.90 (2H, m), 2.07 (1H, m), 2.17 (6H, s), 3.20 (3H, s), 3.40 (2H, s), 3.92 (3H, s), 3.94 (1H, m), 5.19 (1H, m), 7.19 (1H, d), 7.71 (1H, m), 7.77 (1H, s), 8.02 (1H, s), 8.31 (1H, d); MS m/z 582 [M+H]⁺.

Example 373:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.16 mmol scale, utilising 4-amino-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide (single undefined isomer) (Intermediate 249; 50 mg, 0.16 mmol) heating by microwave irradiation at 150 °C for 1 hour, as a white solid (50 mg, 54%).

5 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.11 (6H, s), 1.30 (4H, m), 1.75 (12H, m), 2.12 (1H, m), 2.18 (6H, s), 3.20 (3H, s), 3.40 (2H, s), 3.69 (1H, m), 3.92 (3H, s), 5.18 (1H, m), 7.19 (1H, d), 7.73 (1H, m), 7.76 (1H, s), 8.02 (1H, s), 8.30 (1H, d); MS m/z 582 [M+H]⁺.

Example 374:

10 **N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide**

The title compound was prepared by an analogous method to the preparation of Example 346, utilising 10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 75 mg, 0.17 mmol) and 4-(azetidin-1-yl)cyclohexan-1-amine
15 (Intermediate 226; 39 mg, 0.25 mmol) as an off white solid (35 mg, 36%) assigned as the trans isomer.

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.92 - 1.00 (2H, m), 1.10 (6H, s), 1.29 - 1.39 (2H, m), 1.58 - 1.94 (15H, m), 3.07 (4H, t), 3.19 (3H, s), 3.38 (2H, s), 3.67 - 3.76 (1H, m), 3.94 (3H, s), 5.19 (1H, quintet), 7.45 - 7.48 (2H, m), 7.67 (1H, s), 7.99 (1H, s), 8.00 (1H, d), 8.36 (1H, d);

20 MS m/z 576 [M+H]⁺.

Example 375:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

The title compound was isolated from the reaction above to produce Example 374, as an off white solid (35 mg, 36%) assigned as the cis isomer.

30 ¹H NMR (400.132 MHz, DMSO-d₆) δ 1.03 (6H, s), 1.24 - 1.31 (2H, m), 1.37 - 1.42 (2H, m), 1.50 - 1.70 (10H, m), 1.78 - 1.86 (4H, m), 2.12 - 2.16 (1H, m), 2.96 - 3.04 (4H, m), 3.12 (3H,

s), 3.31 (2H, s), 3.69 - 3.79 (1H, m), 3.87 (3H, s), 5.12 (1H, quintet), 7.42 - 7.46 (2H, m), 7.58 (1H, s), 7.91 (1H, s), 7.96 (1H, d), 8.28 (1H, d); MS m/z 576 [M+H]⁺.

Example 376:

5 **4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide**
10-chloro-2-cyclopentyl-4,4-diethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 250; 111 mg, 0.33 mmol), p-toluenesulphonic acid monohydrate (155 mg, 0.81 mmol) and 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-
10 benzamide (Intermediate 206; 100 mg, 0.33 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The sample was transferred to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title
15 compound as a white solid (55 mg, 27%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.01 (s, 6H), 1.80 - 1.48 (m, 14H), 2.02 - 1.94 (m, 2H), 2.56 (s, 2H), 2.69 (s, 4H), 3.28 (s, 3H), 3.39 (d, 2H), 3.42 (s, 2H), 3.98 (s, 3H), 5.42 (quintet, 1H), 7.20 (d, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.84 (s, 1H), 8.43 (d, 1H), 9.14 (s, 1H); MS m/z 606 [M+H]⁺.

20

25 **Example 377:**

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

10-chloro-2-cyclopentyl-4,4-diethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 250; 100 mg, 0.30 mmol), p-toluenesulphonic acid monohydrate (142 mg, 0.75 mmol) and 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-
30

3-yl]benzamide (Intermediate 202; 91 mg, 0.30 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The sample was transferred to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the
5 resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (80 mg, 44%)

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.09 - 1.07 (m, 2H), 1.44 - 1.38 (m, 2H), 1.63 - 1.48 (m, 6H), 1.80 - 1.66 (m, 6H), 2.03 - 1.94 (m, 3H), 2.56 - 2.49 (m, 4H), 3.14 - 3.11 (m, 2H), 3.28 (s, 3H), 3.42 (s, 2H), 3.97 (s, 3H), 4.58 - 4.47 (m, 1H), 5.42 - 5.32 (m, 1H), 5.94 (d, 1H), 7.25 (dd, 1H), 7.25 (d, 1H), 7.25 (d, 1H), 7.44 (d, 1H), 7.60 (s, 1H), 7.83 (s, 1H), 8.47 (d, 1H); MS m/z 604 [M+H]⁺.

Example 378:

**4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-
15 8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 204; 96 mg, 0.30 mmol), as a white solid (25 mg, 13%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.07 - 1.04 (m, 2H), 1.36 - 1.30 (m, 2H), 1.63 - 1.49 (m, 6H), 1.82 - 1.66 (m, 7H), 2.04 - 1.91 (m, 4H), 2.57 - 2.51 (m, 4H), 3.11 - 3.08 (m, 2H), 3.29 (s, 3H), 3.44 (s, 2H), 3.95 (s, 3H), 4.58 - 4.46 (m, 1H), 5.36 (quintet, 1H), 6.55 (dd, 1H), 7.57 (d, 1H), 7.67 (s, 1H), 7.85 (s, 1H), 8.37 (d, 1H); MS m/z 622 [M+H]⁺.

Example 379:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205;
30 89 mg, 0.30 mmol), as a white solid (35 mg, 20%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.10 (t, 3H), 1.62 - 1.49 (m, 6H), 1.81 - 1.65 (m, 6H), 2.08 - 1.98 (m, 4H), 2.19 - 2.13 (m, 2H), 2.43 (q, 2H), 2.89 - 2.86 (m, 2H), 3.29 (s, 3H), 3.44 (s, 2H), 3.95 (s, 3H), 4.09 - 3.99 (m, 1H), 5.34 (quintet, 1H), 6.68 (dd, 1H), 7.55 (d, 1H), 7.67 (s, 1H), 7.84 (s, 1H), 8.37 (d, 1H); MS m/z 596 [M+H]⁺.

5

Example 380:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 79 mg, 0.30 mmol), as a white solid (30 mg, 18%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (t, 6H), 1.64 - 1.48 (m, 6H), 1.80 - 1.66 (m, 6H), 2.00 - 1.92 (m, 2H), 2.07 - 2.05 (m, 2H), 2.20 - 2.14 (m, 2H), 2.31 (s, 3H), 2.84 - 2.81 (m, 2H), 3.28 (s, 3H), 3.42 (s, 2H), 4.03 - 3.92 (m, 4H), 5.38 (quintet, 1H), 5.89 (d, 1H), 7.22 (dd, 1H), 7.41 (d, 1H), 7.59 (s, 1H), 7.84 (s, 1H), 8.48 (d, 1H); MS m/z 564 [M+H]⁺.

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Example 381:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 83 mg, 0.30 mmol), as a white solid (90 mg, 52%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.77 (t, 6H), 1.03 (t, 3H), 1.56 - 1.41 (m, 6H), 1.73 - 1.59 (m, 6H), 1.95 - 1.87 (m, 2H), 2.10 - 1.98 (m, 4H), 2.37 (q, 2H), 2.86 - 2.83 (m, 2H), 3.22 (s, 3H), 3.35 (s, 2H), 3.98 - 3.91 (m, 4H), 5.31 (quintet, 1H), 5.82 (d, 1H), 7.15 (dd, 1H), 7.34 (d, 1H), 7.52 (s, 1H), 7.77 (s, 1H), 8.41 (d, 1H); MS m/z 578 [M+H]⁺.

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Example 382:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-

1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethylpiperidin-4-yl)benzamide

30

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 108 mg, 0.35 mmol) 4-amino-3-chloro-N-(1-ethyl-4-piperidyl)benzamide (Intermediate 212; 118 mg, 0.42 mmol), and p-toluenesulphonic acid monohydrate (133 mg, 0.7 mmol) were combined in 4-methyl-2-pentanol (4 mL) and
5 heated by microwave irradiation at 160 °C for 1 hour. The reaction mixture was loaded onto to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (38 mg, 20%).

10 ¹H NMR (400.13 MHz, DMSO-d₆) δ 0.66 - 0.69 (2H, m), 0.90 - 0.93 (2H, m), 1.00 (3H, t), 1.41 - 1.70 (8H, m), 1.77 - 1.85 (4H, m), 1.90 - 1.96 (2H, m), 2.32 (2H, q), 2.88 (2H, d), 3.18 (3H, s), 3.47 (2H, s), 3.72 - 3.76 (1H, m), 4.74 - 4.82 (1H, m), 7.79 (1H, dd), 7.98 - 8.00 (2H, m), 8.08 (1H, s), 8.20 (1H, d), 8.30 - 8.34 (1H, m)
MS m/z 552 [M+H]⁺.

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Example 383:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

20 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.33 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 91 mg, 0.33 mmol) and p-toluenesulphonic acid monohydrate (156 mg, 0.81 mmol) were heated at 140 °C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction mixture was loaded onto to an SCX-3 cartridge
25 (10 g) pre-wet with methanol, then washed with methanol and eluted with 2% 7N ammonia/methanol. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (89 mg, 50%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.67 - 0.69 (2H, t), 0.90 - 0.93 (2H, t), 1.01 (3H, t), 1.51 -
30 1.51 (1H, m), 1.52 (1H, d), 1.56 - 1.62 (4H, m), 1.68 (1H, s), 1.70 (1H, d), 1.78 (1H, d), 1.81 (1H, s), 1.93 (4H, d), 2.33 (2H, q), 2.90 (2H, d), 3.19 (3H, s), 3.49 (2H, s), 3.61 - 3.65 (1H,

m), 3.96 (3H, s), 4.86 (1H, m), 7.47 (1H, t), 7.50 (1H, d), 7.68 (1H, s), 8.00 (1H, s), 8.07 (1H, d), 8.40 (1H, d); MS m/z 549 [M+H]⁺.

Example 384:

5 **4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide**

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 86 mg,
10 0.30 mmol), as a white solid (20 mg, 11%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.67 - 0.69 (2H, t), 0.90 - 0.93 (2H, t), 1.52 (2H, d), 1.61 (2H, t), 1.65 - 1.71 (7H, m), 1.89 - 1.92 (3H, m), 2.58 (2H, t), 3.18 (3H, s), 3.20 (2H, t) – found under water, 3.39 (2H, q), 3.49 (2H, s), 3.95 (3H, s), 4.86 (1H, s), 7.46 (1H, d), 7.48 - 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, s), 8.31 (1H, t), 8.40 - 8.42 (1H, m); MS m/z 535
15 [M+H]⁺.

Example 385:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide
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The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 99 mg, 0.30 mmol), as a white solid (114 mg, 61%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.67 - 0.70 (2H, t), 0.90 - 0.93 (2H, t), 0.95 (2H, s), 1.42 - 1.48 (2H, m), 1.43 - 1.49 (2H, m), 1.54 (2H, t), 1.60 - 1.63 (1H, m), 1.68 (1H, s), 1.70 (1H, d), 1.89 - 1.97 (4H, m), 2.08 (1H, d), 2.16 - 2.24 (2H, m), 2.42 (3H, s), 2.98 - 3.01 (2H, d), 3.18 (3H, s), 3.49 (2H, s), 3.97 (3H, s), 4.34 (1H, m), 4.87 (1H, m), 7.47 (1H, d), 7.50 (1H, t), 7.68 (1H, s), 7.92 (1H, d), 8.00 (1H, s), 8.40 (1H, d); MS m/z 575 [M+H]⁺.

30 **Example 386:**

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 92 mg, 0.30 mmol), as a white solid (89 mg, 50%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.67 - 0.69 (2H, m), 0.89 (6H, s), 0.90 - 0.93 (2H, t), 1.51 (1H, d), 1.54 (1H, s), 1.58 (1H, d), 1.61 - 1.62 (1H, m), 1.69 (2H, d), 1.90 (2H, d), 2.21 (2H, s), 2.29 (6H, s), 3.19 (3H, s), 3.21 (2H, d), 3.48 (2H, s), 3.96 (3H, s), 4.86 (1H, m), 7.41 - 7.43 (1H, m), 7.47 (1H, d), 7.70 (1H, s), 7.99 (1H, s), 8.41 (1H, d), 8.44 (1H, t); MS m/z 551 [M+H]⁺.

Example 387:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 194; 78 mg, 0.30 mmol), as a white solid (82 mg, 50%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.67 - 0.70 (2H, t), 0.92 (2H, t), 1.51 (1H, d), 1.55 (1H, d), 1.60 - 1.63 (2H, m), 1.70 (2H, t), 1.90 (2H, s), 2.19 (6H, s), 2.41 (2H, t), 3.18 (3H, s), 3.37 (2H, q), 3.49 (2H, s), 3.95 (3H, s), 4.86 (1H, m), 7.46 (1H, d), 7.48 - 7.51 (1H, d), 7.69 (1H, s), 7.99 (1H, d), 8.27 (1H, t), 8.39 - 8.42 (1H, m); MS m/z 509 [M+H]⁺.

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Example 388:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

30

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 108 mg, 0.35 mmol) and 4-amino-3-fluoro-N-(9-methyl-9-azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 162; 102 mg, 0.35 mmol) were combined with p-toluenesulphonic acid monohydrate (167 mg, 0.88 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 25 minutes at 160 °C. The cooled reaction mixture was diluted with methanol (10 mL) and loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed with methanol (2 x 5 mL) and eluted with 7 N methanolic ammonia (10 mL). Product containing fractions were evaporated and the resultant material purified by base modified reverse phase preparative HPLC to give the title compound as a white solid (54 mg, 28 %).

¹H NMR (400 MHz, DMSO-d₆) δ 0.65 (t, 2H), 0.9 (m, 4H), 1.5 (m, 7H), 1.65 (m, 2H), 1.85 (m, 4H), 2.05 (m, 1H), 2.2 (m, 2H), 2.4 (s, 3H), 3.0 (d, 2H), 3.2 (s, 3H), 3.45 (s, 2H), 4.3 (m, 1H), 4.8 (m, 1H), 7.65 (m, 1H), 7.75 (m, 1H), 7.95 (m, 2H), 8.15 (t, 1H), 8.65 (s, 1H); MS m/z 562 [M+H]⁺.

Example 389:

5-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 85 mg, 0.30 mmol), 4-amino-5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 173; 101 mg, 0.33 mmol) and XANTPHOS (16 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (210 mg, 0.59 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (17 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (100 mg, 60%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 - 0.71 (2H, m), 0.92 - 0.95 (2H, m), 1.51 - 1.64 (6H, m), 1.66 - 1.71 (2H, m), 1.77 - 1.80 (2H, m), 1.85 - 1.99 (4H, m), 2.17 (3H, s), 2.74 (2H, d), 3.19 (3H, s), 3.50 (2H, s), 3.66 - 3.73 (1H, m), 4.80 - 4.88 (1H, m), 7.68 (1H, d), 8.04 - 8.09 (3H, m), 8.35 - 8.39 (1H, m); MS m/z 556 [M+H]⁺.

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Example 390:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2-dimethylaminoethyl)benzamide
 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.33 mmol) and 4-amino-3-chloro-N-(2-dimethylaminoethyl)benzamide (Intermediate 213; 89 mg, 0.37 mmol) were dissolved in 1,4 dioxane (4 mL) and caesium carbonate (234 mg, 0.72 mmol) was added. The reaction mixture was sparged with nitrogen for 15 minutes prior to addition of tris-dibenzylideneacetonedipalladium (II) (19 mg, 0.02 mmol) followed by XANTPHOS (19 mg, 15 0.03 mmol). The reaction mixture was heated at 100 °C overnight, cooled to room temperature and diluted with DCM (20 mL). The resultant mixture was filtered and the filtrate loaded onto an SCX-3 (5 g) cartridge. The cartridge was washed through with methanol (50 mL) and then eluted with 2M ammonia in methanol (50 mL). Evaporation of the ammoniacal fraction afforded an amber gum which was purified by acid modified reverse
 20 phase preparative HPLC. The resultant material was dissolved in MeOH/Water and poured onto an SCX-3 cartridge (2 g) and cartridge which was then washed with methanol and eluted with 2M ammonia in methanol, and the ammoniacal solution evaporated to yield the title compound as a solid (7 mg, 3%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.67 (m, 2H), 0.91 (m, 2H), 1.41 - 1.69 (m, 6H), 1.83 (m, 2H), 2.19 (s, 6H), 2.41 (t, 2H), 3.18 (s, 3H), 3.35 (m, 2H), 3.47 (s, 2H), 4.78 (m, 1H), 7.78 (m, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.10 (s, 1H), 8.32 (d, 1H), 8.37 (t, 1H); MS m/z 512 [M+H]⁺.

Example 391:

30 **3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide**

The title compound was prepared by an analogous method to the preparation of Example 390, utilising 4-amino-3-chloro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 215; 97 mg, 0.36 mmol), as a white solid (7 mg, 3%).

5 ¹H NMR (400.132 MHz, DMSO-d₆) δ 0.67 (m, 2H), 0.91 (m, 2H), 1.50 (m, 4H), 1.67 (m, 6H), 1.83 (m, 2H), 2.58 (t, 2H), 3.18 (s, 3H), 3.38 (m, 2H), 3.47 (s, 2H), 4.78 (m, 1H), 7.79 (m, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.10 (s, 1H), 8.32 (d, 1H), 8.42 (t, 1H); MS m/z 538 [M+H]⁺.

10 **Example 392:**

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 390, utilising 4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide
15 (Intermediate 107; 103 mg, 0.36 mmol), as a white solid (4 mg, 2%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.67 (m, 2H), 0.88 (s, 6H), 0.91 (m, 2H), 1.41 - 1.70 (m, 6H), 1.83 (m, 2H), 2.18 (s, 2H), 2.27 (s, 6H), 3.19 (m, 5H), 3.46 (s, 2H), 4.77 (m, 1H), 7.75 (m, 1H), 7.94 (d, 1H), 7.99 (s, 1H), 8.13 (s, 1H), 8.29 (d, 1H), 8.46 (t, 1H); MS m/z 554
20 [M+H]⁺.

Example 393:

5-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide
25

The title compound was prepared by an analogous method to the preparation of Example 389, utilising 4-amino-5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide (Intermediate 174; 90 mg, 0.30 mmol), as a white solid (102mg, 60%).

30 ¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 - 0.71 (2H, m), 0.92 - 0.95 (2H, m), 1.00 (3H, t), 1.49 - 2.01 (14H, m), 2.32 (2H, q), 2.84 (2H, d), 3.19 (3H, s), 3.50 (2H, s), 3.68 - 3.74 (1H,

235

m), 4.82 – 4.88 (1H, m), 7.68 (1H, d), 8.04 – 8.08 (3H, m), 8.35 - 8.39 (1H, m); MS m/z 570 [M+H]⁺.

Example 394:

5 **5-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide**

The title compound was prepared by an analogous method to the preparation of Example 389, utilising 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

10 (Intermediate 175; 94 mg, 0.30 mmol), as a white solid (65 mg, 37%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 - 0.71 (2H, m), 0.92 - 0.95 (2H, m), 1.340 – 1.35(2H, m), 1.49 – 1.94 (14H, m), 2.25 - 2.30 (7H, m), 3.19 (3H, s), 3.50 (2H, s), 3.67 – 3.71 and 3.91 – 3.97 (each 0.5H, m), 4.80 – 4.88 (1H, m), 7.65 - 7.68 (1H, m), 8.01 - 8.04 (2H, m), 8.08 (1H, d), 8.34 - 8.38 (1H, m); MS m/z 584 [M+H]⁺.

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Example 395:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

20 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.33 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 102 mg, 0.36 mmol) and caesium carbonate (213 mg, 0.65 mmol) added to dioxane (5 mL) and the suspension bubbled with nitrogen for 10 minutes. tris-dibenzylideneacetonedipalladium (II) (18 mg, 0.02 mmol) and
25 XANTPHOS (17 mg, 0.03 mmol) were added and the mixture heated at 110 °C overnight.

The mixture was filtered, and the filtrate loaded onto to an SCX-3 cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a light orange

30 gum (99 mg, 55%).

¹H NMR (399.9 MHz, DMSO-d₆) δ0.69 (2H, t), 0.93 (2H, t), 1.05 (3H, t), 1.52 – 1.58 (4H, m), 1.61 (2H, m), 1.65 – 1.67 (2h, m), 1.80 (2H, d), 1.85 (2H, d), 2.10 – 2.12 (2H, t), 2.41 (2h, q), 2.91 (2H, d), 3.17 (3H, s), 3.45 (2H, s), 3.75 (1H, m), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 554 [M+H]⁺.

5

Example 396:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

10 The title compound was prepared by an analogous method to the preparation of Example 395, utilising 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 97 mg, 0.36 mmol), as an off-white solid (122 mg, 69%)

¹H NMR (399.9 MHz, DMSO-d₆) δ0.69 (2H, t), 0.93 (2H, t), 1.05 (3H, t), 1.52 – 1.58 (4H, m), 1.61 (2H, m), 1.65 – 1.67 (2h, m), 1.80 (2H, d), 1.85 (2H, d), 2.10 – 2.12 (2H, t), 2.22
15 (3H, s), 2.91 (2H, d), 3.17 (3H, s), 3.45 (2H, s), 3.75 (1H, m), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 540 [M+H]⁺.

Example 397:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 395, utilising 4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 230; 97 mg, 0.36 mmol), as a pale yellow gum (121 mg, 69%).

25 ¹H NMR (399.9 MHz, DMSO-d₆) δ0.69 (2H, t), 0.93 (2H, t), 1.48 – 1.55 (4H, m), 1.58 – 1.64 (6H, m), 1.85 – 1.92 (2H, m), 2.57 (4H, m), 2.68 (2H, t), 3.17 (3H, s), 3.40 (2H, m), 3.45 (2H, s), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 540 [M+H]⁺.

30 **Example 398:**

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 80 mg, 0.26 mmol), 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 73 mg, 0.26 mmol) and p-toluenesulphonic acid monohydrate (124 mg, 0.65 mmol) were combined in 4-methyl-2-pentanol (3 mL) and heated at 100 °C for 18 hours. The cooled reaction mixture was loaded on to an SCX-2 column (5 g) pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) then eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (85 mg, 59%)

¹H NMR (399.902 MHz, CDCl₃) δ 0.62 (m, 2H), 1.11 (m, 2H), 1.46 (m, 2H), 1.72 (m, 4H), 1.79 (m, 4H), 2.03 (m, 2H), 2.58 (m, 4H), 2.72 (m, 2H), 3.29 (s, 3H), 3.47 (s, 2H), 3.60 (m, 2H), 3.95 (s, 3H), 4.96 (m, 1H), 7.31 (m, 1H), 7.56 (d, 1H), 7.70 (s, 1H), 7.87 (s, 1H), 8.41 (d, 1H); MS m/z 552 [M+H]⁺.

Example 399:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.32 mmol), 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 87 mg, 0.32 mmol) and 4-toluenesulphonic acid monohydrate (154 mg, 0.81 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (80 mg, 46%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.67 – 0.72 (2H, m), 0.91 – 0.96 (2H, m), 1.53 – 1.75 (7H, m), 1.87 – 1.96 (2H, m), 2.13 – 2.22 (1H, m), 2.26 (3H, s), 2.34 – 2.45 (2H, m), 2.57 –

2.64 (1H, m), 2.66 - 2.70 (1H, m), 3.18 (3H, s), 3.50 (2H, s), 3.93 (3H, s), 4.35 - 4.43 (1H, m), 4.83 - 4.92 (1H, m), 7.22 (1H, d), 7.77 (1H, s), 7.98 - 8.00 (1H, m), 8.03 (1H, s), 8.35 (1H, d); MS m/z 539 [M+H]⁺.

5 **Example 400:**

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 109 mg, 0.36 mmol), aniline (Intermediate 229; 83 mg, 0.324 mmol), and caesium carbonate (211 mg, 0.648 mmol) added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris-dibenzylideneacetonedipalladium (II) (11 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol) were added and the mixture heated to 100 °C for 16 hours. The reaction mixture was cooled to room temperature filtered, and the filter cake washed with DCM and the filtrate evaporated. The residue was dissolved in DCM and purified on a silica column eluting with a gradient of 0 - 5% 2M ammonia in MeOH / DCM over 30 column volumes. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (95 mg, 56%).
20 ¹H NMR (399.902 MHz, CDCl₃) δ 0.64 (m, 2H), 1.12 (m, 2H), 1.46 (m, 2H), 1.74 (m, 5H), 2.02 (m, 2H), 2.29 (m, 1H), 2.42 (m, 4H), 2.67 (m, 2H), 2.90 (m, 1H), 3.29 (s, 3H), 3.48 (s, 2H), 4.65 (m, 1H), 4.93 (m, 1H), 6.96 (m, 1H), 7.28 (m, 1H), 7.80 (m, 1H), 7.88 (s, 1H), 8.46 (m, 1H); MS m/z 526 [M+H]⁺.

25 **Example 401:**

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 101 mg, 0.33 mmol), p-toluenesulphonic acid monohydrate (155 mg, 0.81 mmol) and 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-

30

3-methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The sample was transferred to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated
5 and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (34 mg, 18%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.63 - 0.60 (m, 2H), 1.01 (s, 6H), 1.10 - 1.07 (m, 2H), 1.51 - 1.43 (m, 2H), 1.74 - 1.61 (m, 4H), 1.83 - 1.76 (m, 4H), 2.05 - 1.98 (m, 2H), 2.56 (s, 2H), 2.72 - 2.65 (m, 4H), 3.28 (s, 3H), 3.39 (d, 2H), 3.46 (s, 2H), 3.98 (s, 3H), 4.98 (quintet, 1H),
10 7.20 (dd, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.87 (s, 1H), 8.46 (d, 1H), 9.15 (s, 1H); MS m/z 576 [M+H]⁺.

Example 402:

**3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-
15 1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide**

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-chloro-benzoic acid (Intermediate 253; 52 mg, 0.12 mmol) was suspended in DMF (4 mL). DIPEA (62 ul, 0.35 mmol) was added to give a straw coloured solution. Endo-
20 9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 26 mg, 0.16 mmol) was added, followed by HATU (67 mg, 0.17 mmol) and the resultant mixture was stirred at ambient temperature overnight.

The reaction mixture was evaporated to an amber gum, which was partitioned between DCM (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was
25 separated by gravity elution through a PTFE filter cup and the filtrate evaporated to dryness to afford an amber oil which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (46 mg, 56%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.68 (m, 2H), 0.92 (m, 4H), 1.39 - 1.70 (m, 9H), 1.80 - 2.08 (m, 5H), 2.19 (m, 2H), 2.41 (s, 3H), 2.98 (m, 2H), 3.18 (s, 3H), 3.47 (s, 2H), 4.31 (m,
30 1H), 4.78 (m, 1H), 7.80 (m, 1H), 7.99 (s, 1H), 8.00 (d, 1H), 8.05 (d, 1H), 8.08 (s, 1H), 8.32 (d, 1H); MS m/z 578 [M+H]⁺.

Example 403:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, utilising, 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 75 mg, 0.24 mmol), and 4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide (Intermediate 245; 70 mg, 0.26 mmol) heating by microwave irradiation at 160 °C for 1 hour, as an off-white foam (50 mg, 39%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.04 (t, 3H), 1.10 (s, 6H), 1.55 - 1.93 (m, 9H), 2.15 (m, 1H), 2.43 (m, 4H), 2.65 (m, 1H), 2.73 (m, 1H), 3.19 (s, 3H), 3.38 (s, 2H), 3.95 (s, 3H), 4.40 (m, 1H), 5.19 (m, 1H), 7.51 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.28 (d, 1H), 8.37 (d, 1H); MS m/z 536 [M+H]⁺.

Example 404:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 55 mg, 0.17 mmol), 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 204; 53 mg, 0.17 mmol) and p-toluenesulphonic acid monohydrate (82 mg, 0.43 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 2 hours. The reaction mixture was cooled and absorbed on to an SCX column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (35mg, 35%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.68 - 0.71 (2H, m), 0.91 - 0.94 (4H, m), 1.40 - 1.46 (3H, m), 1.51 - 1.73 (6H, m), 1.86 - 1.94 (4H, m), 1.99 - 2.09 (1H, m), 2.18 - 2.25 (2H, m), 2.42

(3H, s), 2.98 (2H, d), 3.19 (3H, s), 3.51 (2H, s), 3.94 (3H, s), 4.27 - 4.35 (1H, m), 4.84 - 4.92 (1H, m), 7.22 (1H, d), 7.66 - 7.69 (1H, m), 7.77 (1H, s), 8.03 (1H, s), 8.35 (1H, d); MS m/z 592 [M+H]⁺.

5 **Example 405:**

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 70 mg, 0.23 mmol), 4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 254; 70 mg, 0.22 mmol), and p-toluenesulphonic acid monohydrate (136 mg, 0.71 mmol) were stirred and heated together in 4-methyl-2-pentanol (3 mL) at 110 °C for 18 hours.

The cooled reaction solution was loaded onto an SCX-3 (5g) column pre-wet with MeOH.

15 The column was washed with MeOH (2 column volumes) and the product eluted with 2M NH₃/MeOH. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (38 mg, 29%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.34 (2H, m), 0.50 (2H, m), 0.69 (2H, m), 0.92 (2H, m), 1.61 (12H, m), 1.92 (2H, m), 2.44 (2H, s), 2.50 (2H, s), 3.18 (3H, s), 3.36 (2H, d), 3.51 (2H, s), 3.93 (3H, s), 4.89 (1H, m), 7.37 (1H, d), 7.80 (1H, s), 8.03 (1H, s), 8.37 (2H, d), 8.41 (1H, m); MS m/z 592 [M+H]⁺.

Example 406:

25 **4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-3-fluoro-benzamide**

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 231 mg, 0.75 mmol), 4-amino-N-(1-ethylpiperidin-4-yl)-3-fluorobenzamide (200 mg, 0.75 mmol) and p-toluenesulfonic acid monohydrate (335 mg, 1.88 mmol) were suspended in 4-Methyl-2-pentanol (5 mL) and sealed into a microwave tube. The reaction was heated to 160 °C for 30 minutes in the microwave

reactor and allowed to cool to room temperature.

The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford an orange / brown oil which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a white solid (48 mg, 12%).

¹H NMR (400 MHz, DMSO-d₆) δ 0.65 (t, 2H), 0.9 (t, 2H), 1.0 (t, 3H), 1.5 (m, 7H), 1.6 (m, 2H), 1.9 (t, 2H), 2.3 (q, 2H), 2.9 (d, 2H), 3.2 (s, 3H), 3.4 (s, 2H), 3.6 (m, 1H), 4.75 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.6 (s, 1H); MS m/z 537 [M+H]⁺.

Example 407:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 121 mg, 0.39 mmol) and 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 116 mg, 0.39 mmol) were taken up in 4-methyl-2-pentanol (4 mL) and p-toluenesulphonic acid monohydrate (150 mg, 0.79 mmol) added. The reaction mixture was heated at 160 °C by microwave irradiation for 1 hour. The cooled reaction mixture was poured into a mixture of methanol & water (5:2 v/v, 7 mL) and the resultant solution loaded onto an SCX-3 cartridge (5 g), which had been pre-wet with methanol. The cartridge was washed through with methanol (40 mL) and eluted with 2M ammonia in methanol (30 mL). The ammoniacal solution was evaporated to give an amber gum afforded which was purified by base modified reverse phase preparative HPLC which was re-purified by flash chromatography on a silica column eluting with 2.5-10% ammonia/methanol in DCM. Product containing fractions were combined and evaporated and the residue triturated with diethyl ether and resultant solid dried under vacuum, at 60 °C, for 3 hours to yield the title compound as a flocculent white solid (86 mg, 39%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.67 - 0.70 (2H, m), 0.91 - 0.94 (2H, m), 1.00 (3H, t), 1.48 - 1.99 (14H, m), 2.32 (2H, q), 2.82 - 2.85 (2H, m), 3.18 (3H, s), 3.50 (2H, s), 3.69 - 3.79

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(1H, m), 3.93 (3H, s), 4.82 - 4.91 (1H, m), 7.20 (1H, d), 7.76 (1H, s), 7.79 - 7.82 (1H, m), 8.02 (1H, s), 8.34 (1H, d); MS m/z 566 [M+H]⁺.

Example 408:

5 **7-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide**

To 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5H)-one (Intermediate 130; 108 mg, 0.35 mmol) and 7-amino-N-(1-methylpiperidin-4-yl)benzo[d][1,3]dioxole-4-carboxamide (Intermediate 223; 98 mg, 0.35 mmol) in 4-methyl-2-pentanol (3 mL) was added p-toluenesulphonic acid monohydrate (139 mg, 0.73 mmol) and the reaction mixture heated at 160 °C by microwave irradiation for 1 hour.

After cooling the reaction mixture was diluted with MeOH (5 mL) and water (2 mL). The mixture was then submitted to ion exchange chromatography, using an SCX-2 column (10 g). After eluting through with methanol (100 mL) the crude product was eluted from the column using 2M ammonia in methanol (50 mL) and evaporated to afford a brown residue, which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a grey solid (43 mg, 22 %).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.57 - 0.59 (2H, m), 0.81 - 0.83 (2H, m), 1.31 - 1.60 (8H, m), 1.69 - 1.78 (4H, m), 1.92 - 1.97 (2H, m), 2.09 (3H, s), 2.58 - 2.65 (2H, m), 3.09 (3H, s), 3.36 (2H, s), 3.63 - 3.73 (1H, m), 4.71 (1H, quintet), 6.07 (2H, s), 7.14 (1H, d), 7.22 (1H, d), 7.45 (1H, d), 7.87 (1H, s), 8.51 (1H, s); MS m/z 548 [M+H]⁺.

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Example 409:

30 **4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide**

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclohexane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 255; 80 mg, 0.24 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 63mg, 0.24mmol) and p-toluenesulphonic acid monohydrate (114 mg, 0.60 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were evaporated and the residue purified on a silica column (2% 7N ammonia in methanol/DCM) to give the title compound as a white solid. (70 mg, 52%)

¹H NMR (399.9 MHz, DMSO-d₆) δ 1.31 - 1.37 (2H, m), 1.50 - 1.80 (14H, m), 1.89 - 2.06 (6H, m), 2.18 (3H, s), 2.79 (2H, d), 3.21 (3H, s), 3.43 (2H, s), 3.71 - 3.79 (1H, m), 3.96 (3H, s), 4.98 - 5.06 (1H, m), 7.47 - 7.51 (2H, m), 7.70 (1H, s), 8.02 (1H, s), 8.07 (1H, d), 8.38 (1H, d); MS m/z 562 [M+H]⁺.

Example 410:

3-methoxy-4-[[6-methyl-5-oxo-2-(2-oxocyclopentyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-6-methyl-2-(2-oxocyclopentyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 261; 58 mg, 0.19 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 53 mg, 0.20 mmol) and p-toluene sulphonic acid monohydrate (80 mg, 0.42 mmol) were dissolved in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation at 150 °C for 30 minutes. After cooling, the reaction mixture was dissolved in methanol (5 mL) and water (5 mL) and poured directly onto an SCX-3 cartridge (5 g). The cartridge was washed with methanol (50 mL), before elution of products with 2M ammonia in methanol (50 mL). The ammoniacal fraction was evaporated and the residue was purified by base modified reverse phase preparative HPLC to yield the title compound as a yellow solid (11 mg, 7%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.60 (m, 2H), 1.73 - 2.09 (m, 8H), 2.17 (s, 3H), 2.25 (m, 2H), 2.62 (m, 2H), 2.78 (m, 2H), 3.19 (s, 3H), 3.60 (m, 2H), 3.74 (m, 1H), 3.93 (s, 3H), 4.67 (m, 1H), 7.48 (m, 2H), 7.74 (s, 1H), 8.06 (d, 1H), 8.13 (s, 1H), 8.18 (d, 1H); MS m/z 522 [M+H]⁺.

Example 411:

2-chloro-4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-fluoro-N-(1-methyl-4-piperidyl)benzamide

2-amino-9-cyclohexyl-5-methyl-8,9-dihydro-5H-pyrimido[5,4-b][1,4]diazepin-6(7H)-one
5 (Intermediate 263; 100 mg, 0.36 mmol), 4-bromo-2-chloro-5-fluoro-N-(1-methylpiperidin-4-yl)benzamide (Intermediate 262; 133 mg, 0.38 mmol), xantphos (12.61 mg, 0.02 mmol), palladium(II) acetate (163 mg, 0.73 mmol) and caesium carbonate (14.20 mg, 0.04 mmol) were added to dioxane (10 mL) and heated at 103 °C overnight. The resulting solution was filtered and passed through a 5g SCX-3 column. The obtained yellow foam was triturated
10 with hot ethyl acetate to afford a yellow solid.

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.16 - 1.08 (m, 1H), 1.43 - 1.35 (m, 2H), 1.63 - 1.48 (m, 5H), 1.80 - 1.71 (m, 6H), 2.08 - 1.99 (m, 2H), 2.19 (s, 3H), 2.59 - 2.56 (m, 2H), 2.78 - 2.75 (m, 2H), 3.17 (s, 3H), 3.71 - 3.60 (m, 3H), 4.41 - 4.36 (m, 1H), 7.30 (d, 1H), 8.06 (s, 1H), 8.16 (d, 1H), 8.26 (d, 1H), 8.78 (s, 1H); MS m/z 544 [M+H]⁺.

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Example 412:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one
20 (Intermediate 266; 33 mg, 0.113 mmol), 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 29 mg, 0.108 mmol) and caesium carbonate were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. tris(dibenzylideneacetone) palladium (II) (4 mg, 0.006 mmol) and XANTPHOS (6 mg, 0.1 mmol) were added and the mixture heated at 100 °C for 16 hours. The reaction mixture was
25 cooled to room temperature and filtered. The filter-cake was washed with DCM and the filtrate evaporated. The residue was dissolved in DCM and purified on a silica column eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM over 30 column volumes. Fractions containing product were combined and evaporated to a solid, which was triturated with isohexane then filtered and dried to yield the title compound as a pale yellow solid (46
30 mg, 81%).

¹H NMR (399.902 MHz, CDCl₃) δ1.18 (m, 1H), 1.57 (m, 6H), 1.78 (m, 1H), 1.91 (m, 4H), 2.06 (m, 2H), 2.17 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.80 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 4.01 (m, 1H), 4.48 (m, 1H), 6.58 (m, 1H), 7.29 (m, 1H), 7.82 (m, 1H), 7.94 (s, 1H), 8.38 (m, 1H); MS m/z 528 [M+H]⁺.

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Example 413:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2,5-difluoro-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 269; 50 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (42 mg, 46%).

¹H NMR (399.902 MHz, CDCl₃) δ0.39 (m, 2H), 0.57 (m, 2H), 1.17 (m, 1H), 1.54 (m, 4H), 1.75 (m, 5H), 1.92 (m, 4H), 2.49 (s, 2H), 2.54 (m, 4H), 2.68 (m, 2H), 3.29 (s, 3H), 3.46 (m, 2H), 3.72 (m, 2H), 4.50 (m, 1H), 7.29 (m, 1H), 7.83 (m, 1H), 7.94 (s, 1H), 8.32 (m, 1H), 8.64 (m, 1H); MS m/z 569 [M+H]⁺.

Example 414:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 229; 41 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (49 mg, 59%).

¹H NMR (399.902 MHz, CDCl₃) δ1.18 (m, 1H), 1.54 (m, 4H), 1.76 (m, 2H), 1.91 (m, 4H), 2.29 (m, 1H), 2.42 (m, 4H), 2.68 (m, 4H), 2.90 (m, 1H), 3.29 (s, 3H), 3.72 (m, 2H), 4.48 (m, 1H), 4.66 (m, 1H), 6.94 (m, 1H), 7.29 (m, 1H), 7.81 (m, 1H), 7.94 (s, 1H), 8.37 (m, 1H); MS m/z 514 [M+H]⁺.

Example 415:

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4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 46 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (60 mg, 69%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.10 (t, 3H), 1.18 (m, 1H), 1.55 (m, 6H), 1.78 (m, 1H), 1.91 (m, 4H), 2.11 (m, 4H), 2.43 (q, 2H), 2.68 (m, 2H), 2.89 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 4.04 (m, 1H), 4.48 (m, 1H), 6.59 (m, 1H), 7.28 (m, 1H), 7.82 (m, 1H), 7.94 (s, 1H), 8.38 (m, 1H); MS m/z 542 [M+H]⁺.

Example 416:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 230; 43 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (64 mg, 76%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.18 (m, 1H), 1.54 (m, 4H), 1.77 (m, 5H), 1.90 (m, 4H), 2.57 (m, 4H), 2.70 (m, 4H), 3.29 (s, 3H), 3.58 (m, 2H), 3.71 (m, 2H), 4.49 (m, 1H), 7.29 (m, 2H), 7.82 (m, 1H), 7.94 (s, 1H), 8.39 (m, 1H); MS m/z 526 [M+H]⁺.

Example 417:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 162; 150 mg, 0.515 mmol), the final product being taken up in methanol (1 mL) diluted with water and freeze dried, as a cream coloured solid (201 mg, 71%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.06 (m, 2H), 1.18 (m, 1H), 1.33 (m, 2H), 1.52 (m, 4H), 1.77 (m, 1H), 1.95 (m, 8H), 2.52 (m, 5H), 2.67 (m, 2H), 3.11 (m, 2H), 3.29 (s, 3H), 3.70 (m,

2H), 4.49 (m, 2H), 5.75 (d, 1H), 7.24 (m, 1H), 7.52 (m, 2H), 7.92 (s, 1H), 8.56 (m, 1H); MS m/z 550 [M+H]⁺.

Example 418:

5 **4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 154 mg, 0.509 mmol), the final product being purified by base modified
10 reverse phase preparative HPLC, as a white solid (137 mg, 48%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.04 (m, 2H), 1.19 (m, 1H), 1.31 (m, 2H), 1.53 (m, 6H), 1.79 (m, 1H), 1.96 (m, 6H), 2.54 (m, 5H), 2.67 (m, 2H), 3.10 (m, 2H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.50 (m, 2H), 5.77 (d, 1H), 7.25 (m, 1H), 7.40 (d, 1H), 7.69 (s, 1H), 7.91 (s, 1H), 8.49 (d, 1H); MS m/z 562 [M+H]⁺.

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Example 419:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-yl)methyl]cyclopropyl]methyl]benzamide

20 The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-yl)methyl]cyclopropyl]methyl]benzamide (Intermediate 254; 65 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (4 mg, 3%).

25 MS m/z 580 [M+H]⁺. Retention time 3.69 minutes

Example 420:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

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The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 55 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (20 mg, 19%).

5 ¹H NMR (399.902 MHz, CDCl₃) δ 1.20 (m, 1H), 1.56 (m, 4H), 1.78 (m, 2H), 1.92 (m, 4H), 2.32 (m, 1H), 2.43 (m, 4H), 2.68 (m, 4H), 2.89 (m, 1H), 3.28 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.52 (m, 1H), 4.67 (m, 1H), 7.00 (m, 1H), 7.56 (m, 1H), 7.76 (s, 1H), 7.92 (s, 1H), 8.31 (d, 1H); MS m/z 526 [M+H]⁺.

10 **Example 421:**

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-3-methoxy-N-(1-methylpyrrolidin-3-yl)benzamide (Intermediate 187; 51
15 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (37 mg, 36%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.22 (m, 1H), 1.52 (m, 4H), 1.77 (m, 2H), 1.94 (m, 4H), 2.23 (m, 1H), 2.44 (m, 4H), 2.56 (m, 1H), 2.67 (m, 2H), 2.81 (m, 1H), 2.98 (m, 1H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 4.70 (m, 1H), 6.48 (d, 1H), 7.31 (m, 1H), 7.41
20 (m, 1H), 7.70 (s, 1H), 7.91 (s, 1H), 8.49 (d, 1H); MS m/z 508 [M+H]⁺.

Example 422:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

25 The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 60 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (27 mg, 24%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.10 (t, 3H), 1.21 (m, 1H), 1.55 (m, 6H), 1.78 (m, 1H),
30 1.92 (m, 4H), 2.12 (m, 4H), 2.43 (q, 2H), 2.68 (m, 2H), 2.89 (m, 2H), 3.28 (s, 3H), 3.71 (m,

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2H), 3.95 (s, 3H), 4.05 (m, 1H), 4.52 (m, 1H), 6.67 (m, 1H), 7.56 (d, 1H), 7.74 (s, 1H), 7.92 (s, 1H), 8.32 (d, 1H); MS m/z 554 [M+H]⁺.

Example 423:

5 **4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide**

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 57 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative

10 HPLC, as a white solid (61 mg, 56%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.11 (t, 3H), 1.21 (m, 1H), 1.54 (m, 6H), 1.78 (m, 1H), 1.94 (m, 4H), 2.12 (m, 4H), 2.44 (q, 2H), 2.67 (m, 2H), 2.92 (m, 2H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.03 (m, 1H), 4.50 (m, 1H), 5.88 (d, 1H), 7.23 (m, 1H), 7.39 (m, 1H), 7.68 (s, 1H), 7.91 (s, 1H), 8.50 (d, 1H); MS m/z 536 [M+H]⁺.

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Example 424:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide (Intermediate 196; 51 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (50 mg, 48%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.22 (m, 1H), 1.54 (m, 4H), 1.76 (m, 3H), 1.95 (m, 4H), 2.30 (s, 6H), 2.51 (m, 2H), 2.67 (m, 2H), 3.28 (s, 3H), 3.58 (m, 2H), 3.70 (m, 2H), 3.97 (s, 25 3H), 4.53 (m, 1H), 7.27 (m, 1H), 7.48 (m, 1H), 7.72 (s, 1H), 7.91 (s, 1H), 8.38 (m, 1H), 8.50 (d, 1H); MS m/z 510 [M+H]⁺.

30 **Example 425:**

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 228; 57 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (19 mg, 17%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.20 (m, 1H), 1.56 (m, 4H), 1.77 (m, 5H), 1.91 (m, 4H), 2.58 (m, 4H), 2.70 (m, 4H), 3.28 (s, 3H), 3.60 (m, 2H), 3.71 (m, 2H), 3.95 (s, 3H), 4.53 (m, 1H), 7.32 (m, 1H), 7.57 (d, 1H), 7.73 (s, 1H), 7.92 (s, 1H), 8.33 (d, 1H); MS m/z 540 [M+H]⁺.

Example 426:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 194; 48 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (31 mg, 31%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.22 (m, 1H), 1.54 (m, 4H), 1.76 (m, 1H), 1.94 (m, 4H), 2.29 (s, 6H), 2.54 (m, 2H), 2.67 (m, 2H), 3.28 (s, 3H), 3.53 (m, 2H), 3.70 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 6.74 (m, 1H), 7.32 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.91 (s, 1H), 8.50 (d, 1H); MS m/z 496 [M+H]⁺.

Example 427:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 204; 65 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (52 mg, 44%).

¹H NMR (399.902 MHz, CDCl₃) δ1.04 (m, 2H), 1.21 (m, 1H), 1.32 (m, 2H), 1.56 (m, 6H), 1.79 (m, 1H), 1.95 (m, 6H), 2.54 (m, 5H), 2.68 (m, 2H), 3.09 (m, 2H), 3.28 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.53 (m, 2H), 6.53 (m, 1H), 7.59 (d, 1H), 7.75 (s, 1H), 7.93 (s, 1H), 8.31 (d, 1H); MS m/z 580 [M+H]⁺.

5

Example 428:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one
10 (Intermediate 267; 89 mg, 0.3 mmol) and 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 61; 76 mg, 0.3 mmol) were combined with p-toluenesulphonic acid monohydrate (143 mg, 0.75 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 30 minutes at 160 °C. The cooled reaction mixture was diluted with methanol (10 mL) and filtered and the filtrate loaded onto an SCX-3 cartridge (5
15 g) pre-wet with methanol. The cartridge was washed with methanol (2 x 10 mL) and eluted with 7 N methanolic ammonia (20 mL). The basic fraction was evaporated to give a yellow solid, which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (55 mg, 37%).

¹H NMR (400 MHz, DMSO-d₆) δ1.15 (m, 2H), 1.45 (m, 3H), 1.6 (m, 4H), 1.7 (m, 1H), 1.8
20 (m, 6H), 1.95 (t, 2H), 2.15 (s, 3H), 2.6 (m, 2H), 2.7 (m, 2H), 3.15 (s, 3H), 3.65 (m, 2H), 3.7 (m, 1H), 4.4 (t, 1H), 7.5 (m, 2H), 7.7 (m, 2H), 8.1 (s, 1H), 9.6 (s, 1H); MS m/z 511 [M+H]⁺.

Example 429:

25 **4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-(1-methyl-4-piperidyl)benzamide**

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 267; 89 mg, 0.3 mmol) and 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 65; 76 mg, 0.3 mmol) were combined with p-
30 toluenesulphonic acid monohydrate (143 mg, 0.75 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 30 minutes at 160 °C The cooled reaction mixture was

diluted with methanol (10 mL) and filtered and the filtrate loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed with methanol (2 x 10 mL) and eluted with 7 N methanolic ammonia (20 mL). The basic fraction was evaporated to give a yellow gum, which was purified by base modified reverse phase preparative HPLC to give the title compound as a white solid (56 mg, 37 %).

¹H NMR (400 MHz, DMSO-d₆) δ 1.1 (m, 1H), 1.3 (q, 2H), 1.55 (m, 5H), 1.75 (m, 6H), 1.95 (t, 2H), 2.2 (s, 3H), 2.6 (m, 2H), 2.75 (d, 2H), 3.2 (s, 3H), 2.6 (m, 2H), 2.75 (d, 2H), 3.2 (s, 3H), 3.6 (m, 2H), 3.7 (m, 1H), 4.3 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 8.0 (s, 1H), 8.1 (m, 2H), 8.7 (s, 1H); MS m/z 511 [M+H]⁺.

Example 430:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 100 mg, 0.31 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 83 mg, 0.31 mmol) and p-toluenesulphonic acid monohydrate (149 mg, 0.78 mmol) were heated at 140 °C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction mixture was loaded onto an SCX-3 column was pre-wet with methanol and the column washed with methanol and eluted with 2% 7N ammonia/methanol. The ammoniacal fraction was evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (97 mg, 57%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.68 - 0.71 (2H, t), 0.92 - 0.95 (2H, t), 1.40 - 1.50 (4H, m), 1.59 - 1.63 (2H, m), 1.65 - 1.68 (1H, m), 1.77 (2H, s), 1.79 (4H, t), 1.86 (1H, s), 1.93 - 1.98 (2H, m), 2.18 (3H, s), 2.80 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.70 - 3.76 (1H, m), 3.96 (3H, s), 4.45 (1H, m), 7.46 (1H, m), 7.48 - 7.51 (1H, d), 7.67 (1H, s), 7.96 (1H, s), 8.09 (1H, d), 8.39 (1H, d); MS m/z 547 [M+H]⁺.

Example 431:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

5 The title compound was prepared by an analogous method to the preparation of Example 430, utilising 4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide (Intermediate 196; 79 mg, 0.31 mmol), , as a white solid (96 mg, 58%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.68 - 0.71 (2H, t), 0.92 - 0.95 (2H, t), 1.47 - 1.51 (2H, m), 1.68 (4H, q), 1.76 - 1.78 (4H, m), 1.85 (2H, d), 2.15 (6H, s), 2.28 (2H, t), 3.17 (3H, s),
 10 3.25 (2H, t), 3.51 (2H, s), 3.96 (3H, s), 4.45 (1H, m), 7.45 - 7.47 (1H, m), 7.51 (1H, d), 7.67 (1H, s), 7.96 (1H, s), 8.40 (1H, d), 8.41 (1H, d); MS m/z 537 [M+H]⁺.

Example 432:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 430, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 95 mg, 0.31 mmol), , as a white solid (111 mg, 61%).

20 ¹H NMR (399.9 MHz, DMSO-d₆) δ 0.68 - 0.71 (2H, m), 0.93 (2H, d), 0.93 (2H, d), 1.42 (2H, d), 1.45 - 1.47 (3H, m), 1.49 (2H, d), 1.77 (4H, d), 1.85 (4H, d), 1.93 (2H, t), 2.21 (1H, d), 2.42 (3H, s), 2.99 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.98 (3H, s), 4.29 - 4.34 (1H, m), 4.45 (1H, m), 7.47 (1H, d), 7.48 - 7.52 (1H, s), 7.67 (1H, s), 7.92 (1H, d), 7.97 (1H, s), 8.39 - 8.41 (1H, d); MS m/z 589 [M+H]⁺.

25

Example 433:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

255

The title compound was prepared by an analogous method to the preparation of Example 430, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 87 mg, 0.31 mmol), , as a white solid (122 mg, 70%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.68 - 0.71 (2H, t), 0.92 - 0.95 (2H, t), 1.01 (3H, t), 1.45 (3H, t), 1.57 - 1.61 (2H, m), 1.77 (4H, d), 1.82 - 1.86 (3H, m), 1.88 (2H, t), 1.93 (2H, d), 2.33 (2H, q), 2.90 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.74 - 3.78 (1H, m), 3.96 (3H, s), 4.41 - 4.45 (1H, m), 7.46 (1H, d), 7.48 - 7.51 (1H, m), 7.67 (1H, s), 7.96 (1H, s), 8.09 (1H, d), 8.39 - 8.41 (1H, m); MS m/z 563 [M+H]⁺.

10 **Example 434:**

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 100 mg, 0.31 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 98 mg, 0.34 mmol) and caesium carbonate (204 mg, 0.62 mmol) added to dioxane (5 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol) added and the mixture heated at 110 °C overnight. The mixture was filtered and the filtrate loaded onto an SCX-3 column was pre-wet with methanol and the column washed with methanol and eluted with 2% 7N ammonia/methanol. The ammoniacal fraction was evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white crystalline solid (19 mg, 11%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 - 0.72 (2H, t), 0.93 - 0.96 (2H, t), 1.00 (3H, t), 1.42 (2H, t), 1.48 (2H, d), 1.49 - 1.54 (2H, m), 1.63 (2H, d), 1.70 (2H, d), 1.78 (4H, s), 1.95 (2H, d), 2.30 - 2.35 (2H, m), 2.84 (2H, d), 3.17 (3H, s), 3.50 (2H, s), 3.75 (1H, m), 4.46 (1H, m), 7.41 - 7.45 (1H, m), 7.98 (1H, d), 7.99 (1H, s), 8.13 - 8.18 (1H, m), 8.79 (1H, s); MS m/z 589 [M+H]⁺.

Example 435:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

5 2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 97 mg, 0.3 mmol) and 4-amino-3-fluoro-N-(9-methyl-9-azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 162; 88 mg, 0.3 mmol) were combined with p-toluenesulphonic acid monohydrate (143 mg, 0.75 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 30 minutes at 160 °C. The cooled
10 reaction mixture was diluted with methanol (5 mL) and loaded onto an SCX-3 (5 g) cartridge pre-wet with methanol. The cartridge was washed with methanol (2 x 10 mL) and product eluted with 7 N methanolic ammonia (20 mL). Product containing fractions were evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (82 mg, 48%).

15 ¹H NMR (400 MHz, DMSO-d₆) δ 0.7 (m, 2H), 0.95 (m, 4H), 1.15 (m, 1H), 1.35 (m, 2H), 1.45 (m, 4H), 1.7 (m, 4H), 1.8 (d, 2H), 1.95 (m, 2H), 2.05 (m, 1H), 2.15 (m, 2H), 2.9 (s, 3H), 2.95 (d, 2H), 3.15 (s, 3H), 3.45 (s, 2H), 4.35 (m, 2H), 7.65 (m, 1H), 7.7 (m, 1H), 7.9 (s, 1H), 7.95 (m, 1H), 8.2 (t, 1H), 8.55 (s, 1H); MS m/z 576 [M+H]⁺.

20 **Example 436:**

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 434,
25 utilising 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 93 mg, 0.34 mmol), as a white solid (76 mg, 44%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.69 - 0.72 (2H, t), 0.93 - 0.96 (2H, t), 1.44 (4H, m), 1.54 - 1.61 (2H, m), 1.71 (2H, d), 1.78 (4H, d), 1.94 - 1.99 (2H, m), 2.17 (3H, s), 2.73 (2H, d), 3.17 (3H, s), 3.29 (2H, d), 3.50 (2H, s), 3.65 - 3.72 (1H, m), 4.46 (1H, m), 7.41 - 7.45 (1H, m), 7.96
30 (1H, d), 7.98 (1H, s), 8.13 - 8.18 (1H, m), 8.78 (1H, s); MS m/z 554 [M+H]⁺.

Example 437:

5-chloro-4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

5 2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 103 mg, 0.32 mmol), 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 92 mg, 0.29 mmol), and XANTPHOS (16 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (210 mg, 0.59 mmol) was added and the system purged with a stream of nitrogen
 10 for 15 minutes before tris(dibenzylideneacetone) palladium (II) (17 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, and the column then washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the residue purified by base
 15 modified reverse phase preparative HPLC to yield the title compound as a white solid (49 mg, 28%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.71 (2H, m), 0.94 (2H, m), 1.10 (2H, m), 1.25 - 1.84 (16H, m), 2.09 - 2.19 (7H, m), 3.18 (3H, s), 3.52 (2H, s), 3.63 - 3.70 and 3.88 - 3.94 (each 0.5H, m), 4.43 (1H, m), 7.67 (1H, d), 8.00 - 8.04 (3H, m), 8.27 (1H, d); MS m/z 598 [M+H]⁺.

20

Example 438:

25 **4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide**

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 103 mg, 0.32 mmol), 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 87 mg, 0.32 mmol)
 30 and p-toluenesulphonic acid monohydrate (154 mg, 0.81 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX

column, which was then washed with methanol and eluted with ammonia in methanol.

Product containing fractions were combined and evaporated and purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (70 mg, 40%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.70 - 0.73 (2H, m), 0.93 - 0.96 (2H, m), 1.10 1.20 (1H, m), 1.40 - 1.54 (4H, m), 1.64 - 1.84 (6H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.33 - 2.47 (2H, m), 2.56 - 2.64 (1H, m), 2.66 - 2.71 (1H, m), 3.17 (3H, s), 3.53 (2H, s), 3.94 (3H, s), 4.34 - 4.41 (1H, m), 4.45 - 4.50 (1H, m), 7.22 (1H, d), 7.74 (1H, s), 7.99 (1H, s), 8.01 - 8.03 (1H, m), 8.26 (1H, d); MS m/z 554 [M+H]⁺.

10 **Example 439:**

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5H)-one (Intermediate 270; 86 mg, 0.27 mmol) and 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 75 mg, 0.27 mmol) were taken up in 4-methyl-2-pentanol (3 mL) and p-toluenesulphonic acid monohydrate (102 mg, 0.54 mmol) added. The reaction mixture was heated at 160 °C for 1 hour by microwave irradiation. After cooling, the reaction mixture was diluted with methanol (5 mL) and water (5 mL) and the resultant solution loaded onto an SCX-3 (5 g) cartridge.

The cartridge was washed with methanol (40 mL) and then eluted with 2M ammonia in methanol (25 mL). Evaporation of the ammoniacal solution gave an opaque cream coloured film which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white foam (83 mg, 55%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.69 (m, 2H), 0.90 (s, 6H), 0.93 (m, 2H), 1.16 (m, 1H), 1.44 (m, 4H), 1.62 - 1.88 (m, 5H), 2.22 (s, 2H), 2.28 (s, 6H), 3.17 (s, 3H), 3.21 (d, 2H), 3.50 (s, 2H), 3.96 (s, 3H), 4.45 (m, 1H), 7.40 (m, 1H), 7.47 (d, 1H), 7.68 (s, 1H), 7.96 (s, 1H), 8.40 (d, 1H), 8.50 (t, 1H); MS m/z 564 [M+H]⁺.

Example 440:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

5 The title compound was prepared by an analogous method to the preparation of Example 439, on a 0.33 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) heating thermally at 120 °C over the weekend, as a white solid (46 mg, 24%).

¹H NMR (400.132 MHz, CDCl₃) δ 0.57 - 0.54 (m, 2H), 0.93 (s, 6H), 1.12 - 1.02 (m, 4H), 1.46
10 - 1.25 (m, 4H), 1.74 - 1.64 (m, 4H), 1.82 (d, 4H), 2.48 (s, 2H), 2.64 - 2.58 (m, 4H), 3.20 (s, 3H), 3.33 (d, 2H), 3.39 (s, 2H), 3.90 (s, 3H), 4.53 - 4.47 (m, 1H), 7.19 - 7.17 (m, 1H), 7.43 (s, 1H), 7.58 (s, 1H), 7.77 (s, 1H), 8.38 (d, 1H), 8.92 - 8.88 (m, 1H); MS m/z 590 [M+H]⁺.

Example 441:

15 **4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide**

The title compound was prepared by an analogous method to the preparation of Example 439, on a 0.24 mmol scale, utilising 4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-
20 benzamide (Intermediate 245; 70 mg, 0.26 mmol), as a white solid (57 mg, 38%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.69 (m, 2H), 0.93 (m, 2H), 1.04 (t, 3H), 1.15 (m, 1H), 1.45 (m, 4H), 1.76 (m, 6H), 2.15 (m, 1H), 2.43 (m, 4H), 2.66 (m, 1H), 2.72 (m, 1H), 3.16 (s, 3H), 3.50 (s, 2H), 3.96 (s, 3H), 4.42 (m, 2H), 7.50 (m, 1H), 7.54 (d, 1H), 7.66 (s, 1H), 7.96 (s, 1H), 8.31 (d, 1H), 8.40 (d, 1H); MS m/z 548 [M+H]⁺.

25

Example 442:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

30 The title compound was prepared by an analogous method to the preparation of Example 439, on a 0.17 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-

azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 204; 55 mg, 0.17 mmol), heating thermally at 140 °C for 2 hours, as a white solid (24 mg, 23%).

¹H NMR (399.9 MHz, DMSO-d₆) δ 0.70 - 0.73 (2H, m), 0.90 - 0.96 (4H, m), 1.13 - 1.20 (1H, m), 1.40 - 1.55 (7H, m), 1.67 (1H, d), 1.75 - 1.95 (6H, m), 2.01 - 2.11 (1H, m), 2.18 - 2.26 (2H, m), 2.42 (3H, s), 2.98 (2H, d), 3.17 (3H, s), 3.53 (2H, s), 3.94 (3H, s), 4.27 - 4.34 (1H, m), 4.45 - 1.52 (1H, m), 7.22 (1H, d), 7.68 - 7.72 (1H, m), 7.74 (1H, s), 8.00 (1H, s), 8.26 (1H, d); MS m/z 606 [M+H]⁺.

Example 443:

10 **4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide**

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 54 mg, 0.17 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 50 mg, 0.17 mmol), and p-toluenesulphonic acid monohydrate (81 mg, 0.43 mmol) were stirred together in 4-methyl-2-pentanol (3 mL) and heated at 110 °C for 18 hours. The cooled reaction mixture was loaded onto an SCX-3 (5 g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and eluted with 2M NH₃/MeOH. Solvent evaporation of the combined
20 ammoniacal fractions gave a brown gum which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (48 mg, 49%)

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.70 (m, 2H), 0.94 (m, 2H), 1.00 (t, 3H), 1.14 (m, 2H), 1.61 (m, 12H), 1.96 (m, 2H), 2.32 (q, 3H), 2.83 (d, 2H), 3.17 (s, 3H), 3.52 (s, 2H), 3.72 (m, 1H), 3.93 (s, 3H), 4.47 (m, 1H), 7.19 (d, 1H), 7.73 (s, 1H), 7.82 (m, 1H), 7.99 (s, 1H),
25 8.26 (d, 1H); MS m/z 580 [M+H]⁺.

Example 444:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide
30

The title compound was prepared by an analogous method to the preparation of Example 443, on a 0.18 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 228; 50 mg, 0.18 mmol), as a white solid (58 mg, 57%).
¹H NMR (400.132 MHz, DMSO-d₆) δ 0.71 (m, 2H), 0.94 (m, 2H), 1.15 (m, 2H), 1.61 (m, 12H), 2.50 (m, 4H), 2.58 (t, 3H), 3.16 (s, 3H), 3.39 (m, 2H), 3.52 (s, 2H), 3.93 (s, 3H), 4.48 (m, 1H), 7.30 (d, 1H), 7.76 (bs, 1H), 7.91 (m, 1H), 7.99 (s, 1H), 8.27 (d, 1H); MS m/z 566 [M+H]⁺.

Example 445:

10 **4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide**

The title compound was prepared by an analogous method to the preparation of Example 443, on a 0.16 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 254; 52 mg, 0.16 mmol), as a white solid (53 mg, 55%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.34 (2H, m), 0.51 (2H, m), 0.71 (2H, m), 0.94 (2H, m), 1.16 (1H, m), 1.47 (5H, m), 1.72 (10H, m), 2.44 (2H, s), 2.49 (2H, s), 3.17 (3H, s), 3.37 (2H, d), 3.53 (2H, s), 3.93 (3H, s), 4.48 (1H, m), 7.39 (1H, d), 7.78 (1H, s), 7.99 (1H, s), 8.26 (1H, d), 8.37 (1H, m); MS m/z 606 [M+H]⁺.

Example 446:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-(1-methyl-4-piperidyl)benzamide
 25 **2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one** (Intermediate 270; 200 mg, 0.62 mmol), 4-amino-3-fluoro-N-(1-methylpiperidin-4-yl)benzamide (Intermediate 65; 157 mg, 0.62 mmol) and p-toluenesulfonic acid monohydrate (296 mg, 1.56 mmol) were suspended in 4-Methyl-2-pentanol (5 mL) and sealed into a microwave tube. The reaction was heated at 160 °C for 30
 30 minutes in the microwave reactor and then allowed to cool to room temperature.

The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford a cream coloured solid which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a white solid (125 mg, 37%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.65 (t, 2H), 0.95 (t, 2H), 1.1 (m, 1H), 1.35 (q, 2H), 1.45 (q, 2H), 1.5-1.7 (m, 5H), 1.8 (m, 4H), 1.95 (t, 2H), 2.15 (t, 2H), 2.2 (s, 3H), 2.8 (d, 2H), 3.2 (s, 3H), 3.45 (s, 2H), 3.7 (m, 1H), 4.4 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 2H), 8.6 (s, 1H); MS m/z 536 [M+H]⁺.

Example 447:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

p-Toluenesulphonic acid monohydrate (338 mg, 1.78 mmol) was added to 4-amino-2,5-difluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 274; 220 mg, 0.71 mmol), and 2-chloro-9-cyclopentyl-5-methyl-8,9-dihydro-5H-pyrimido[5,4-b][1,4]diazepin-6(7H)-one (Intermediate 1; 200 mg, 0.71 mmol) in 4-methyl-2-pentanol (4 mL) at 25 °C. The resulting mixture was heated by microwave irradiation at 150 °C for 1 hour. The crude product was purified by ion exchange chromatography, using an SCX-3 (5g) column. The desired product was eluted from the column using 2M NH₃/MeOH and product-containing fractions were evaporated to dryness. The residue was further purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (91 mg, 23%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.90 - 0.93 (2H, m), 1.37 - 1.44 (4H, m), 1.57 - 1.71 (6H, m), 1.86 - 2.04 (4H, m), 2.17 - 2.24 (2H, m), 2.41 (3H, s), 2.58 - 2.61 (2H, m), 2.96 - 2.99 (2H, m), 3.18 (3H, s), 3.62 - 3.64 (2H, m), 4.21 - 4.33 (1H, m), 4.78 - 4.86 (1H, m), 7.42 - 7.46 (1H, m), 7.81 (1H, d), 8.11 (1H, s), 8.20 - 8.25 (1H, m), 8.91 (1H, s); MS m/z 555 [M+H]⁺.

Example 448:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 446, on a 0.65 mmol scale, utilising 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 200mg, 0.65 mmol), as a white solid (50 mg, 13%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.67 - 0.70 (2H, m), 0.90 - 0.93 (4H, m), 1.36 - 1.60 (7H, m), 1.64 - 1.71 (2H, m), 1.85 - 1.93 (4H, m), 1.97 - 2.04 (1H, m), 2.17 - 2.24 (2H, m), 2.40 (3H, s), 2.96 - 2.98 (2H, m), 3.18 (3H, s), 3.48 (2H, s), 4.21 - 4.32 (1H, m), 4.82 - 4.91 (1H, m), 7.42 - 7.46 (1H, m), 7.79 - 7.82 (1H, m), 8.02 (1H, s), 8.23 - 8.28 (1H, m), 8.85 (1H, s); MS m/z 581 [M+H]⁺.

Example 449:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 446, on a 0.62 mmol scale, utilising 2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 200mg, 0.62 mmol), as a white solid (37 mg, 10%).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.69 - 0.72 (2H, m), 0.90 - 0.95 (4H, m), 1.09 - 1.16 (1H, m), 1.33 - 1.50 (8H, m), 1.61 - 1.80 (4H, m), 1.86 - 1.92 (2H, m), 1.97 - 2.04 (1H, m), 2.16 - 2.24 (2H, m), 2.41 (3H, s), 2.96 - 2.98 (2H, m), 3.17 (3H, s), 3.50 (2H, s), 4.21 - 4.32 (1H, m), 4.43 - 4.49 (1H, m), 7.42 - 7.47 (1H, m), 7.81 - 7.84 (1H, m), 7.99 (1H, s), 8.13 - 8.18 (1H, m), 8.76 (1H, s); MS m/z 595 [M+H]⁺.

Example 450:

4-(9'-cyclohexyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

2'-chloro-9'-cyclohexyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (100 mg, 0.33 mmol), 4-amino-3-fluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide (95 mg, 0.33 mmol) and p-Toluenesulfonic acid .
 10 H₂O (155 mg, 0.81 mmol) were suspended in 4-Methyl-2-pentanol (2 mL) and sealed into a microwave tube. The reaction was heated to 160 °C for 25 minutes by microwave irradiation and then cooled to room temperature. The reaction mixture was filtered through a PTFE Filter cup to give an off white solid which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the
 15 desired compound were evaporated to dryness to yield the title compound as a white solid (27 mg, 15 %).

¹H NMR (400.132 MHz, DMSO-d₆) δ 0.8 (t, 2H), 0.9 (d, 2H), 1.1 (t, 2H), 1.2-1.5 (m, 8H), 1.6 (b, 3H), 1.75 (d, 2H), 1.9 (m, 2H), 2.0 (m, 1H), 2.2 (m, 2H), 2.4 (s, 3H), 2.95 (d, 2H), 3.4 (s, 2H), 4.3 (m, 1H), 4.5 (m, 1H), 7.55 (d, 1H), 7.6 (d, 1H), 7.85 (s, 1H), 7.95 (d, 1H), 8.15 (t,
 20 1H), 8.5 (s, 1H), 9.5 (s, 1H); MS m/z 563 [M+H]⁺.

Example 451:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1R,5S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl]benzamide
 25 p-Toluenesulphonic acid monohydrate (143 mg, 0.83 mmol) was added to 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 93 mg, 0.33 mmol) and 4-amino-3-methoxy-N-[(1R,5S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 275; 100 mg, 0.33 mmol) in 4-methyl-2-pentanol (3 mL) at 25°C. The resulting suspension was stirred at 110 °C for 18 hours. The
 30 reaction mixture was cooled to ambient temperature and purified by ion exchange chromatography, using an SCX-2 (5g) column. The desired product was eluted from the

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column using 2M NH₃/MeOH and fractions were evaporated to dryness to afford the crude product as a gum which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluent. Fractions containing the desired compound were combined and evaporated to dryness to afford the title compound as a white solid (15 mg, 8 %).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.36 - 1.40 (2H, m), 1.57 - 1.72 (6H, m), 1.89 - 1.95 (2H, m), 2.33 - 2.41 (2H, m), 2.45 (3H, s), 2.57 - 2.63 (4H, m), 3.17 (3H, s), 3.61 - 3.64 (2H, m), 3.71 - 3.74 (2H, m), 3.89 - 3.91 (2H, m), 3.93 (3H, s), 4.39 - 4.45 (1H, m), 4.74 - 4.82 (1H, m), 7.29 (1H, d), 7.38 (1H, s), 7.75 (1H, s), 8.07 (1H, s), 8.37 (1H, d), 8.83 (1H, d); MS m/z 551 [M+H]⁺.

Example 452:

N-(azepan-3-yl)-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

A solution of tert-butyl 3-[[4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoyl]amino]azepane-1-carboxylate (Example 348; 149 mg, 0.25 mmol) in DCM (2 mL) was treated with TFA (1 mL). The resulting solution was stirred at ambient temperature for 5 hours.

The reaction mixture was diluted with DCM (10 mL) and submitted to ion exchange chromatography, using an SCX-3 column. The column was eluted with DCM (50 mL) and methanol (50 mL) before the desired product was eluted from the column using 2M NH₃/MeOH. The ammoniacal solution was evaporated to dryness to afford the title compound as an amber gum (95 mg, 76 %).

¹H NMR (400.132 MHz, DMSO-d₆) δ 1.41 - 1.92 (16H, m), 2.51 - 2.53 (2H, m), 2.60 - 2.67 (1H, m), 2.73 (1H, t), 2.92 (1H, dd), 3.10 (3H, s), 3.54 - 3.58 (2H, m), 3.88 (3H, s), 3.90 - 3.99 (1H, m), 4.70 - 4.79 (1H, m), 7.38 - 7.43 (2H, m), 7.66 (1H, s), 7.93 (1H, d), 8.01 (1H, s), 8.31 (1H, d); MS m/z 508 (M+H)⁺.

Example 453:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methylazepan-3-yl)benzamide

To a solution of N-(azepan-3-yl)-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide (Example 453; 88 mg, 0.17 mmol) in formaldehyde (1 mL, 13.35 mmol) and acetic acid (100 μ L, 1.75 mmol), was added sodium acetate (142 mg, 1.73 mmol). The reaction mixture was cooled to 0 °C with stirring. Sodium cyanoborohydride (12 mg, 0.19 mmol) was added and the reaction mixture stirred at 0 °C for 5 minutes before removing the cooling bath. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours and then submitted to ion exchange chromatography, using an SCX-3 column. The column was washed with methanol, before the crude products were eluted from the column using 2M NH₃/MeOH. Evaporation of the ammoniacal solution afforded the crude product as an amber gum which was purified by flash silica chromatography, elution gradient 5 to 10% 2M ammonia/MeOH in DCM. Pure fractions were combined and evaporated to dryness to give 4-(9-cyclopentyl-5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrimido[5,4-b][1,4]diazepin-2-ylamino)-3-methoxy-N-(1-methylazepan-3-yl)benzamide as an amber glass (44 mg, 49 %).

¹H NMR (400.132 MHz, CDCl₃) δ 1.53 - 1.86 (12H, m), 1.91 - 1.96 (1H, m), 2.03 - 2.10 (2H, m), 2.45 (3H, s), 2.65 - 2.70 (3H, m), 2.79 - 2.86 (2H, m), 3.30 (3H, s), 3.68 - 3.72 (2H, m), 3.99 (3H, s), 4.25 - 4.33 (1H, m), 4.91 (1H, quintet), 7.18 - 7.25 (1H, m), 7.31 (1H, d), 7.48 (1H, d), 7.65 (1H, s), 7.95 (1H, s), 8.51 (1H, d); MS m/z 522 (M+H)⁺

Preparation of Intermediates:

Intermediate 1:

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

To a cold (0 °C) solution of 9-chloro-6-cyclopentyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one (Intermediate 2; 241 mg, 0.90 mmol) in DMA (20 mL) was added MeI (62 μ L, 0.99 mmol) followed by NaH (39 mg, 0.96 mmol) and the reaction mixture stirred at 0 °C for 30 mins then at ambient temperature for 1 hr. The solution was diluted with Ethyl Acetate (20 mL), washed with water (2 x 30 mL), brine (30 mL), dried (MgSO₄) and the volatiles were removed under reduced pressure. Purification by column chromatography (SiO₂, eluent gradient: 2% MeOH in DCM) afforded the title compound (187 mg, 74%) as a solid.

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^1H NMR (400 MHz, DMSO- D_6) δ_{H} 1.52 - 1.66 (m, 4H), 1.66 - 1.75 (m, 2H), 1.85 - 1.96 (m, 2H), 2.63 - 2.67 (m, 2H), 3.18 (s, 3H), 3.64 - 3.68 (m, 2H), 4.71 - 4.79 (m, 1H), 8.15 (s, 1H); MS 281, 283 $[\text{M}+\text{H}]^+$.

5 **Intermediate 2:**

9-Chloro-6-cyclopentyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

To a solution of methyl 3-[(2-chloro-5-oxidoazonoyl-pyrimidin-4-yl)-cyclopentyl-amino]propanoate (Intermediate 3; 1.00 g, 3.04 mmol) in AcOH (50 mL) was added powdered Fe (1.00 g, 3.04 mmol) and the reaction stirred at 70 °C for 30 mins. The reaction
10 mixture was filtered hot through a pad of celite, washed with AcOH (25 mL) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO_2 , eluent gradient: 0-100% Ethyl Acetate in hexane) gave the title compound (480 mg, 43%) as a solid.
 ^1H NMR (400 MHz, CDCl_3) δ_{H} 1.46 - 1.56 (m, 2H), 1.62 - 1.80 (m, 3H), 1.94 - 2.04 (m, 3H), 2.77 - 2.79 (m, 2H), 3.60 - 3.63 (m, 2H), 5.17 - 5.26 (m, 1H), 7.79 (s, 1H), 7.99 (s, 1H); MS
15 m/z 267, 269 $[\text{M}+\text{H}]^+$.

Intermediate 3:

Methyl 3-[(2-chloro-5-oxidoazonoyl-pyrimidin-4-yl)-cyclopentyl-amino]propanoate

To a solution of methyl 3-(cyclopentylamino)propanoate (2.46 g, 14.37 mmol) in acetone (40
20 mL) was added K_2CO_3 (2.03 g, 14.65 mmol) and 2,4-dichloro-5-nitropyrimidine (3.07 g, 15.80 mmol) and the reaction mixture stirred at ambient temperature under an atmosphere of nitrogen for 18 hrs. The volatiles were removed under reduced pressure and the crude material was dissolved in Ethyl Acetate (50 mL), washed with water (2 x 50 mL), brine (50 mL), dried (MgSO_4) and the volatiles removed under reduced pressure. Purification by
25 column chromatography (SiO_2 , eluent gradient: 0-10% Ethyl Acetate in hexane) afforded the title compound (2.23 g, 53%) as a solid.

^1H NMR (400 MHz, DMSO- d_6): δ_{H} 1.44 - 1.54 (m, 2H), 1.62 - 1.78 (m, 4H), 1.86 - 1.96 (m, 2H), 2.69 (t, 2H), 3.61 (s, 3H), 3.66 (t, 2H), 3.71 - 3.80 (m, 1H), 8.84 (s, 1H); MS m/z 329, 331 $[\text{M}+\text{H}]^+$.

Intermediate 4:**4-Amino-*N*-(1-methyl-4-piperidyl)benzamide**

p-Aminobenzoic acid (137 mg, 1 mmol), 4-amino-*N*-methylpiperidine (114 mg, 1 mmol) and DIPEA (522 μ L, 3 mmol) were dissolved in DMA (5 mL). HATU (570 mg, 1.5 mmol) in DMA (5 mL) was added and the reaction stirred at ambient temperature for 2 h. The volatiles were removed under reduced pressure and NaHCO₃ (50 mL, sat. aq.) was added. The resulting precipitate was removed by filtration and the aqueous phase neutralised with HCL (2N). The reaction mixture was then loaded onto an SCX-2 cartridge washing with copious quantities of water. The crude product was the eluted from the SCX-2 cartridge with NH₃ (60 mL, 7M in MeOH). Purification by column chromatography (SiO₂, eluent: 10% NH₃ [7M in MeOH] in DCM) afforded the title compound (167 mg, 72%) as a solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ _H 1.50 - 1.60 (2H, m), 1.69 - 1.73 (1H, m), 1.72 (1H, t), 1.89 - 1.96 (2H, m), 2.16 (3H, s), 2.75 (2H, d), 3.65 - 3.71 (1H, m), 5.52 - 5.54 (1H, m), 6.52 - 6.55 (2H, m), 7.56 - 7.59 (2H, m), 7.69 (1H, d); MS *m/z* 234 [M+H]⁺.

Intermediate 5:**10-chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one**

To a cold (-78 °C) solution of 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (90 mg, 0.32 mmol) in dry THF (4 mL) was added LiHMDS (640 μ L, 1M in THF, 0.64 mmol) dropwise over 10 mins. MeI (40 μ L, 0.64 mmol) in THF (1 mL) was added and the reaction mixture was stirred at -78 °C for 20 mins and then at 0 °C for 1 hr. The reaction mixture was diluted with DCM (20 mL) and washed with water (2 x 20 mL), brine (40 mL), dried (MgSO₄), filtered and the volatiles removed under reduced pressure to yield the title compound (106 mg, 100%) as a solid.

MS *m/z* 295, 297 [M+H]⁺.

Intermediate 6:

4-[(9-Cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-*b*][1,4]diazepin-2-yl)amino]-3-methoxybenzoic acid

Methyl 4-[(9-cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate (Intermediate 7; 250 mg, 0.61 mmol) and HCl (2 mL, concentrated aqueous) were suspended in water (4 mL) and heated at reflux for 24 h. The reaction mixture was then cooled to ambient temperature and the volatiles were removed under reduced pressure. The solid obtained was dissolved in MeOH:DCM (1:10, 40 mL) and washed with NaHCO₃ (saturated aqueous, 40 mL). The organic layer was then dried (MgSO₄), filtered and the volatiles removed under reduced pressure to afford the title compound (240 mg, 99%) as a solid.

¹H NMR (400MHz, DMSO-d₆) δ_H 1.57 (m, 4H), 1.73 (m, 2H), 1.88 (m, 4H), 2.70 (s, 3H), 2.95 (t, 2H), 3.47 (m, 2H), 3.87 (s, 3H), 4.86 (quintet, 1H), 7.20 (s, 1H), 7.42 (d, 1H), 7.50 (s, 1H), 7.52 (s, 1H), 7.96 (s, 1H), 8.28 (d, 1H); MS m/z 398 [M+H]⁺.

Intermediate 7:

Methyl 4-[(9-cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate

BH₃.SMe₂ (1.36 mL, 5.0 M in Et₂O, 6.8 mmol) was added to solution of methyl 4-[(9-cyclopentyl-5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate (Intermediate 8; 290 mg, 0.68 mmol) in THF (4 mL) and stirred for 5 h at ambient temperature under an atmosphere of nitrogen. HCl (10 mL, concentrated aqueous) was added and the resulting solution was stirred at ambient temperature for 16 h. The HCl solution was then diluted with water (50 mL), and loaded onto an SCX-2 column. The SCX-2 column was then washed with water (50 mL) and MeOH (50 mL). The product was then eluted from the SCX-2 column with NH₃ (50 mL, 7M in MeOH). The volatiles were then removed under reduced pressure to afford the title compound (250 mg, 89%) as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ_H 1.67 (m, 6H), 1.96 (m, 4H), 2.77 (s, 3H), 3.06 (t, 2H), 3.58 (m, 2H), 3.88 (s, 3H), 4.00 (s, 3H), 4.91 (quintet, 1H), 7.57 (m, 3H), 7.71 (s, 1H), 8.59 (d, 1H); MS m/z 412 [M+H]⁺.

Intermediate 8:

270

Methyl 4-[(9-cyclopentyl-5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate

2-Chloro-9-cyclopentyl-5-methyl-5,7,8,9-tetrahydro-6H-pyrimido[4,5-b][1,4]diazepin-6-one (Intermediate 1; 500 mg, 1.78 mmol), methyl 4-amino-3-methoxybenzoate (324 mg, 1.78 mmol) and p-toluenesulfonic acid (847 mg, 4.45 mmol) were suspended in (2R/S)-4-methyl-2-pentanol (10 mL) and heated at reflux for 5 h. The reaction mixture was cooled and loaded onto an SCX-2 column and washed with MeOH (20 mL). The crude product was then eluted from the SCX-2 column with NH₃ (40 mL, 7M in MeOH) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO₂, eluent gradient 0-10% MeOH in DCM) afforded the title compound (290 mg, 38%) as a solid.

¹H NMR (400.132 MHz, DMSO-d₆) δ_H 1.71 (m, 6H), 2.00 (m, 2H), 2.65 (m, 2H), 3.23 (s, 3H), 3.69 (m, 2H), 3.89 (s, 3H), 4.01 (s, 3H), 4.87 (m, 1H), 7.56 (d, 1H), 7.64 (d, 1H), 7.90 (s, 1H), 8.16 (s, 1H), 8.55 (d, 1H); MS m/z 426 [M+H]⁺.

Intermediate 9:

10-Chloro-2,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-methyl-amino]-N-methyl-propanamide (Intermediate 15; 2.09 g, 6.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (171 mg, 0.19 mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (288 mg, 0.50 mmol) and Cs₂CO₃ (2930 mg, 8.99 mmol) in 1,4-dioxane (50 mL) were heated at reflux for 16 h under an atmosphere of nitrogen. The reaction mixture was evaporated then suspended in DCM (20 mL) and filtered through a layer of celite washing with DCM (40 mL). Purification by column chromatography (SiO₂, eluent gradient: 2-10% MeOH in DCM) afforded the title compound (190 mg, 19%) as a foam.

¹H NMR (400 MHz, DMSO-d₆) δ_H 2.67 (tr, 2H), 3.08 (s, 3H), 3.20 (s, 3H), 3.72 (tr, 2H), 8.19 (s, 1H); MS m/z 227 [M+H]⁺.

Intermediate 10

10-Chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-

one

271

Intermediate 11:

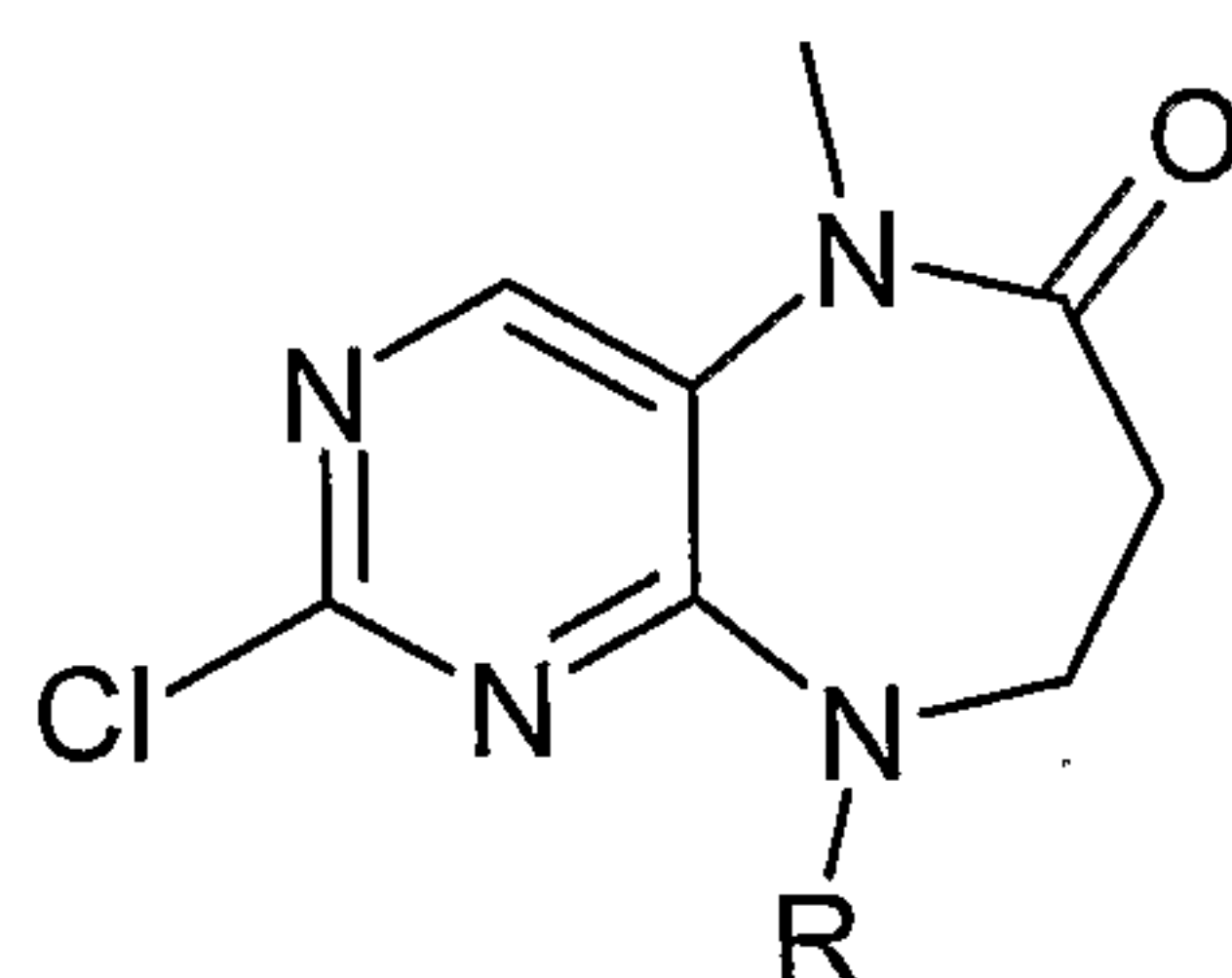
10-Chloro-6-methyl-2-(3-methylbutyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Intermediate 12:

5 **10-Chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one**

Intermediate 13:

10-Chloro-6-methyl-2-(oxan-4-yl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one



10 Intermediates 10-13 were prepared, using the appropriate secondary amide (Intermediates 14, 16-18), by an analogous process to that used in the preparation of Intermediate 9.

Example	R	¹ H NMR (400 MHz, DMSO-d ₆)	MS m/z [M+H] ⁺
10		1.18 (d, 6H), 2.65 (tr, 2H), 3.19 (s, 3H), 3.61 (tr, 2H), 8.12 (s, 1H).	225
11		0.99 (d, 6H), 1.57 (m, 3H), 2.71 (tr, 2H), 3.22 (s, 3H), 3.63 (tr, 2H), 3.78 (tr, 2H), 8.19 (s, 1H).	283
12		1.14 (m, 1H), 1.32 (m, 2H), 1.60 (m, 3H), 1.78 (m, 4H), 2.61 (tr, 2H), 3.18 (s, 3H), 3.65 (tr, 2H), 4.30 (m, 1H), 8.12 (s, 1H).	295
13		1.68 (m, 2H), 1.83 (m, 2H), 2.63 (tr, 2H), 3.41 (tr, 2H), 3.69 (m, 2H), 3.93 (m, 2H), 4.51 (m, 1H), 8.18 (s, 1H).	297

Intermediate 14:**3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-propan-2-yl-amino]-N-methyl-propanamide**

5 5-Bromo-2,4-dichloropyrimidine (1.83 g, 8.00 mmol), N-methyl-3-(propan-2-ylamino)propanamide (Intermediate 14, 1.16 g, 8.00 mmol) and Et₃N (1.2 mL, 8.16 mmol) were combined in MeCN (50 mL) and shaken at ambient temperature for 3 days before the solvent was removed under reduced pressure. Purification by column chromatography (SiO₂, eluent gradient 2-10% MeOH to DCM) to afford the title compound (2.08 g, 78%) as a gum.

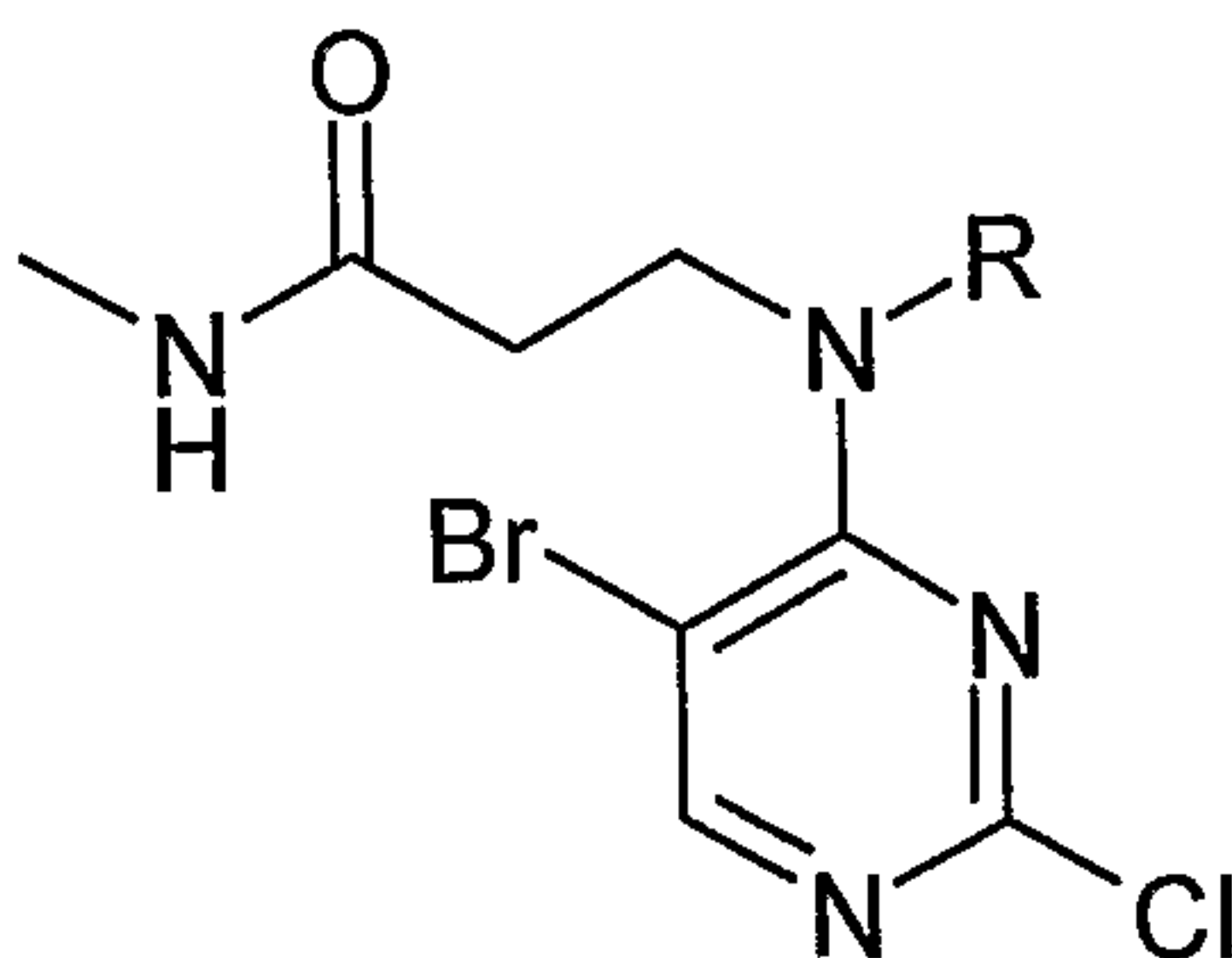
10 ¹H NMR (400 MHz, DMSO-d₆) δ_H 1.16 - 1.20 (6H, m), 2.31 (2H, t), 2.55 - 2.58 (3H, d), 3.65 (2H, t), 4.55 - 4.62 (1H, septet), 7.71 - 7.72 (1H, br s), 8.39 (1H, s); MS m/z 337 [M+H]⁺.

Intermediate 15:**3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-methyl-amino]-N-methyl-propanamide**

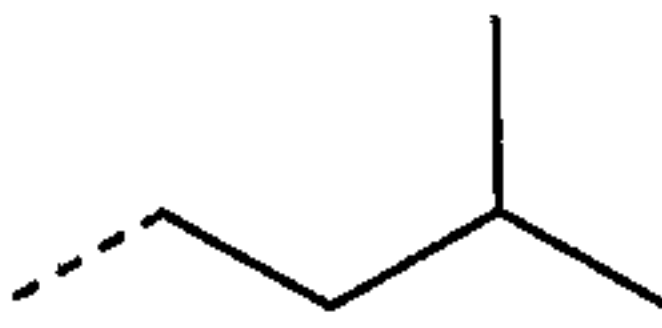
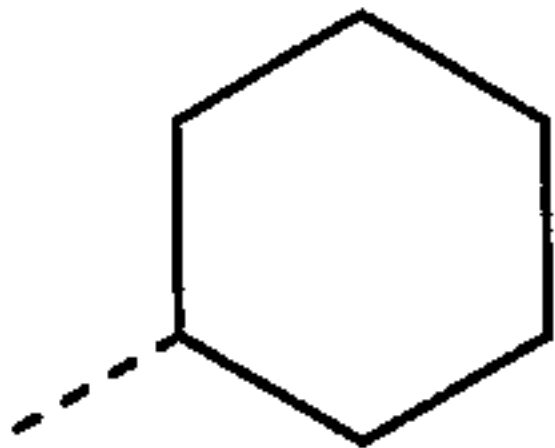
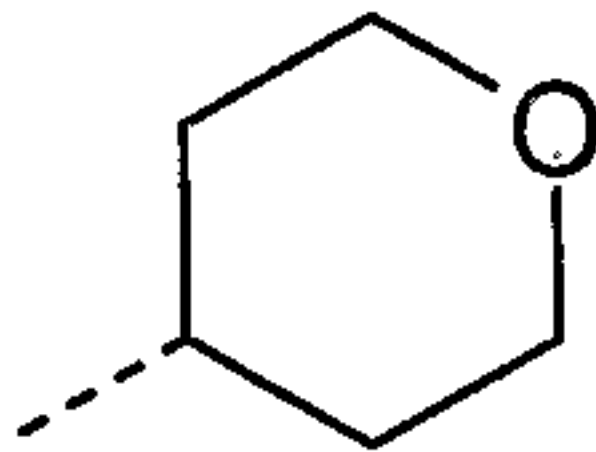
15

Intermediate 16**3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-(3-methylbutyl)amino]-N-methyl-propanamide****Intermediate 17:**

20 **3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-cyclohexyl-amino]-N-methyl-propanamide**

Intermediate 18:**3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-(oxan-4-yl)amino]-N-methyl-propanamide**

25 Intermediates 15-18 were prepared in an analogous manner to Intermediate 14 using 5-bromo-2,4-dichloropyrimidine as the electrophile and the appropriate known or described (Intermediates 19 – 21) β-aminoamides:

Example	R	¹ H-NMR (400 MHz, DMSO-d ₆)	MS m/z [M+H] ⁺
15	Me	2.46 (2H, t), 2.56 - 2.57 (3H, d), 3.19 (3H, s), 3.86 (2H, t), 7.86 (1H, br s), 8.33 (1H, s)	309
16		0.92 (6H, d), 1.48 - 1.52 (2H, m), 1.59 (1H, m), 2.45 (2H, t), 2.57 (3H, d), 3.63 (2H, m), 3.83 (2H, t), 7.84 (1H, br s), 8.32 (1H, s)	365
17		1.10 - 1.15 (1H, m), 1.27 (2H, q), 1.54 - 1.57 (1H, m), 1.59 (1H, d), 1.62 - 1.63 (1H, m), 1.69 - 1.72 (2H, m), 1.78 (2H, d), 2.31 (2H, t), 2.55 (3H, d), 3.67 (2H, t), 4.14 - 4.20 (1H, m), 7.70 (1H, br s), 8.38 (1H, s)	377
18		1.62 - 1.66 (2H, m), 1.82 - 1.89 (2H, m), 2.32 (2H, t), 2.56 (3H, d), 3.33 (2H, d), 3.69 (2H, t), 3.91 - 3.95 (2H, m), 4.34 - 4.40 (1H, m), 7.72 (1H, br s), 8.43 (1H, s)	379

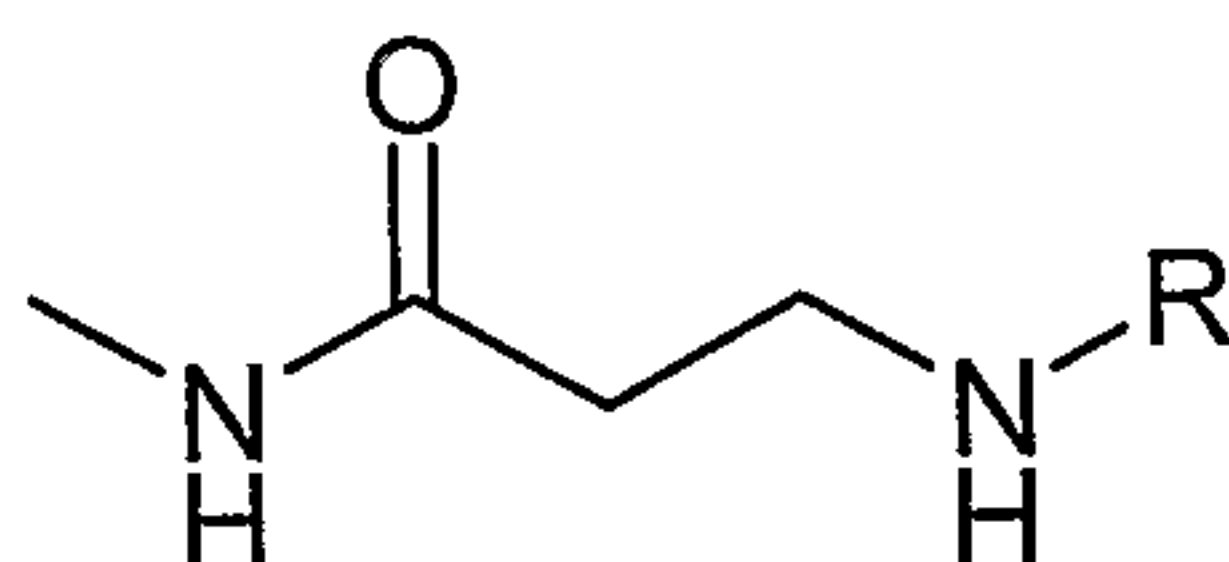
5 **Intermediate 19:**

N-Methyl-3-(propan-2-ylamino)propanamide

N-Methylacrylamide (851 mg, 10.00 mmol) and isopropylamine (1.71 mL, 1.18 g, 20.00 mmol) in MeOH (10 mL) were irradiated to 140 °C for 30 mins in a microwave reaction vessel. The reaction mixture was cooled and loaded onto a SCX-2 column and washed with MeOH (100 mL). The crude product was then eluted from the SCX-2 column with NH₃ (100 mL, 7M in MeOH) and the volatiles removed under reduced pressure to afford the title compound (1.56 g, Quant.) as an oil, which was used without further purification.

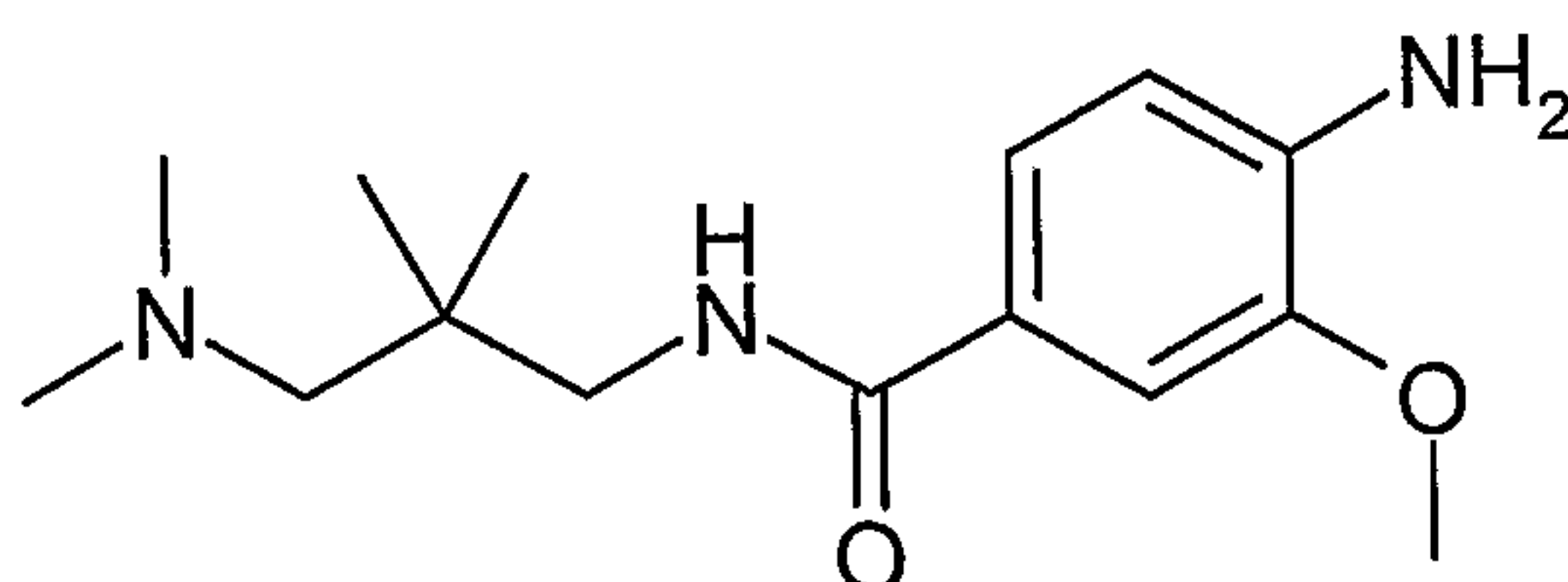
274

^1H NMR (400 MHz, DMSO- d_6) δ_{H} 0.96 (d, 6H), 2.18 (t, 2H), 2.57 (d, 3H), 2.65 - 2.71 (m, 3H), 7.81 (br s, 1H).

Intermediate 20:5 **N-Methyl-3-(3-methylbutylamino)propanamide****Intermediate 21:****N-Methyl-3-(oxan-4-ylamino)propanamide**

- 10 Intermediates 20 and 21 were prepared in an analogous manner to Intermediate 19 using the N-methylacrylamide as the α,β -unsaturated amide and the appropriate commercially available primary amine:

Example	R	^1H NMR (400 MHz, DMSO- d_6)
20		0.87 (d, 6H), 1.28 (dt, 2H), 1.60 (septet, 1H), 2.19 (t, 2H), 2.46 - 2.52 (m, 3H), 2.56 (d, 3H), 2.67 (t, 2H), 7.81 (br s, 1H)
21		1.14 - 1.27 (m, 2H), 1.64 (d, 1H), 1.73 (d, 2H), 2.19 (t, 2H), 2.57 (d, 3H), 2.72 (t, 2H), 3.23 - 3.31 (m, 3H), 3.78 - 3.84 (m, 2H), 7.80 (br s, 1H)

15 **Intermediate 22:****4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide**

A suspension of N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-nitro-benzamide (Intermediate 23; 5.7 g, 18.40 mmol), 5% Pd on charcoal (569 mg) in EtOH (300 mL) was

stirred at 40 °C under a hydrogen atmosphere for 16 h. The reaction mixture was then filtered through celite, washed with copious MeOH and the volatiles removed under reduced pressure to afford the title compound (5.36 g, Quant.) as a foam.

¹H NMR (400 MHz, DMSO-d₆): δ_H 0.88 (m, 6H), 2.18 (s, 2H), 2.28 (s, 6H), 3.18 (m, 2H),
5 3.82 (s, 3H), 5.21 (m, 2H), 6.63 (d, 1H), 7.25 m, 2H), 8.11 (m, 1H); MS m/z 280 [M+H]⁺.

Intermediate 23:

N-(3-Dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-nitro-benzamide

To a suspension of 4-nitro-3-methoxybenzoic acid (Aldrich; 5.0 g, 25.3 mmol), N,N-2-
10 tetramethyl-1,3-propanediamine (Aldrich; 4.64 mL, 27.83 mmol) and DIPEA (8.8 mL, 50.60 mmol) in anhydrous DMA (100 mL) under nitrogen at ambient temperature was added HATU (10.6 g, 27.83 mmol) and the resulting reaction mixture was stirred at 50 °C for 3 h and ambient temperature for a further 12 h. Evaporation removed any volatiles and the residue was dissolved in DCM (100 mL) and washed with NaHCO₃ (100 mL), brine (100 mL), dried
15 (MgSO₄) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO₂, eluent gradient: 2-10% MeOH in DCM) afforded the title compound (5.7 g, 73%) as a solid.

¹H NMR (400 MHz, DMSO-d₆): δ_H 1.06 (s, 6H), 2.42 (s, 2H), 2.82 (s, 6H), 3.30 (s, 2H), 3.98 (s, 3H), 7.57 (dd, 1H), 7.71 (s, 1H), 8.93 (d, 1H); MS m/z 310 [M+H]⁺.

20

Intermediate 24:

1-cyclopropylpiperidin-4-amine

N-benzyl-1-cyclopropyl-piperidin-4-amine (Intermediate 25; 2.3 g 10 mmol), 10% Palladium on Carbon (230 mg) and Methanol (230 mL) were combined and heated with stirring at 30°C
25 under Hydrogen at 5 bar pressure for 16 hours.

The mixture was filtered and concentrated, taken up in DCM, dried (MgSO₄) and concentrated to give the title compound (1.29g, 64%) as a yellow liquid

¹H NMR (399.9 MHz, CDCl₃) δ 0.36 – 0.46 (4H, m), 1.26 – 1.36 (4H, m), 1.52 – 1.58 (1H, m), 1.76 – 1.82 (2H, m), 2.18 – 2.25 (2H, m), 2.63 – 2.70 (1H, m), 2.94 – 2.99 (2H, m); MS
30 m/z 161.90 [M+H]⁺.

Intermediate 25:**N-benzyl-1-cyclopropyl-piperidin-4-amine**

5 1-cyclopropylpiperidin-4-one Intermediate 26 (3g, 21.55mmol), benzylamine (4.7ml, 43.10mmol) and acetic acid (1.25ml) were stirred together and sodium triacetoxyborohydride (6.86g, 32.33mmol) added portion-wise. DCM (20ml) was added and the mixture stirred at room temperature overnight. The mixture was concentrated and partitioned between ethyl acetate and 2M potassium carbonate solution. The aqueous layer was re-extracted with ethyl
10 acetate and the combined organics washed with brine, dried (MgSO₄) and concentrated. Column chromatography (2% 7N ammonia in methanol / DCM) gave a brown liquid which contained Benzylamine and thus was taken up in DCM and stirred with PS-benzaldehyde (NovaBiochem, ≈3.2mmol/g ; ≈1.5 equivalents compared to benzylamine) for 3h. The mixture was filtered and the combined filtrates concentrated to give the title compound
15 (2.33g, 47%) as a brown oil.

¹H NMR (399.9 MHz, CDCl₃) δ0.38 - 0.43 (4H, m), 1.33 - 1.40 (2H, m), 1.46 (1H, s), 1.52 - 1.57 (1H, m), 1.86 - 1.90 (2H, m), 2.18 - 2.24 (2H, m), 2.51 - 2.56 (1H, m), 2.96 - 3.01 (2H, m), 3.82 (2H, s), 7.22 - 7.25 (1H, m), 7.29 - 7.33 (4H, m)

Intermediate 26:**1-cyclopropylpiperidin-4-one**

1-Ethyl-1-methyl-4-oxopiperidinium iodide (Journal of the Chemical Society (1949), 708-15; 15 g, 55.74 mmol) was added to cyclopropylamine (Aldrich; 19.3 mL, 278.69 mmol) in toluene (150 mL). Sodium hydrogen carbonate (469 mg, 5.57 mmol) in water (21 mL) was
25 added and the mixture heated at 78°C over night. The mixture was cooled and the layers separated. The aqueous layer was extracted (x2) with ethyl acetate and the combined organics washed with brine, dried (MgSO₄) and concentrated. Column chromatography of the residue (2% MeOH/DCM) gave the title compound (4.1g, 53%) as a pale brown liquid.
¹H NMR (399.9 MHz, CDCl₃) δ0.47 - 0.53 (4H, m), 1.74 (1H, d), 2.40 - 2.44 (4H, m), 2.92
30 (4H, t)

Intermediate 27:**4-amino-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide**

2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)-4-nitro-benzamide Intermediate 28; 1.3 g, 4.2
5 mmol) 10% Palladium on Carbon (100 mg) and Methanol (50 mL) were combined and
stirred at 25°C under Hydrogen at 1 bar pressure for 18 hours.

The reaction mixture was filtered through a plug of celite, washing with ethanol and
concentrated under reduced pressure to give the title compound (1.16 g, 100%) as a yellow
solid.

10 ¹H NMR (399.902 MHz, DMSO-D6) δ 1.54 (qd, 2H), 1.72 - 1.80 (m, 2H), 1.97 (td, 2H),
2.16 (s, 3H), 2.70 (br d, 2H), 3.67 - 3.74 (m, 1H), 3.78 (s, 3H), 5.55 (s, 2H), 6.39 (d, 1H), 7.05
(d, 1H), 7.34 (t, 1H); MS m/z 282.27 [M+H]⁺.

Intermediate 28:**15 2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)-4-nitro-benzamide**

To a stirred solution of 2-fluoro-5-methoxy-4-nitro-benzoic acid (Intermediate 29; 861 mg,
4.00 mmol) in DMA (20 mL) was added 4-amino-1-methylpiperidine (Fluorochem; 503 mg,
4.40 mmol) followed by DIPEA (1.4 mL, 8.00 mmol) and HATU (1.68 g, 4.40 mmol) and the
resulting yellow solution stirred at room temperature for 1 hr.. The solvent was removed
20 under reduced pressure and the residue taken up in methanol (approx 10 mL) and loaded onto
a 20 g SCX-2 cartridge washing with methanol (50 mL) and eluting with 7 N methanolic
ammonia (50 mL) to give a yellow solid, 1.47 g. This was purified by flash silica
chromatography (Companion, 40 g, 0-5% ammonia in methanol /.DCM) to give the desired
product as a pale yellow solid (1.25g, 4.00 mmol, 100%).

25 ¹H NMR (399.902 MHz, DMSO-D6) δ 1.54 (qd, 2H), 1.77 - 1.85 (m, 2H), 1.98 (td, 2H),
2.17 (s, 3H), 2.74 (br d, 2H), 3.72 (m, 1H), 3.96 (s, 3H), 7.43 (d, 1H), 7.98 (d, 1H), 8.46 (d,
1H);); MS m/z 161.90 [M+H]⁺.

Intermediate 29:

2-fluoro-5-methoxy-4-nitro-benzoic acid

2,5-Difluoro-4-nitrobenzoic acid (Fluorochem; 100 mg, 0.43 mmol) and caesium carbonate (708 mg, 2.17 mmol) were taken up in dry DMF (2 mL) and dry methanol (120 μ L, 2.88 mmol) was added and the reaction stirred at room temperature for 2 hrs. The reaction mixture
5 was diluted with Ethyl Acetate (50 mL) and water (50 mL) and acidified to pH1 with 2N HCl solution. The organics were removed and the aqueous further extracted with Ethyl Acetate (2 x 50 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried over MgSO_4 and concentrated under reduced pressure to give the title compound as a yellow solid (91 mg, 0.42 mmol, 98%).

10 ^1H NMR (399.902 MHz, CDCl_3) δ 4.00 (s, 3H), 7.63 (d, 1H), 7.70 (d, 1H), 10.78 (br s, 1H); MS m/z 215.27 $[\text{M}+\text{H}]^+$.

Intermediate 30:**15 Benzyl (1R,5S)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate**

Benzyl (1R,5S)-6-[(2-methylpropan-2-yl)oxycarbonylamino]-3-azabicyclo[3.1.0]hexane-3-carboxylate (Bioorganic & Medicinal Chemistry Letters (2004), 14(11), 2773-2776, Compound 9; 6.74g, 20.3mmol) was stirred and dissolved in DCM (90 mL) at ambient temperature and TFA (10ml) was added. The solution was stirred at room temperature for 2
20 hours. Sat. bicarbonate (100ml) was added followed by potassium carbonate solid until neutral. The DCM layer was separated and washed once more with water. The DCM solution was dried (MgSO_4), filtered and evaporated to a gum.

Yield = 4.05g (86%)

^1H NMR (400.132 MHz, CDCl_3) δ 1.48 (s, 2H), 2.00 (s, 1H), 3.43 (m, 4H), 5.02 (s, 2H), 7.25
25 (m, 7H).

Intermediate 31:**Methyl (1S,3R)-3-aminocyclopentane-1-carboxylate Hydrochloride Salt**

(1S,3R)-3-aminocyclopentane-1-carboxylic acid (Acros; 952 mg, 7.37 mmol) was suspended
30 in MeOH (15 mL) and cooled in an acetone / ice bath. Thionyl chloride (1.1 mL, 14.74 mmol) was added dropwise and the resulting pale yellow solution stirred in the acetone / ice bath for

30 minutes and then allowed to warm to room temperature, stirred at room temperature for 1 hr then heated at reflux for 1 hr. Solvents were evaporated to give the title compound as a cream solid after drying under high vacuum. (1.32g 100%)

¹H NMR (399.902 MHz, DMSO-D6) δ1.65 (m, 1H), 1.76 (m, 1H), 1.93 (m, 3H), 2.27 (m, 1H), 2.87 (m, 1H), 3.49 (m, 1H), 3.64 (s, 3H), 8.09 (s, 3H)

Intermediate 32:

[(2R)-1-(cyclopropylmethyl)pyrrolidin-2-yl]methanamine

Preparation contained in WO98/39295

Intermediate 33:

[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methanamine

To a solution of 1-(pyrrolidine-1-carbonyl)cyclopropane-1-carboxamide (Intermediate 34; 5.0 g, 27.5 mmol) in anhydrous THF (150 mL) was slowly added a 1 M anhydrous THF solution of Lithium Aluminium Hydride (138 mL, 138 mmol) controlling the reaction temperature at 40°C with an ice / water bath.

The resultant clear solution was stirred overnight at room temperature under an inert gas flow to give a cloudy suspension.

Water (5.24 mL) was carefully added to the reaction mixture maintaining the reaction temperature at < 30°C with an ice / water bath to give thick white slurry. 15% w/v aqueous Sodium Hydroxide solution (5.24 mL) was carefully added followed by water (15.71 mL). The reaction was filtered and the filtrate evaporated to dryness to give the title compound (3.26 g, 77%)

Intermediate 34:

1-(pyrrolidine-1-carbonyl)cyclopropane-1-carboxamide

To 1-(aminocarbonyl)-1-cyclopropane carboxylic acid (Aldrich; 25 g, 193.6 mmol) in DCM (625 mL) was added HATU (73.61 g, 193.6 mmol) and the suspension stirred for 30 minutes.

Pyrrolidine (Aldrich; 24.25 mL) and Hunig's base (67 mL) was added and the reaction stirred at room temperature over the weekend.

The reaction was evaporated to dryness, DCM added and extracted with water (3x 150 mL).

The aqueous extracts were evaporated to dryness and the resultant material triturated with Ethyl acetate to give the title compound as a white solid 11.14 g, 32%)

Intermediate 35:

5 **2-methoxy-N'-(2-pyrrolidin-1-ylethyl)benzene-1,4-diamine**

To a stirred solution of 4-fluoro-2-methoxy-1-nitro-benzene (Fluorochem; 2.57 g; 15 mmol) in DMA was 2-pyrrolidin-1-ylethanamine (Aldrich; 1.88 g, 16.5 mmol) followed by DIPEA (2.97 mL, 18 mmol). The mixture was heated at 80°C for 20 hours, then cooled to room temp. The mixture was concentrated *in vacuo*, dissolved in DCM and purified by SCX (50 g SCX 2
10 column). The product was eluted from the column with 7N ammonia in methanol, concentrated *in vacuo* to give the title compound (53 mg) which was dissolved in Methanol as a 0.05 mmol solution and reduced using an H-cube hydrogenator. 10% Pd/C catalyst, 1 bar hydrogen (full hydrogen setting), 3 mL / min flow- rate at 50°C. The resultant solution was concentrated *in vacuo*, and the resultant material purified by column chromatography, eluting
15 with 0-10% ammonia/methanol in DCM, to give the title compound as a solid.
MS m/z 236 [M+H]⁺, Retention Time 1.50 minutes.

In a similar manner intermediates 36-42 were prepared from the specified amines

20 **Intermediate 36:**

2-methoxy-N'-methyl-N'-(1-methyl-4-piperidyl)benzene-1,4-diamine

Intermediate 37:

2-methoxy-4-[4-(2-methoxyethyl)piperazin-1-yl]aniline

25

Intermediate 38:

2-methoxy-4-[4-(1-piperidyl)-1-piperidyl]aniline

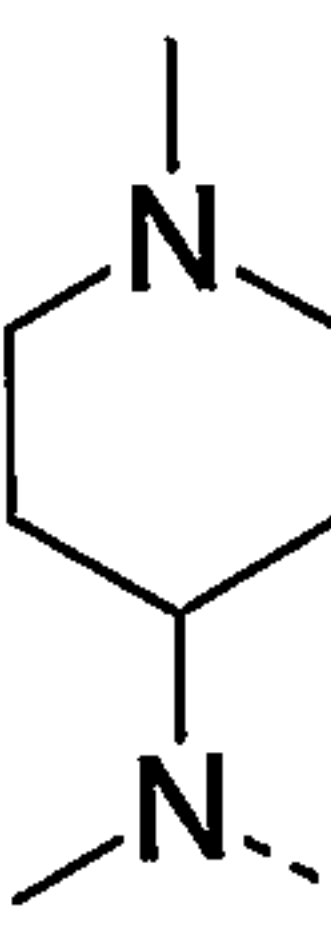
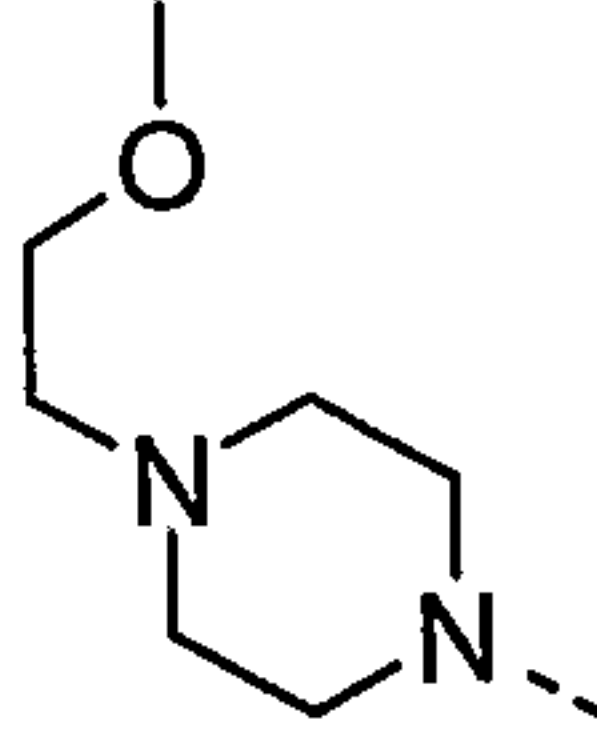
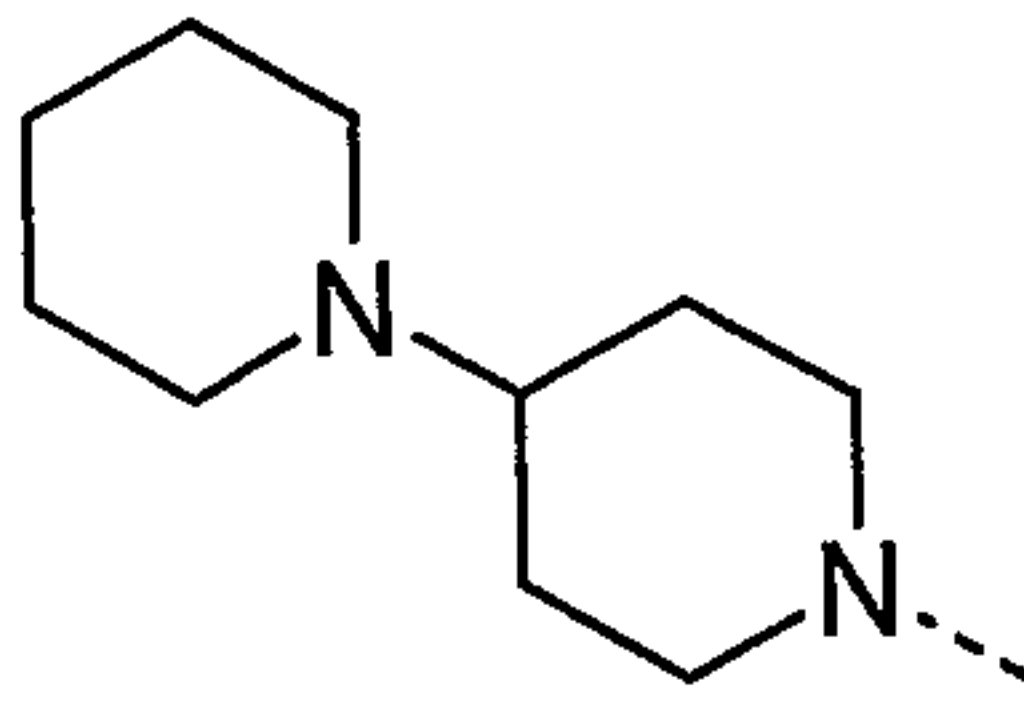
30 **Intermediate 39:**

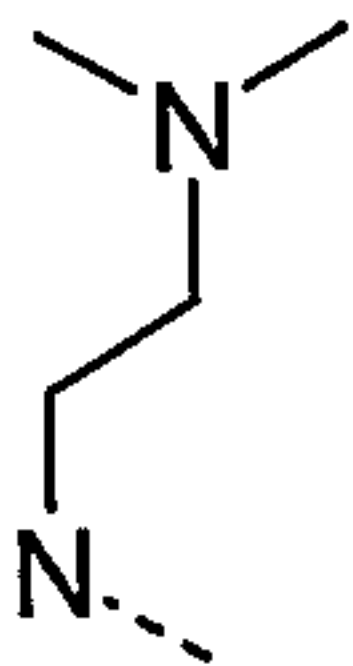
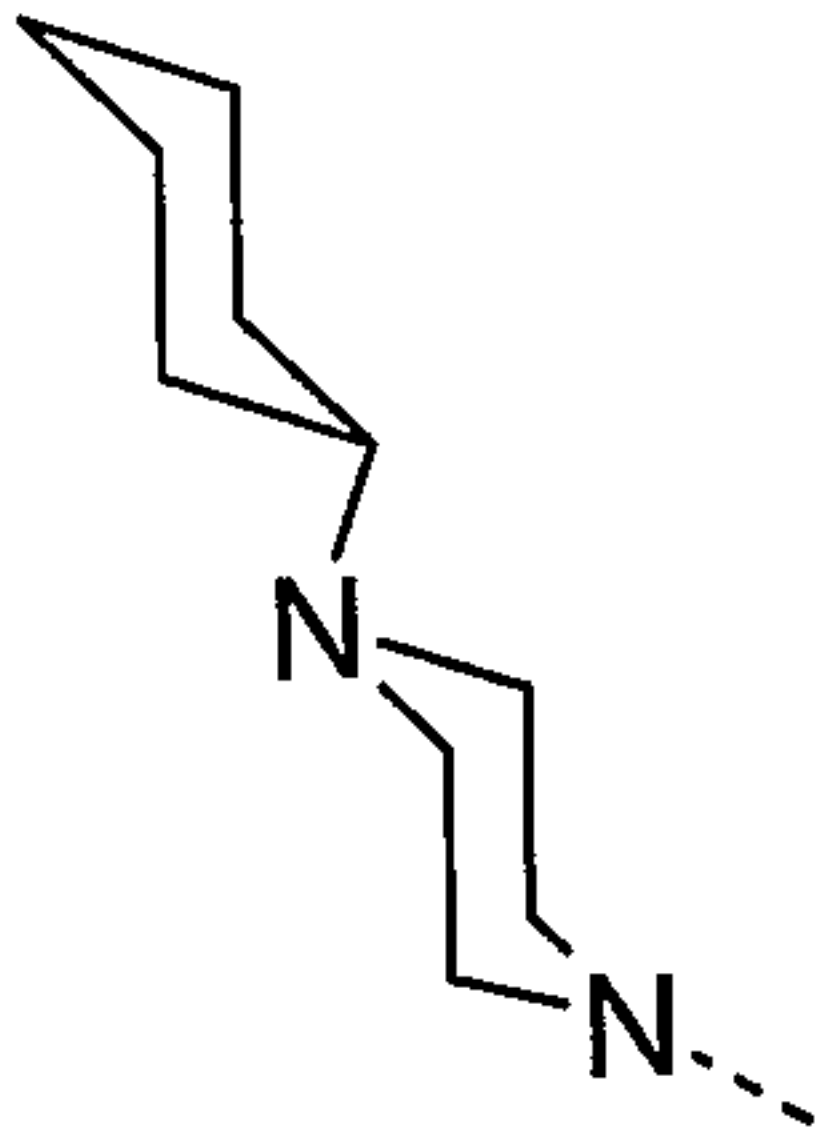
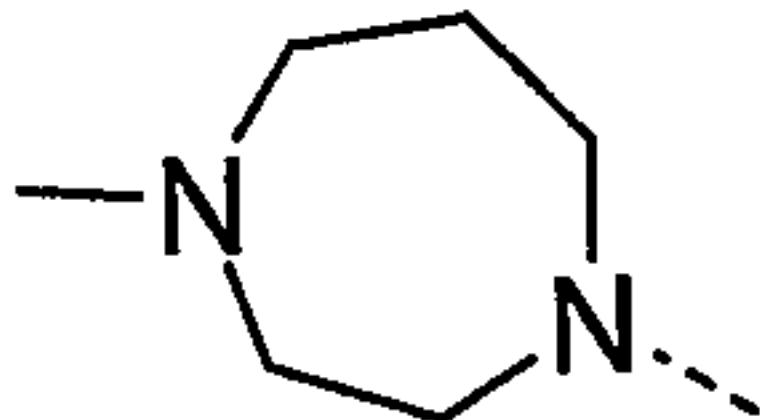
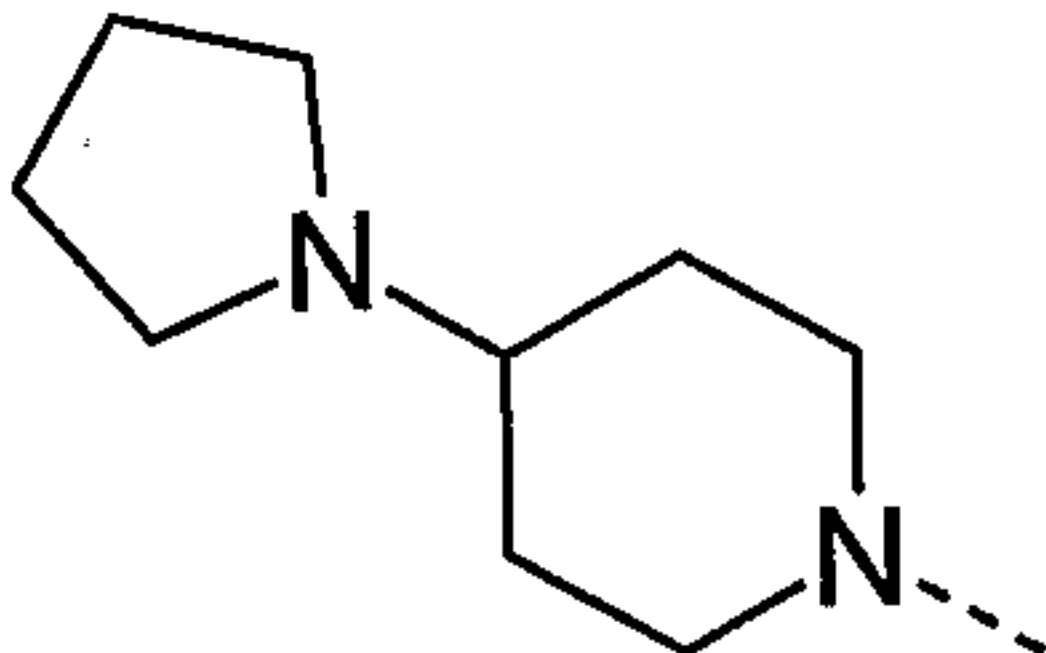
281

N'-(2-dimethylaminoethyl)-2-methoxy-benzene-1,4-diamine**Intermediate 40:****4-(4-cyclohexylpiperazin-1-yl)-2-methoxy-aniline**

5

Intermediate 41:**2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)aniline****Intermediate 42:**10 **2-methoxy-4-(4-pyrrolidin-1-yl-1-piperidyl)aniline**

Intermediate	R	Source	MS m/z [M+H] ⁺	Retention time
36		Aldrich	250	1.39
37		Fluorochem	266	1.45
38		Aldrich	290	1.84

Intermediate	R	Source	MS m/z [M+H] ⁺	Retention time
39		Aldrich	210	1.26
40		Bulletin of the Chemical Society of Japan (1961), 34 655-9	290	2.02
41		Aldrich	236	1.48
42		Fluorochem	279	1.79

Intermediate 43:**2-methoxy-4-[(1-methyl-4-piperidyl)oxy]aniline**

To a stirred solution of 4-(3-methoxy-4-nitro-phenoxy)-1-methyl-piperidine (Intermediate 44;
 5 12.86 g, 48.34 mmol) in ethanol (250 mL) under nitrogen was added in one portion the Pd/C
 catalyst (10%, 1.29 g). The resulting mixture was evacuated and backfilled with nitrogen 4 x
 before hydrogen gas was introduced via a balloon. The reaction mixture was stirred at room
 temperature for 18 hrs. The catalyst was removed by filtration through celite and the filtrate
 concentrated under reduced pressure to give a light red oil (11.1 g, 47.0 mmol, 97%).

¹H NMR (399.902 MHz, DMSO-D₆) δ 1.52 - 1.63 (m, 2H), 1.82 - 1.90 (m, 2H), 2.06 - 2.15 (m, 2H), 2.17 (s, 3H), 2.56 - 2.65 (m, 2H), 3.73 (s, 3H), 4.10 (septet, 1H), 4.28 (s, 2H), 6.32 (dd, 1H), 6.45 (d, 1H), 6.53 (d, 1H); MS m/z 237.21 [M+H]⁺.

5 **Intermediate 44:**

4-(3-methoxy-4-nitro-phenoxy)-1-methyl-piperidine

To a solution of 4-Fluoro-2-methoxy-1-nitrobenzene (Apollo Scientific; 10.3 g, 60 mmol) in toluene (50 mL) and 25% KOH aq. (50 mL), were added at room temperature, 4-hydroxy-1-methylpiperidine (13.8 g, 120 mmol) and tetra-n-butylammonium bromide (3.87 g, 12 mmol).

10 The mixture was heated at 60 °C for 18 hrs. The reaction mixture was cooled to room temperature, poured onto ice-water (300 mL) and extracted with Ethyl Acetate (3 x 150 mL). The organic layer was extracted with dil HCl (2 M HCl, 300 mL)

The acidic aqueous layer was taken to pH 4/5 with 2 M NaOH solution and split between 2 x 50 g SCX-2 cartridges, washing with water and eluting with 7 N methanolic ammonia to give
15 the title compound as a yellow oil, which slowly solidified over time (12.86 g, 80%)

¹H NMR (399.902 MHz, DMSO-D₆) δ 1.64 - 1.72 (m, 2H), 1.93 - 2.00 (m, 2H), 2.17 - 2.24 (m, 5H), 2.59 - 2.64 (m, 2H), 3.92 (s, 3H), 4.60 (septet, 1H), 6.71 (dd, 1H), 6.78 (d, 1H), 7.94 (d, 1H); MS m/z 267.24 [M+H]⁺.

20 **Intermediate 45:**

2-methoxy-4-(1-methylpyrrolidin-3-yl)oxy-aniline

To a stirred solution of 3-(3-methoxy-4-nitro-phenoxy)-1-methyl-pyrrolidine (Intermediate 46; 5.50 g, 20.68 mmol) in ethanol (125 mL) under nitrogen was added in one portion the Pd/C catalyst (10%, 500 mg). The resulting mixture was evacuated and backfilled with
25 nitrogen (x 4) before hydrogen gas was introduced via a balloon. The reaction mixture was stirred at room temperature for 18 hrs. The catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure to give the title compound as a light red oil (4.74 g, 100%)

¹H NMR (399.902 MHz, CDCl₃) δ 1.94 - 2.02 (m, 1H), 2.22 - 2.30 (m, 1H), 2.36 - 2.45 (m, 1H), 2.38 (s, 3H), 2.73 - 2.83 (m, 3H), 3.50 (s, 2H), 3.81 (s, 3H), 4.74 (octet, 1H), 6.26 (dd, 1H), 6.45 (d, 1H), 6.61 (d, 1H); MS m/z 223.22 [M+H]⁺.

5 **Intermediate 46:**

3-(3-methoxy-4-nitro-phenoxy)-1-methyl-pyrrolidine

To a solution of 4-Fluoro-2-methoxy-1-nitrobenzene (Apollo Scientific; 4.28 g, 25 mmol) in toluene (20 mL) and 25% KOH aq. (20 mL), were added at room temperature, 1-methyl-3-pyrrolidiniol (5.0 g, 50 mmol) and tetra-n-butylammonium bromide (1.66 g, 5 mmol). The
10 mixture was heated at 60 °C for 18 hrs. The reaction mixture was cooled to room temperature, poured onto ice-water (200 mL) and extracted with Ethyl Acetate (3 x 100 mL). The organic layer was washed with 2 M HCl (250 mL) and then loaded onto a 50 g SCX-2 cartridge, washing with water and eluting with 7 N methanolic ammonia to give the title compound as a yellow oil, which solidified on standing (5.50 g, 87%).

15 ¹H NMR (399.902 MHz, DMSO-D₆) δ 1.73 - 1.84 (m, 1H), 2.27 (s, 3H), 2.31 - 2.37 (m, 2H), 2.65 (dd, 1H), 2.68 - 2.73 (m, 1H), 2.77 (dd, 1H), 3.92 (s, 3H), 5.02 - 5.07 (m, 1H), 6.62 (dd, 1H), 6.73 (d, 1H), 7.95 (d, 1H); MS m/z 253.23 [M+H]⁺.

Intermediate 47:

20 **2-methoxy-4-(2-morpholin-4-ylethoxy)aniline**

To 4-[2-(3-methoxy-4-nitro-phenoxy)ethyl]morpholine (Intermediate 48; 16.97 g, 60 mmol, 1eq) in ethanol (120 mL) was added 10% palladium on charcoal (850mg, 5%wt). The reaction was stirred at room temperature for 19 hours. After filtering off the palladium residues the solvent was evaporated under reduced pressure. The product was dissolved in ethyl acetate
25 (100mL) and extracted twice with 2M HCl. The aqueous layers were combined, washed with ethyl acetate then basified by the addition of 2N NaOH. The basic layer was re-acidified and captured onto mp-TsOH resin. After washing several times with methanol the product was released using 10% ammonia in methanol. After evaporation *in vacuo* the title compound was obtained as a dark brown oil. (14.5 g, 89%)

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¹H NMR (300.132 MHz, DMSO-D₆) δ2.49 - 2.51 (4H, m), 2.69 (2H, t), 3.60 (4H, t), 3.74 (3H, s), 3.98 (2H, t), 4.62 (2H, s), 6.30 (1H, dd), 6.46 (1H, d), 6.54 (1H, d); MS m/z 253 [M+H]⁺.

Intermediate 48:**5 4-[2-(3-methoxy-4-nitro-phenoxy)ethyl]morpholine**

To a solution of 4-fluoro-2-methoxy-1-nitro-benzene (Apollo Scientific; 10.27 g, 60 mmol) in toluene (50 mL) and 25% KOH (aq) (50 mL), was added 4-(2-hydroxyethyl)morpholine (Aldrich; 15.75 g, 120 mmol) and tetra-n-butylammonium bromide (3.87 g, 12 mmol) at room temperature. The mixture was heated at 60°C for 22 hours. The reaction mixture was cooled
10 to room temperature, poured into water and extracted three times with ethyl acetate. The organic layers were combined and washed twice with 2M sodium hydroxide then brine. Dried with magnesium sulphate, filtered and evaporated under reduced pressure to yield the title compound as a yellow oil (16.97 g, 100%)

¹H NMR (300.132 MHz, DMSO-D₆) δ2.48 (4H, t), 2.72 (2H, t), 3.58 (4H, t), 3.93 (3H, s), 4.23
15 (2H, t), 6.68 (1H, dd), 6.81 (1H, d), 7.94 (1H, d); MS m/z 283 [M+H]⁺.

Intermediate 49:**N-[(4-aminophenyl)methyl]pyridine-2-carboxamide**

Pyridine-2-carboxylate (Aldrich; 0.35 g, 2.84 mmol), 4-aminobenzylamine (Aldrich; 0.51 g, 4.26 mmol) and HATU (1.65g, 4.26mmol) were dissolved in DMF (7.5ml). *N,N*-Diisopropylethylamine (1.5ml, 8.53mmol) was added and the mixture stirred at room temperature for 2h. The mixture was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the residue purified by normal phase chromatography (2% MeOH/DCM) to give a yellow
25 solid (440mg). which was suspended in DCM/Et₂O and filtered to give the title compound as a pale yellow solid (235mg, 36%).

¹H NMR (399.9 MHz, DMSO-d₆) δ4.33 (2H, d), 4.94 (2H, s), 6.50 - 6.53 (2H, m), 7.00 - 7.03 (2H, m), 7.58 - 7.62 (1H, m), 7.98 - 8.07 (2H, m), 8.62 - 8.64 (1H, m), 8.98 (1H, t); MS m/z 228.03 [M+H]⁺.

Intermediate 50:**1-(3-amino-4-methoxy-phenyl)-N,N-dimethyl-pyrrolidin-3-amine**

4-methoxy-N-(1-methyl-4-piperidyl)-3-nitro-benzamide (Intermediate 51; 400 mg, 1.4 mmol) 10% Palladium on Carbon (40 mg) and Methanol (50 mL) were combined and stirred
5 at 25°C under Hydrogen at 5 bar pressure for 2 hours.

The reaction mixture was filtered and evaporated to dryness. The residue was purified by column chromatography using 5% 7N ammonia in MeOH/DCM as the solvent system.

Product containing fractions were combined and evaporated to give the title compound as a white solid (305mg, 85%).

10 ¹H NMR (399.9 MHz, DMSO-d₆) δ1.55 - 1.61 (2H, m), 1.70 - 1.74 (2H, d), 1.89 - 1.96 (2H, t), 2.16 (3H, s), 2.74 - 2.77 (2H, d), 3.68 (1H, m), 3.81 (3H, s), 4.79 (2H, s), 6.81 (1H, d), 7.06 - 7.09 (1H, m), 7.14 (1H, d), 7.86 (1H, d); MS m/z 264.28 [M+H]⁺.

Intermediate 51:**15 4-methoxy-N-(1-methyl-4-piperidyl)-3-nitro-benzamide**

3-Nitro-4-methoxybenzoic acid (Aldrich; 300mg, 1.52mmol), 1-methyl-4-aminopiperidine (Fluorochem; 174mg, 1.52mmol), HATU (868mg, 2.28mmol) and DIPEA (796uL, 4.56mmol) were stirred in DMF (6mL) at room temperature for 2 hours. The reaction mixture was loaded onto an SCX-3 column pre-washed with methanol. The column was washed with
20 methanol and then eluted with 2% 7N ammonia/methanol. Product containing fractions were combined and evaporated to give the title compound as an orange solid (341mg, 76.4%).

¹H NMR (399.9 MHz, DMSO-d₆) δ1.55 - 1.59 (2H, m), 1.75 (2H, d), 1.91 - 1.95 (2H, m), 2.17 (3H, s), 2.70 - 2.79 (2H, d), 3.68 - 3.78 (1H, m), 3.99 (3H, s), 7.46 (1H, d), 8.16 - 8.19 (1H, m), 8.41 (2H, d); MS m/z 294.31 [M+H]⁺.

25

Intermediate 52:**4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide**

3-chloro-N-(2-morpholin-4-ylethyl)-4-nitro-benzamide (Intermediate 53; 1.2 g, 3.82 mmol), iron powder (1.29 g, 22.95 mmol) and ammonium chloride (144 mg, 2.68 mmol) were heated
30 in ethanol (27 mL) and water (9 mL) at reflux for 1h. A few drops of acetic acid were added and heating continued for a further 1h. The reaction mixture was cooled, filtered and the

filtrate concentrated. The residue was partitioned between DCM and sat NaHCO₃. The organic layer was washed with brine, dried (MgSO₄) and concentrated. Column chromatography of the residue gave the title compound as a white crystalline solid. (650mg, 60%)

5 ¹H NMR (399.9 MHz, DMSO-d₆ + D₂O) δ2.38 – 2.46 (6H, m), 3.30 – 3.36 (2H, m), 3.55 – 3.59 (4H, m), 5.83 (1H, partially exchanged NH₂), 6.79 (1H, d), 7.53 – 7.55 (1H, m), 7.73 (1H, d), 8.10 (1H, s); MS m/z 284.08 [M+H]⁺.

Intermediate 53:

10 **3-chloro-N-(2-morpholin-4-ylethyl)-4-nitro-benzamide**

3-chloro-4-nitro-benzoyl chloride (Intermediate 54; 1.1 g, 5.00 mmol) was dissolved in DCM (10 mL) and N,N-diisopropylethylamine (1.05 mL, 6.00 mmol) added. The mixture was cooled in an ice/water bath and 4-(2-aminoethyl)morpholine (Aldrich; 0.66 mL, 5.00 mmol) 15 in DCM (5 mL) added dropwise. The mixture was allowed to warm to room temperature and stirred for 0.5 hr. The reaction mixture was washed with brine, 2N NaOH, dried (MgSO₄) and concentrated. Column chromatography of the residue (2% MeOH/DCM) gave the title compound as a yellow solid. (1.2 g, 76%)

¹H NMR (399.9 MHz, DMSO-d₆) δ2.43 (4H, t), 2.48 (2H, t), 3.39 – 3.44 (2H, m), 3.58 (4H, 20 m), 7.98 – 8.01 (1H, m), 8.16 (1H, m), 8.19 (1H, d), 8.78 (1H, t); MS m/z 314.16 [M+H]⁺.

Intermediate 54:

3-chloro-4-nitro-benzoyl chloride

3-Chloro-4-nitrobenzoic acid (Apin; 1g, 4.96 mmol) was suspended in toluene (10 mL) and 25 thionyl chloride (1.1 mL, 14.88 mmol) added. The mixture was heated to 85°C for 45min. Further thionyl chloride (1.1 mL) was added and the mixture heated at reflux. 0.5 hr. The reaction mixture was allowed to cool and stand overnight. The mixture was concentrated to give the title compound as a yellow liquid (1.15g, 100%).

¹H NMR (399.9 MHz, CDCl₃) δ7.87 (1H, s), 8.07 – 8.10 (1H, m), 8.23 (1H, d); MS m/z 30 198.92 [M+H]⁺.

Intermediate 55:**4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide**

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 56; 1.8 g, 6 mmol)

5 hydrogenated over 2 hours with agitation at 298K and pressure of 5 bar using a 5% Pt/C catalyst and EtOH (50 mL) solvent. The catalyst was filtered and the filtrate concentrated to give a yellow crystalline solid which was dissolved in DCM and purified by column chromatography (5% MeOH/DCM) to give the title compound as a pale yellow crystalline solid (1.62 g, 100%)

10 ¹ H NMR (399.9 MHz, DMSO-d₆) δ1.53 - 1.60 (2H, m), 1.71 - 1.74 (2H, m), 1.90 - 1.95 (2H, m), 2.16 (3H, s), 2.33 - 2.35 (1H, m), 2.67 - 2.69 (1H, m), 2.76 (2H, d), 3.66 - 3.70 (1H, m), 5.82 (2H, d), 6.78 (1H, d), 7.56 - 7.58 (1H, m), 7.76 (1H, d), 7.89 (1H, d); MS m/z 268.14 [M+H]⁺.

15 **Intermediate 56:**

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

3-chloro-4-nitro-benzoyl chloride (Intermediate 54; 2.2 g, 10.00 mmol) was dissolved in DCM (20 mL) and N,N-diisopropylethylamine (2.095 mL, 12.00 mmol) added. The mixture was cooled in an ice/water bath and 4-amino-1-methylpiperidine (Fluorochem; 1.14 g, 10.00

20 mmol) in DCM (10 mL) added dropwise. The mixture was allowed to warm to room temperature and stirred for 0.5 hr. A white precipitate resulted. The reaction mixture was washed with 2N NaOH, filtered and the filter cake washed with water and dried on a sinter over the weekend to give the title compound as a white solid (1.80g, 60%) as a white solid.

¹H NMR (399.9 MHz, DMSO-d₆) δ1.53 - 1.63 (2H, m), 1.79 (2H, t), 1.92 - 1.99 (2H, m), 2.17

25 (3H, s), 2.78 (2H, d), 3.70 - 3.77 (1H, m), 7.99 - 8.02 (1H, m), 8.18 (2H, t), 8.60 (1H, d); MS m/z 298.2 [M+H]⁺.

30 **Intermediate 57:**

10-amino-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 250 mg; 0.89 mmol), Diphenylmethanimine (Fluka; 178 mg, 0.979 mmol) and caesium carbonate (580 mg, 1.78 mmol) were added to dioxane (3 mL and the suspension bubbled with nitrogen for 10 minutes. Tris(Dibenzylideneacetone)Dipalladium(0) (49 mg; 0.053 mmol) and XANTPHOS (46 mg, 0.080 mmol) were added and the mixture heated to 100 °C for 16 hrs. The reaction mixture was cooled to room temperature filtered and the filter cake washed with DCM. The filtrate was evaporated and the resultant material taken up in DCM and purified on silica (the column was made neutral prior to purification by wetting with iso-hexane, running a solution of 5% triethylamine in iso-hexane through followed by iso-hexane, material was then added) eluting with a gradient of 40 – 60% Ethyl Acetate / iso-hexane then 60% Ethyl Acetate / iso-hexane. Fractions containing the imine intermediate were combined and evaporated to a yellow solid (162 mg, 43%), which was dissolved in THF (10 mL). 2M aq HCl (3 mL) was added and the solution stirred at room temperature for 20 minutes. The reaction mixture was added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and the a product eluted with 2M ammonia in MeOH. Solvents were evaporated to give the title compound as a white solid (80 mg, 80% from imine)

¹H NMR (399.902 MHz, DMSO-D₆) δ 1.46 (m, 4H), 1.59 (m, 2H), 1.83 (m, 2H), 3.03 (s, 3H), 3.46 (m, 2H), 4.60 (m, 1H), 5.99 (s, 2H), 7.75 (s, 1H);); MS m/z 262 [M+H]⁺.

20

Intermediate 58:**4-bromo-2,6-difluoro-N-(1-methyl-4-piperidyl)benzamide**

4-bromo-difluorobenzoic acid (Fluorochem; 3.0 g, 12.66 mol) and HBTU (5.3 g, 13.92 mol) were added to DMF (80 mL), to this was added the required 4-amino-1-methylpiperidine (Fluorochem; 1.59 g, 13.93 mol) and DIPEA (5.0 mL, 27.85 mol), the reaction was stirred for 48 hours, after which the solvent was removed in vacuo to yield a brown gum. The gum was treated with 2.0 M NaOH (50 mL) and extracted with DCM (3 x 200 mL). Combined extracts were dried and solvent removed *in vacuo* to yield a dark orange gum which was recrystallised from hot acetonitrile to give the title compound as a white solid (1.9 g, 45%).

¹H NMR (400.132 MHz, DMSO-D₆) δ 8.64 (d, 1H), 7.55 (d, 2H), 3.74 - 3.64 (m, 1H), 2.74 - 2.65 (m, 2H), 2.15 (s, 3H), 1.98 (t, 2H), 1.82 - 1.74 (m, 2H), 1.52 - 1.42 (m, 2H); MS m/z 334 [M+H]⁺.

5 **Intermediate 59:**

4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

2,5-difluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 60; 633 mg 2.1 mmol), 10% Palladium on Carbon (70 mg) and Methanol (50 mL) were combined and stirred at 25°C under Hydrogen at 3 bar pressure for 16 hours..

10 The catalyst was filtered off and the filtrate evaporated to give the title compound as a yellow solid. (554 mg, 97%)

¹H NMR (400.132 MHz, CDCl₃) δ 1.58 (m, 2H), 2.03 (m, 2H), 2.18 (m, 2H), 2.30 (s, 3H), 2.78 (m, 2H), 3.99 (m, 1H), 4.14 (s, 2H), 6.47 (m, 2H), 7.71 (m, 1H); MS m/z 334 [M+H]⁺.

15 **Intermediate 60:**

2,5-difluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

1,5-Difluoro-4-nitrobenzoic acid (Fluorochem; 1 g, 4.92 mmol), 4-Amino-1-methylpiperidine (Fluorochem; 620 mg, 5.41 mmol), HAT (2.05 g, 5.41 mmol), DIPEA (2.57 mL, 14.76 mmol) and DMF (10 mL) were combined and stirred at room temperature for 20 18 hrs. Solvents were evaporated and the resultant material partitioned between DCM and water. Both phases were acidified with 2M aq HCl and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated *in vacuo* and the resultant material taken up in DCM and purified on silica eluting 25 with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 5% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to give the title compound as a yellow solid. (635 mg, 43%)

¹H NMR (400.132 MHz, DMSO-D₆) δ 1.53 (m, 2H), 1.80 (m, 2H), 1.98 (m, 2H), 2.16 (s, 3H), 2.73 (m, 2H), 3.70 (m, 1H), 7.79 (m, 1H), 8.21 (m, 1H), 8.59 (d, 1H); MS m/z 300

30 [M+H]⁺.

Intermediate 61:**4-amino-2-fluoro-N-(1-methyl-4-piperidyl)benzamide**

2-fluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 62; 1.62 g, 5.8 mmol),
5 10% Palladium on Carbon (160 mg) and Methanol (50 mL) were combined and stirred at
25°C under Hydrogen at 5 bar pressure for 16 hours..

The catalyst was filtered off and the filtrate evaporated to give a brown solid which was
trituated with 5% MeOH / DCM . The precipitate was collected by filtration and dried under
vacuum to yield the title compound as a beige solid (560 mg, 39%).

10 ¹H NMR (400.132 MHz, DMSO-D6) δ1.74 (m, 2H), 1.99 (m, 2H), 2.76 (s, 3H), 3.09 (m,
2H), 3.42 (m, 2H), 3.97 (m, 1H), 5.89 (s, 2H), 6.30 (m, 1H), 6.39 (m, 1H), 7.37 (m, 1H), 7.67
(s, 1H), 9.11 (s, 1H);); MS m/z 252 [M+H]⁺.

Intermediate 62:**2-fluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide**

15 2-Fluoro-4-nitrobenzoic acid (Aldrich; 3 g, 16.21 mmol), 4-Amino-1-methylpiperidine
(Fluorochem; 2.03 g, 17.83 mmol), HATU (6.77 g, 17.83 mmol), DIPEA (8.5 mL, 48.63
mmol) and DMF (30 mL) were combined and stirred at ambient temperature for 18 hrs.
Solvents evaporated and partitioned between DCM (200 ml) and water (100 ml). The aqueous
20 phase was re-extracted with DCM (100 ml). The combined organic phases were dried
(MgSO₄) and evaporated. The resultant material was taken up in DCM and purified on silica
eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 5% 2M ammonia in
MeOH / DCM. Fractions containing product were combined and evaporated to give the title
compound as a yellow solid (2.67 g, 59%)

25 ¹H NMR (400.132 MHz, DMSO-D6) δ1.53 (m, 2H), 1.80 (m, 2H), 2.26 (m, 5H), 2.85 (m,
2H), 3.74 (m, 1H), 7.72 (m, 1H), 8.06 (m, 1H), 8.12 (m, 1H), 8.54 (d, 1H); MS m/z 282
[M+H]⁺.

Intermediate 63:

4-amino-3-methyl-N-(1-methyl-4-piperidyl)benzamide

3-methyl-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 64: 3.34 g) 10% Palladium on Carbon (350 mg) and Methanol (50 mL) were combined and stirred at 25°C under Hydrogen at 5 bar pressure for 16 hours..

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The catalyst was filtered off and washed with EtOH. The filtrate was evaporated to yield a cream solid., which was triturated with DCM filtered and dried under vacuum to give the title compound as a white solid (1.2 g)

¹H NMR (400.132 MHz, DMSO-D6) δ1.75 (m, 2H), 1.96 (m, 2H), 2.08 (s, 3H), 2.74 (s, 3H),
10 3.04 (m, 2H), 3.38 (m, 2H), 3.96 (m, 1H), 5.36 (s, 2H), 6.58 (d, 1H), 7.47 (m, 2H), 7.86 (d, 1H), 9.13 (s, 1H); MS m/z 248 [M+H]⁺.

The following intermediate was prepared in a manner analogous to Intermediate 62 utilising 3-Methyl-4-nitrobenzoic acid, available from Aldrich, as the starting Nitro acid.

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Intermediate 64:**3-methyl-N-(1-methyl-4-piperidyl)-4-nitro-benzamide**

3-methyl-N-(1-methyl-4-piperidyl)-4-nitro-benzamide was prepared in a manner analogous to Intermediate 62 utilising 3-Methyl-4-nitrobenzoic acid, available from Aldrich, as the starting
20 Nitro acid.

¹H NMR (400.132 MHz, DMSO-D6) δ1.71 (m, 2H), 1.92 (m, 2H), 3.16 (m, 2H), 3.91 (m, 1H), 7.86 (m, 1H), 7.92 (s, 1H), 8.06 (d, 1H), 8.56 (d, 1H); MS m/z 278 [M+H]⁺.

Intermediate 65:**25 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide**

4-Amino-3-Fluorobenzoic acid (Fluorochem; 1 g, 6.44 mmol), 4-Amino-1-methylpiperidine (Fluorochem; 811 mg, 7.09 mmol), HATU (2.70 g, 7.09 mmol), DIPEA (3.4 mL, 19.32 mmol) and DMF (15 mL) were combined and stirred for 18 hrs at room temperature. The solvent was evaporated and the resultant material dissolved in DCM (with a little MeOH to
30 aid solubility) and chromatographed on silica eluting with a gradient of 0 – 10% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to give an

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orange solid which was dissolved in MeOH and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated to yield the title compound as a beige solid. (1.72 g, 100%)

¹H NMR (399.902 MHz, CDCl₃) δ 1.55 (m, 2H), 2.03 (m, 2H), 2.14 (m, 2H), 2.29 (s, 3H), 2.81 (m, 2H), 3.95 (m, 1H), 4.01 (s, 2H), 5.77 (d, 1H), 6.75 (m, 1H), 7.34 (m, 1H), 7.45 (m, 1H); MS m/z 252 [M+H]⁺.

Intermediate 66:

10 **4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-(2-methoxyethoxy)benzoic acid**

To a stirred solution of Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-methoxyethoxy)benzoate (Intermediate 67; 164 mg, 0.35 mmol) in ethanol (3 mL) was added a solution of lithium hydroxide (22 mg, 0.92 mmol) in water (1 mL). The reaction was stirred at ambient temperature overnight. A further addition of lithium hydroxide (20 mg) as a solution in water (1 mL) was added and stirring continued for 2.5 hrs and then heated to 50°C for 4 hrs. The reaction mixture was evaporated and the residue diluted with water (5 mL). The resultant opaque solution was treated with a few drops of 2M HCl (aq.) to adjust the pH to 2-3. A precipitate formed which was collected by suction filtration, washing through with more water and dried under vacuum, at 55°C, for 3 hours to afford the title compound as an off white solid (113 mg, 71%)

¹H NMR (400.132 MHz, DMSO-D₆) δ 1.65 (m, 6H), 1.91 (m, 2H), 2.67 (m, 2H), 3.18 (s, 3H), 3.70 (m, 2H), 3.75 (m, 2H), 4.27 (m, 2H), 4.84 (m, 1H), 7.57 - 7.63 (m, 2H), 8.13 (s, 1H), 8.27 (d, 1H), 8.72 (m, 1H); MS m/z 456.4 [M+H]⁺.

Intermediate 67:

30 **Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-**

trien-9-yl)amino]-3-(2-methoxyethoxy)benzoate

To 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 222 mg, 0.79 mmol) was added a solution of Methyl 4-amino-3-(2-methoxyethoxy)benzoate (Intermediate 68; 203 mg, 0.90 mmol) in ethanol (4 mL). Water (12 mL) was added followed by concentrated hydrochloric acid (36%; 160 µl). The reaction was heated to 80°C and stirred overnight. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~50 mL with water and the solution basified to pH 9 by addition of a few drops of aq. Ammonia. The resultant emulsion was treated with a little brine and extracted with DCM (2 x 50 mL). Combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to give an amber gum which was purified by flash chromatography on silica (40g Si cartridge; ISCO companion), eluting first with a rising gradient of 25-75% ethyl acetate in iso-hexane and then a rising gradient of 0-10% methanol in DCM. Product containing fractions were combined and evaporated to give a yellow oil which crystallised on standing overnight. This solid was triturated with diethyl ether, solid collected by suction filtration and dried to afford the title compound as a cream solid (173 mg, 47 %)

¹H NMR (400.132 MHz, CDCl₃) ? 1.59 - 1.81 (m, 6H), 2.04 (m, 2H), 2.67 (m, 2H), 3.29 (s, 3H), 3.48 (s, 3H), 3.70 (m, 2H), 3.81 (m, 2H), 3.90 (s, 3H), 4.27 (m, 2H), 4.89 (m, 1H), 7.58 (m, 1H), 7.69 (m, 1H), 7.87 (s, 1H), 7.95 (s, 1H), 8.56 (d, 1H); MS m/z 470 [M+H]⁺.

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Intermediate 68:**Methyl 4-amino-3-(2-methoxyethoxy)benzoate**

To a solution of Methyl 3-hydroxy-4-aminobenzoate (ABCR: 97 mg, 0.58 mmol) in acetone (3 mL), in a microwave tube, was added Methoxyethyl bromide (Aldrich; 85 µl, 0.90 mmol) and powdered potassium carbonate (120 mg, 0.87 mmol). The reaction was heated in a microwave (150W, CEM explorer) to 100°C and held for 30 minutes.

A further addition of Methoxyethyl bromide (40 µl, 0.43 mmol) was made and the reaction heated to 120°C for a further 30 minutes.

The reaction was repeated in two batches as follows. To a solution of Methyl 3-hydroxy-4-aminobenzoate (135 mg, 0.81 mmol) in acetone (4 ml), in a microwave tube. Was added

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Potassium Carbonate (185 mg, 1.34 mmol) and Methoxyethyl bromide (115 μ l, 1.22 mmol) The reaction was heated to 120°C in a microwave and held for 1 hour. The reactions was cooled, treated with a further aliquot of methoxyethyl bromide (58 μ l, 0.62 mmol) and re-heated to 120°C holding for a further hour.

5 All three batches were combined and evaporated to dryness. The residue was partitioned between DCM (25 mL) and water (25 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (20 mL). Combined organic phases were washed with brine, dried over magnesium sulphate and evaporated to give a brown oil which was purified by flash chromatography on silica (40g Cartridge) eluting with a rising gradient of 25-50% ethyl
10 acetate in iso-hexane. Product containing fractions were combined and evaporated to give the title compound as a dark orange oil (256 mg, 56%).

^1H NMR (400.132 MHz, DMSO- D_6) δ 3.38 (s, 3H), 3.74 (m, 2H), 3.80 (s, 3H), 4.16 (m, 2H), 5.61 (s, 2H), 6.72 (d, 1H), 7.37 (m, 1H), 7.45 (m, 1H); MS m/z 226 $[\text{M}+\text{H}]^+$.

15 **Intermediate 69:**

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoic acid

To a stirred solution of Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoate
20 (Intermediate 70; 128 mg, 0.28 mmol) in Ethanol (3 mL) was added a solution of lithium hydroxide (26 mg, 0.92 mmol) in water (1.5 mL). The reaction was allowed to stir at 70°C for 4 hours, cooled, evaporated and the residue diluted with water (10 mL). The resultant solution was treated with a few drops of 2M HCl (aq.) until a precipitate persisted, pH $\sim$ 3-4. The precipitate was collected by suction filtration, washing through with more water. Solid
25 was dried under suction overnight to afford the title compound as a white solid (108 mg, 88 %)

^1H NMR (400.132 MHz, DMSO- D_6) δ 1.36 (d, 6H), 1.57 - 1.77 (m, 6H), 1.95 (m, 2H), 2.61 (m, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 4.69 - 4.85 (m, 2H), 7.52 - 7.56 (m, 2H), 7.83 (s, 1H), 8.10 (s, 1H), 8.46 (d, 1H), 12.62 (s, 1H); MS m/z 440 $[\text{M}+\text{H}]^+$.

Intermediate 70:**Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoate**

To 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 190 mg, 0.68 mmol) was added a solution of Methyl 4-amino-3-propan-2-yloxy-benzoate (Intermediate 71, 145 mg, 0.69 mmol) in ethanol (4 mL), followed by water (12 mL). Concentrated hydrochloric acid (36%; 140 μ l) was added and the reaction heated to 80°C, with stirring, overnight. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~40 mL with water and the solution basified to pH 9 by addition of a few drops of aq. ammonia. The resultant emulsion was treated with a little brine and extracted with DCM (2 x 30 mL). The biphasic mixture was poured into a PTFE cup and the organic phase allowed to drip through under gravity. Evaporation of the organic phase afforded an amber gum, which was purified by flash chromatography on silica (40g Si cartridge; ISCO companion), eluting with a rising gradient of 25-100% ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a colourless gum which was triturated with a small amount of diethyl ether and the resultant solid collected by suction filtration and dried to afford the title compound as a white solid (132 mg, 43 %)

^1H NMR (400.132 MHz, DMSO- D_6) δ 1.36 (d, 6H), 1.58 - 1.77 (m, 6H), 1.95 (m, 2H), 2.60 (m, 2H), 3.18 (s, 3H), 3.64 (m, 2H), 3.83 (s, 3H), 4.77 (m, 2H), 7.53 (m, 1H), 7.57 (m, 1H), 7.78 (s, 1H), 8.10 (s, 1H), 8.51 (d, 1H); MS m/z 452 $[\text{M}+\text{H}]^+$.

Intermediate 71:**Methyl 4-amino-3-propan-2-yloxy-benzoate**

Methyl 3-hydroxy-4-aminobenzoate (ABCR: 100 mg, 0.60 mmol) & caesium carbonate (396 mg, 1.22 mmol) were taken up in acetone (4 mL) and 2-iodopropane (90 μ l, 0.90 mmol) added and reaction heated in microwave (CEM discover; 150 W) to 120°C and held for 30 mins. A further aliquot of 2-iodopropane (90 μ l, 0.90 mmol) was added and reaction heated again to 120°C in microwave, holding for a further 30 mins. The reaction was repeated twice on a 0.89 mmol scale

Reaction mixtures were combined and evaporated to dryness and the residue partitioned between, ethyl acetate (40 ml) and water (50 ml). The organic phase was separated and the aqueous re-extracted with ethyl acetate (40 ml). Combined organic extracts were washed with brine, dried over magnesium sulphate and evaporated to give a brown oil which was
5 purified by column chromatography, on silica (40 g cartridge; ISCO companion) eluting with a rising gradient of 5-50% ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to dryness to afford the product as a yellow oil (301 mg, 60%)
 ^1H NMR (400.132 MHz, DMSO- D_6) δ 1.28 (d, 6H), 3.75 (s, 3H), 4.53 (m, 1H), 5.51 (s, 2H), 6.66 (d, 1H), 7.31 (m, 1H), 7.37 (m, 1H); MS m/z 209.4 $[\text{M}+\text{H}]^+$.

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Intermediate 72:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-(2-dimethylaminoethoxy)benzoic acid

Methyl 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-
15 10-yl)amino]-3-hydroxy-benzoate (Intermediate 73; 63 mg, 0.15 mmol) was dissolved in DMA (2 mL) and treated sequentially with potassium carbonate powder (fine mesh; 106 mg, 0.79 mmol) and dimethylaminoethyl bromide hydrobromide (ASDI; 61 mg, 0.26 mmol). The reaction mixture was heated to 100°C, with stirring for 1 hour and allowed to cool overnight, before pouring into water (40 ml). The mixture was extracted with DCM (2 x 30 ml) and the
20 organic extracts washed with brine, dried over magnesium sulphate, filtered and evaporated to give a brown liquid which was taken up in methanol and poured onto an SCX-3 cartridge (2 g). The cartridge was washed with methanol (~30 ml) before eluting products with 2M ammonia/methanol (~20 ml). The ammoniacal wash was evaporated to give the title compound as a brown gum (41 mg, 57%)
25 MS m/z 483.4 $[\text{M}+\text{H}]^+$, Retention Time 2.41 minutes.

Intermediate 73:

**Methyl 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-
30 trien-10-yl)amino]-3-hydroxy-benzoate**

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 180 mg, 0.64 mmol) and Methyl 3-hydroxy-4-aminobenzoate (ABCR; 123 mg, 0.73 mmol) were taken up in ethanol (4 mL) and water (12 mL). Concentrated hydrochloric acid (36%; 130 μ l) was added and the reaction heated to 80°C and stirred
5 overnight. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~30 ml with water and the solution basified to pH 9 by addition of a few drops of aqueous Ammonia. The resultant mixture was extracted with DCM (2 x 50 ml). A solid persisted at the phase boundary. This solid was collected by suction filtration and dried to give the title compound as a purple/grey solid (64 mg, 24%)

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The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to a pink/brown solid (153 mg) which was triturated with DCM (5 mL). The solid was then collected by suction filtration and dried to give the title compound as a dusky pink solid (79 mg, 30 %)

15 ^1H NMR (400.132 MHz, DMSO- D_6) δ 1.57 - 1.75 (m, 6H), 1.95 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.80 (s, 3H), 4.82 (m, 1H), 7.44 (m, 2H), 7.84 (s, 1H), 8.09 (s, 1H), 8.36 (d, 1H); MS m/z 412.3 $[\text{M}+\text{H}]^+$.

Intermediate 74:

20 4-amino-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide

To a solution of 4-amino-3-(trifluoromethoxy)benzoic acid (Maybridge ; 1.05 g, 4.75 mmol) in DMF (20 ml) was added 4-amino-1-methylpiperidine (Fluorochem; 604 mg, 5.29 mmol) followed by DIPEA (1.6 ml, 9.19 mmol) and HATU (2.06 g, 5.42 mmol). The reaction mixture was stirred at ambient temperature O/N. The reaction mixture was evaporated to
25 dryness and the residue partitioned between DCM (75 mL) and saturated aqueous sodium bicarbonate solution (75 mL). The aqueous phase was re-extracted with DCM (50 ml) and the combined organic phases washed with brine, dried over magnesium sulphate, filtered and evaporated to give the title compound as an amber gum (1.17 g, 78%)

^1H NMR (400.132 MHz, DMSO- D_6) δ 1.75 (m, 2H), 1.93 (m, 2H), 2.64 (s, 3H), 2.87 (m,
30 2H), 3.93 (m, 1H), 5.93 (s, 2H), 6.80 (d, 1H), 7.64 (m, 2H), 8.08 (d, 1H); MS m/z 316.4 $[\text{M}+\text{H}]^+$.

Intermediate 75:**4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-ethoxy-benzoic acid**

To a solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 280 mg, 1 mmol) and 4-amino-3-ethoxybenzoic acid (WO 2001077101; 205 mg, 1.13 mmol) in ethanol (5 mL) was added water (15 mL) and conc hydrochloric acid (0.17 mL, 2 mmol). The mixture was heated under reflux for 36 hours. The reaction was cooled and a brown solid precipitated. This was filtered and dried, triturated under cold acetonitrile and then dried *in vacuo*. To yield the title compound as a brown solid (190 mg; 45%)

MS m/z 426 [M+H]⁺. Retention Time 1.58 minutes

Intermediate 76:

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-propan-2-yl-amino]-N-methyl-propanamide (Intermediate 77; 2.67 g, 7.96 mmol) was dissolved in dioxane (80 mL) and tris(dibenzylideneacetone) palladium (II) (146 mg, 0.16 mmol), XANTPHOS (277 mg, 0.48 mmol) and Caesium carbonate (3.76 g, 11.54 mmol) added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100°C for 24 hours. The mixture was filtered and concentrated and the residue purified by column chromatography (1% MeOH/DCM) to give the title compound as a viscous yellow oil (1.25 g, 62%).
¹H NMR (399.9 MHz, CDCl₃) δ 1.18 (6H, d), 2.59 - 2.61 (2H, m), 3.22 (3H, s), 3.59 - 3.62 (2H, m), 4.82 - 4.88 (1H, m), 7.87 (1H, s); MS m/z 255.16 [M+H]⁺.

Intermediate 77:**3-[(5-bromo-2-chloro-pyrimidin-4-yl)-propan-2-yl-amino]-N-methyl-propanamide**

N-methyl-3-(propan-2-ylamino)propanamide (Intermediate 78; 2 g, 13.87 mmol), 5-bromo-2,4-dichloropyrimidine (Aldrich; 3.8 g, 16.64 mmol) and triethylamine (2.3 mL, 16.64 mmol) were heated in acetonitrile (85 mL) at 100°C for 3h. The mixture was cooled and

300

concentrated. The residue was dissolved in DCM, washed with water, dried (MgSO₄) and concentrated. Column chromatography (0.5 – 1 – 2% 7N ammonia in methanol/DCM) gave:

The the title compound as a pale yellow oil that crystallised on standing (2.67 g, 20%)

¹H NMR (399.9 MHz, DMSO-d₆) δ1.20 (6H, d), 2.31 (2H, t), 2.55 (3H, d), 3.65 (2H, t), 4.55 -
5 4.62 (1H, m), 7.72 (1H, s), 8.39 (1H, s); MS m/z 337.05 [M+H]⁺.

Intermediate 78:

N-methyl-3-(propan-2-ylamino)propanamide

Isopropylamine (Aldrich; 1.5ml, 17.62mmol) and methyl acrylamide (ABCR; 1.0g,
10 11.75mmol) were combined in methanol (10ml). The mixture was heated in a microwave at
140°C for 30min. The reaction was repeated and the combined reaction mixtures were
concentrated to remove excess amine. The residue was re-dissolved in methanol and absorbed
onto an SCX column (50g), washed with methanol and eluted with ammonia/methanol.
Concentration of the product containing fractions gave the title compound as a colourless oil
15 (3.2g, 94%) .

¹H NMR (399.9 MHz, CDCl₃) δ1.00 (6H, d), 2.27 (2H, t), 2.70 - 2.74 (4H, m), 2.76 - 2.80
(2H, m), 7.50 (1H, s)

Intermediate 79:

20 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 80; 270 mg, 1 mmol),
10% Palladium on Carbon (30 mg) and Methanol (50 mL) were combined and stirred at 25°C
under Hydrogen at 5 bar pressure for 16 hours..

The catalyst was filtered off and solvents evaporated to give the title compound as a cream
25 solid. (280 mg, 98%)

¹H NMR (400.132 MHz, CDCl₃) δ1.49 (m, 2H), 1.95 (m, 2H), 2.09 (m, 2H), 2.24 (s, 3H),
2.75 (m, 2H), 3.89 (m, 1H), 4.27 (s, 2H), 5.69 (d, 1H), 6.68 (m, 1H), 7.41 (m, 1H), 7.62 (m,
1H); MS m/z 268 [M+H]⁺.

30 Intermediate 80:

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

Reagents combined and stirred at room temperature overnight. LCMS after 18 hrs shows complete reaction. Solvents evaporated and residues partitioned between DCM (25 ml) and water (25 ml) then gravity filtered through a PTFE cup. Taken up in DCM and purified on silica eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 5% 2M ammonia in MeOH / DCM. The peak corresponding to the product (which was only 1 spot by tlc) was clearly split into 2 on the chromatography trace. The first peak (fractions 6 – 10) was labelled PH17082/048/1 and evaporated to a brown gum. The second peak (fractions 11 – 14) was labelled as PH17082/048/2 and evaporated to a white solid. Both products had identical LCMS traces and showed the mass ion for the desired product. NMR showed a difference in the aliphatic region and an additional small broad peak in the aromatic region of PH17082/048/1. It was concluded that PH17082/048/1 was a salt (possibly PF₆ from HATU).

PH17082/048/1 was dissolved in MeOH and added to a 2g SCX-2 column pre-wet with MeOH (2 column volumes). The column was then flushed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH. This was then combined with the solid of PH17082/048/2 and evaporated to an off-white solid, 315mg.

¹H NMR (500.133 MHz, DMSO-D₆) δ1.66 (m, 2H), 1.85 (m, 2H), 2.14 (m, 2H), 2.25 (s, 3H), 2.83 (m, 2H), 3.78 (m, 1H), 7.97 (m, 1H), 8.09 (m, 1H), 8.12 (m, 1H), 8.26 (d, 1H); MS m/z 298 [M+H]⁺.

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Intermediate 81:

10-chloro-2-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

Tris(dibenzylideneacetone)dipalladium(0) (52 mg, 0.06 mmol), XANTPHOS (98 mg, 0.17 mmol) and caesium carbonate (1.32 g, 4.06 mmol) were added to a stirred solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-ethyl-amino]-N-methyl-propanamide (Intermediate 82; 900 mg, 2.80 mmol) in 1,4-dioxane (28 mL). The apparatus was evacuated and backfilled with nitrogen twice and then heated to 100 °C for 18 hrs. The reaction mixture was filtered through a celite pad and dry loaded onto silica for purification by flash silica chromatography (companion, 40 g, 0-10% MeOH/DCM) to give the title compound as a yellow solid (638 mg, 2.65 mmol, 95%).

¹H NMR (399.902 MHz, DMSO-D₆) δ 1.17 (t, 3H), 2.66 - 2.69 (m, 2H), 3.19 (s, 3H), 3.57 (q, 2H), 3.72 - 3.74 (m, 2H), 8.13 (s, 1H); MS m/z 241.14 [M+H]⁺.

Intermediate 82:

5 **3-[(5-bromo-2-chloro-pyrimidin-4-yl)-ethyl-amino]-N-methyl-propanamide**

5-Bromo-2,4-dichloropyrimidine (Aldrich; 1.14 g, 5.00 mmol), 3-ethylamino-N-methyl-propanamide (Intermediate 83; 0.642 g, 5.00 mmol) and triethylamine (0.71 mL, 5.10 mmol) were combined in acetonitrile (25 mL) and heated to 100 °C for 4 hrs. The solvent was removed under reduced pressure and the residue taken up in Ethyl Acetate, washed with water
10 and purified by flash silica chromatography (companion, 40 g, 0-10% Methanol/DCM) to give the title compound as a white solid (1.06 g, 3.3 mmol, 66%).

¹H NMR (399.902 MHz, DMSO-D₆) δ 1.18 (t, 3H), 2.46 (t, 2H), 2.58 (d, 3H), 3.67 (q, 2H), 3.81 (t, 2H), 7.85 (m, 1H), 8.31 (s, 1H); MS m/z 320.95 [M+H]⁺.

15 **Intermediate 83:**

3-ethylamino-N-methyl-propanamide

N-methylacrylamide (ABCR: 851 mg, 10.00 mmol) and ethylamine (2 M in methanol, 10 mL, 20.00 mmol) were combined in a microwave reaction vessel, which was sealed and irradiated at 140 °C for 30 mins. The reaction mixture was allowed to cool and then loaded
20 directly onto a 50 g SCX-2 cartridge, washing with methanol (100 mL) and eluting the desired product with 7 N methanolic ammonia (100 mL). Concentration under reduced pressure of product containing fractions gave the title compound as a clear oil (1.285 g; 99%)
¹H NMR (399.9 MHz, DMSO-d₆) δ 0.93 - 0.99 (3H, m), 2.19 (2H, t), 2.52 - 2.52 (2H, m), 2.54 - 2.59 (3H, d), 2.68 (2H, t), 7.80 (1H, br s)

25

Intermediate 84:

10-chloro-6-methyl-2-(2-methylpropyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methylpropyl)amino]-N-methyl-propanamide
30 (Intermediate 85; 3.26 g, 9.32 mmol) was suspended in dioxane (70 mL), Caesium Carbonate (6 g, 18.64 mmol) was added and the mixture bubbled with nitrogen for 10

minutes. Tris(dibenzylideneacetone)dipalladium(0) (512 mg, 0.56 mmol) and XANTPHOS (485 mg, 0.839 mmol) were added and the mixture heated at 100 °C for 24 hrs. The reaction mixture was cooled to room temperature, solvent evaporated and the residues partitioned between DCM (250 mL) and water (250 mL). The aqueous phase was re-extracted with DCM (200 mL) and the combined organic phases dried over MgSO₄ and evaporated to a dark brown gum which was taken up in DCM and purified on silica, eluting with a gradient of 30 – 50% Ethyl Acetate / iso-hexane then 50% Ethyl Acetate / iso-hexane. Fractions containing product were combined and evaporated to a yellow solid, which was heated at reflux in iso-hexane (50 mL) for 15 minutes and allowed to cool to room temperature overnight. The resulting solid was filtered and dried to give the title compound as a pale yellow solid (1.02 g, 41%)

¹H NMR (400.132 MHz, CDCl₃) δ 0.85 (d, 6H), 2.03 (m, 1H), 2.65 (m, 2H), 3.23 (s, 3H), 3.45 (d, 2H), 3.69 (m, 2H), 7.89 (s, 1H); MS m/z 269 [M+H]⁺.

Intermediate 85:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methylpropyl)amino]-N-methyl-propanamide
5-Bromo-2,4-dichloropyrimidine (Aldrich; 2.82 g, 12.37 mmol), N-methyl-3-(2-methylpropylamino)propanamide (Intermediate 86; 1.78 g; 11.25 mmol), Triethylamine (1.65 mL, 11.81 mmol) and DCM (40 mL) were combined and stirred over the weekend at room temperature. The reaction mixture was washed saturated aqueous sodium bicarbonate solution and gravity filtered through a PTFE cup and solvent evaporated. The residue was dissolved in DCM and passed through a silica column eluting with a gradient of 30 – 50% Ethyl Acetate / iso-hexane over 10 column volumes then 50% Ethyl Acetate / iso-hexane. Fractions containing product combined and evaporated to give the title compound as a white solid. (3.26 g, 83%)

¹H NMR (400.132 MHz, CDCl₃) δ 0.84 (d, 6H), 1.98 (m, 1H), 2.44 (m, 2H), 2.75 (d, 3H), 3.58 (m, 2H), 3.91 (m, 2H), 5.57 (s, 1H), 8.11 (s, 1H); MS m/z 351 [M+H]⁺.

Intermediate 86:

N-methyl-3-(2-methylpropylamino)propanamide

N-methylacrylamide (ABCR; 1 g, 11.75 mmol) was dissolved in EtOH (5 mL). Isobutylamine (Aldrich; 2.33 mL, 23.5 mmol) was added and stirred at ambient temperature

in a stoppered flask over the weekend. The reaction was then transferred to a microwave reactor vessel and heated in a microwave for 10 minutes at 140 °C. Solvents were evaporated *in vacuo* to give the title compound as a colourless liquid. (1.78 g, 96%)

¹H NMR (400.132 MHz, CDCl₃) δ 0.93 (d, 6H), 1.74 (m, 1H), 2.35 (m, 2H), 2.43 (d, 2H),
5 2.78 (d, 3H), 2.85 (m, 2H), 7.88 (s, 1H)

10

Intermediate 87:

2-butan-2-yl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-butan-2-yl-amino]-N-methyl-propanamide (Intermediate 88; 559 mg, 1.60 mmol) in anhydrous 1,4-dioxane (15 mL) was
15 added Caesium Carbonate (1.04 g, 3.19 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) and XANTPHOS (88 mg, 0.152 mmol). The reaction was heated to 100°C and stirred under nitrogen for 18 hrs. The reaction mixture was cooled and diluted to ~40 ml with DCM. The reaction mixture was filtered to remove insoluble material, washing filter
20 cake through with DCM. The filtrate was evaporated to give a brown gum which was purified by flash chromatography on silica (40g cartridge; ISCO companion) eluting with a 25-75% gradient of ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a waxy off white solid which was trituration with hot iso-hexane afforded, on cooling, and collection by suction filtration the title compound as a pale yellow solid (121
25 mg, 28%)

¹H NMR (400.132 MHz, DMSO-D₆) δ 0.83 (t, 3H), 1.16 (d, 3H), 1.57 (m, 2H), 2.65 (m, 2H), 3.18 (s, 3H), 3.49 - 3.66 (m, 2H), 4.57 (m, 1H), 8.12 (s, 1H); MS m/z 269 [M+H]⁺.

Intermediate 88:

30 **3-[(5-bromo-2-chloro-pyrimidin-4-yl)-butan-2-yl-amino]-N-methyl-propanamide**

To a solution of 3-(butan-2-ylamino)-N-methyl-propanamide (Intermediate 89; 563 mg, 3.56 mmol) in DCM (7 mL) was added triethylamine (550 μ l, 3.94 mmol) and, as a solid, 5-bromo-2,4-dichloropyrimidine (Aldrich; 890 mg, 3.90 mmol). The reaction was stirred at ambient temperature overnight.

5 Saturated aqueous Sodium Bicarbonate solution (10 mL) was added and the mixture shaken. The organic phase was collected by gravity elution through a PTFE filter cup. The DCM solution was injected directly onto 40g Si cartridge and eluted with a 25-75% gradient of ethyl acetate in hexane. Product containing fractions were combined and evaporated to afford the title compound as a colourless crystalline solid (565 mg; 45%)

10 ^1H NMR (400.132 MHz, CDCl_3) δ 0.83 (t, 3H), 1.28 (d, 3H), 1.58 (m, 1H), 1.72 (m, 1H), 2.44 (m, 2H), 2.83 (d, 3H), 3.64 (m, 1H), 3.85 (m, 1H), 4.58 (m, 1H), 5.78 (m, 1H), 8.23 (s, 1H); MS m/z 351 $[\text{M}+\text{H}]^+$.

Intermediate 89:

15 3-(butan-2-ylamino)-N-methyl-propanamide

A mixture of N-methylacrylamide (ABCR; 500 mg, 5.87 mmol), sec-butylamine (Aldrich; 530 mL, 5.22 mmol) and ethanol (4 mL) was heated in a microwave to 140°C for 45 minutes and then at 150°C for 30 minutes. The reaction mixture was cooled and poured onto an SCX-2 cartridge (5g) and cartridge washed through with methanol (~50 mL). Products were then
20 eluted with 2M ammonia in methanol (~50 mL) and evaporated to afford the title compound as a straw coloured oil (563 mg; 61%)

^1H NMR (400.132 MHz, CDCl_3) δ 0.92 (t, 3H), 1.06 (d, 3H), 1.31 - 1.53 (m, 2H), 2.34 (m, 2H), 2.57 (m, 1H), 2.78 - 2.94 (m, 5H), 7.77 (s, 1H)

25 Intermediate 90:

10-chloro-2-cyclobutyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclobutyl-amino]-N-methyl-propanamide (Intermediate 91; 600 mg, 1.73 mmol) in anhydrous 1,4-dioxane (15 mL) was added Caesium Carbonate (1.1 g, 3.38 mmol). Nitrogen was bubbled through the reaction
30 mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone)dipalladium(0) (99

mg, 0.11 mmol) and XANTPHOS (95 mg, 0.16 mmol). The reaction was heated to 100°C and stirred under nitrogen overnight

The reaction mixture was cooled and diluted to ~40 ml with DCM, filtered to remove insoluble material, washing filter cake through with DCM and evaporated to give a
5 brown/green solid which was purified by flash chromatography on silica (120g cartridge; ISCO companion) eluting with a 25-100% gradient of ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a waxy off white solid which was trituration with warm iso-hexane which afforded, on cooling and collection by suction filtration the title compound as a pale yellow solid (216 mg, 47%)

10 ¹H NMR (400.132 MHz, DMSO-D₆) δ 1.68 (m, 2H), 2.09 (m, 2H), 2.21 (m, 2H), 2.63 (m, 2H), 3.19 (s, 3H), 3.69 (m, 2H), 4.43 (m, 1H), 8.19 (s, 1H); MS m/z 267.4 [M+H]⁺.

Intermediate 91:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclobutyl-amino]-N-methyl-propanamide

15 Using 3-(cyclobutylamino)-N-methyl-propanamide - Intermediate 92 and analogous conditions to Intermediate 88 the title compound was obtained as a white solid (609 mg)

¹H NMR (400.132 MHz, CDCl₃) δ 1.62 - 1.79 (m, 2H), 2.16 - 2.34 (m, 4H), 2.45 (m, 2H), 2.81 (d, 3H), 3.95 (m, 2H), 4.72 (m, 1H), 5.72 (m, 1H), 8.24 (s, 1H)

Intermediate 92:

3-(cyclobutylamino)-N-methyl-propanamide

Using cyclobutanamine - Aldrich and analogous conditions to Intermediate 89 the title compound was obtained as a pale yellow oil (541 mg)

25 ¹H NMR (400.132 MHz, CDCl₃) δ 1.64 - 1.75 (m, 4H), 2.23 (m, 2H), 2.33 (m, 2H), 2.77 - 2.81 (m, 5H), 3.26 (m, 1H), 7.32 (m, 1H)

Intermediate 93:

10-chloro-2-(cyclopropylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a partial solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(cyclopropylmethyl)amino]-N-methyl-propanamide (Intermediate 94; 426 mg, 1.18 mmol) in anhydrous 1,4-dioxane (15 mL) was added Caesium Carbonate (790 mg, 2.42 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of

5 Tris(dibenzylideneacetone)dipalladium(0) (69 mg, 0.075 mmol) and XANTPHOS (62 mg, 0.107 mmol). The reaction was heated to 100°C and stirred under nitrogen for 18 hrs.

The reaction mixture was cooled and diluted to ~40 ml with DCM, filtered to remove insoluble material, washing the filter cake through with DCM, and evaporated to give a brown gum which was purified by flash chromatography on silica (40g cartridge; ISCO

10 companion) eluting with a 25-75% gradient of ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a crystalline yellow translucent solid.

Trituration with hot iso-hexane afforded, on cooling, and collection by suction filtration the title compound as a pale yellow solid (165 mg, 50%)

¹H NMR (400.132 MHz, DMSO-D₆) δ 0.00 (m, 2H), 0.33 (m, 2H), 0.59 (m, 1H), 1.44 (q, 15 2H), 2.60 (m, 2H), 3.11 (s, 3H), 3.55 (m, 2H), 3.68 (m, 2H), 8.05 (s, 1H)
MS m/z 281.4 [M+H]⁺.

Intermediate 94:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(cyclopropylmethyl)amino]-N-methyl-
20 **propanamide**

Using 3-(cyclopropylmethylamino)-N-methyl-propanamide- Intermediate 95 and analogous conditions to Intermediate 88 the title compound was obtained as a white solid (431 mg)

¹H NMR (400.132 MHz, CDCl₃) δ 0.35 (m, 2H), 0.60 (m, 2H), 1.14 (m, 1H), 2.57 (m, 2H), 2.84 (d, 3H), 3.66 (d, 2H), 4.03 (m, 2H), 5.79 (m, 1H), 8.21 (s, 1H); MS m/z 349.0 [M+H]⁺.

25

Intermediate 95:

3-(cyclopropylmethylamino)-N-methyl-propanamide

Using 2-Cyclopropylethanamine- Aldrich and analogous conditions to Intermediate 89 the title compound was obtained as a pale yellow oil (590 mg)

¹H NMR (400.132 MHz, CDCl₃) δ 0.13 (m, 3H), 0.51 (m, 2H), 0.94 (m, 1H), 2.36 (m, 2H), 2.49 (d, 2H), 2.81 (d, 3H), 2.90 (m, 2H), 7.59 (s, 1H).

Intermediate 96:

5 **10-chloro-2-[(2,4-dimethoxyphenyl)methyl]-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one**

To a solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-[(3,5-dimethoxyphenyl)methyl]amino]-N-methyl-propanamide (Intermediate 97; 2.1 g, 4.73 mmol) in 1,4-dioxane (50 mL) was added Caesium Carbonate (3.4 g, 10.44 mmol) and the
10 reaction mixture sparged with argon for 20 minutes.
Tris(dibenzylideneacetone)dipalladium(0) (260 mg, 0.28 mmol) and XANTPHOS (248 mg, 0.43 mmol) were added and reaction mixture heated to 100°C and left to stir under nitrogen overnight.

The reaction mixture was cooled and diluted to ~100 ml with DCM., filtered to remove
15 insoluble material, washing filter cake through with DCM and evaporated to give a dark yellow oil with some solid which was taken up in DCM (~20 ml) and insoluble material removed by filtration. The filtrate was purified by flash chromatography on silica (120g cartridge) eluting with a rising gradient of 25-100% ethyl acetate in hexane. Product containing fractions were combined and evaporated to give the title compound as a pale
20 yellow solid (690 mg)

¹H NMR (400.132 MHz, DMSO-D₆) δ 2.71 (m, 2H), 3.20 (s, 3H), 3.63 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 4.68 (s, 2H), 6.48 (m, 1H), 6.59 (d, 1H), 7.06 (d, 1H), 8.17 (s, 1H); MS m/z 363.3 [M+H]⁺.

25 **Intermediate 97:**

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-[(3,5-dimethoxyphenyl)methyl]amino]-N-methyl-propanamide

3-[(3,5-dimethoxyphenyl)methylamino]-N-methyl-propanamide (Intermediate 98; 1 g, 3.96 mmol) was dissolved in DCM (10 mL) and triethylamine (0.68 mL, 4.36 mmol). 5-bromo-
30 2,4-dichloropyrimidine (Aldrich; 993 mg, 4.36 mmol) was added and the mixture stirred at room temperature for 18 hours. The mixture was diluted with DCM and washed with water,

brine, dried (MgSO_4), filtered and evaporated to give a yellow gum which was purified on a 40g ISCO companion eluting with 50-70% ethyl acetate in iso-hexane to give the title compound as a white solid (461mg, 26%).

^1H NMR (400.13MHz; DMSO-d_6) δ 2.5 (m, 2H) under DMSO, 2.55 (d, 3H), 3.72 (s, 6H), 3.8 (t, 2H), 4.85 (s, 2H), 6.41 (s, 3H), 7.84 (bm, 1H), 8.38 (s, 1H); MS m/z 443/445 $[\text{M}+\text{H}]^+$.

Intermediate 98:

3-[(3,5-dimethoxyphenyl)methylamino]-N-methyl-propanamide

10 N-methylacrylamide (ABCR; 500mg, 5.87 mmol) and 3,5-dimethoxybenzylamine (Aldrich; 0.98 mL, 6.46 mmol) were dissolved in ethanol (4 mL) and heated in a microwave at 140°C for 45 minutes. The mixture was poured onto a 20g SCX-2 column, washed with methanol and eluted with 3.5N NH_3 in methanol. The product fractions were evaporated to the title compound as a yellow oil (1.3 g, 88%).

15 ^1H NMR (CDCl_3) 2.36 (t, 2H), 2.78 (d, 3H), 2.88 (t, 2H), 3.72 (s, 2H), 3.79 (s, 6H), 6.36 (m, 1H), 6.45 (m, 2H), 7.31 (bs, 1H); MS m/z 253 $[\text{M}+\text{H}]^+$.

Intermediate 99:

2-benzyl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

20 To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 6.5 mg, 0.16 mmol) in DMA (0.5 mL) was added a solution of 10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 32 mg, 0.15 mmol) in DMA (1.0 mL). The reaction mixture was allowed to stir, under nitrogen, in an ice bath for 15 minutes prior to addition of Benzyl bromide (Aldrich; 20 μL , 0.17 mmol). The reaction mixture was stirred on an ice bath for 15 minutes and then at ambient temperature for 3 hrs. A further addition of Sodium hydride (2 mg) was made and stirring continued for 6 hrs. Saturated ammonium chloride (0.5 mL) was added and the reaction mixture poured directly onto an SCX-3 cartridge (2g). The cartridge was washed with methanol (~30 mL) before eluting products with 2M ammonia in methanol (~30 mL). Product containing fractions were
30 evaporated to dryness to give a colourless gum, which was combined with the cartridge methanol pre-wash and this solution evaporated to dryness. The resultant material was

partitioned between DCM (10 mL) and water (10 mL). The organic phase was collected by gravity elution through a PTFE filter cup and evaporated to give the title compound as a pale yellow opaque gum (46 mg, 89%)

¹H NMR (400.132 MHz, DMSO-D₆) δ 2.71 (m, 2H), 3.22 (s, 3H), 3.66 (m, 2H), 4.82 (s, 2H), 7.27 - 7.38 (m, 5H), 8.21 (s, 1H); MS m/z 303.3 [M+H]⁺.

Intermediate 100:

10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-[(3,5-dimethoxyphenyl)methyl]amino]-N-methyl-propanamide (Intermediate 97; 83 mg, 0.23 mmol) was taken up in DCM (1 mL) and TFA (1 mL) and stirred for 30 minutes. A further addition of TFA (1 mL) was made and stirring continued overnight. The reaction mixture was diluted with DCM (25 mL) and poured directly onto a SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~50 mL). Products were eluted with 2M ammonia in methanol and ammoniacal eluant evaporated to dryness to afford the title compound as an off white solid (34 mg, 70%)

¹H NMR (400.132 MHz, DMSO-D₆) δ 2.66 (m, 2H), 3.21 (s, 3H), 3.52 (m, 2H), 8.14 (m, 1H), 8.28 (m, 1H); MS m/z 213.4 [M+H]⁺.

Intermediate 101:

10-chloro-6-methyl-2-[(2-methyl-1,3-thiazol-4-yl)methyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 13 mg, 0.38 mmol) in DMA (0.5 mL) was added a solution of 10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 63 mg, 0.30 mmol) in DMA (1 mL). The reaction mixture was allowed to stir, under nitrogen, in ice bath for 10 minutes prior to addition of 4-chloromethyl-2-methylthiazole (ASDI; 75 mg, 0.51 mmol). The reaction mixture was stirred in an ice bath for 20 minutes and then warmed to ambient temperature over 1 hour.

The reaction mixture was quenched by careful addition of saturated aqueous ammonium chloride (0.5 mL) and the reaction mixture was partitioned between DCM(10 mL) and water

(10 mL). The organic phase was separated by gravity filtration through a PTFE filter cup and evaporation to dryness to give the title compound as a straw coloured gum (61 mg; 63%)

^1H NMR (400.132 MHz, DMSO- D_6) δ 2.64 (s, 3H), 2.74 (m, 2H), 3.21 (s, 3H), 3.78 (m, 2H), 4.82 (m, 2H), 7.31 (m, 1H), 8.20 (s, 1H); MS m/z 324.3 $[\text{M}+\text{H}]^+$.

5 **Intermediate 102:**

10-chloro-2-(cyclobutylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 13 mg, 0.38 mmol) in DMA (0.5 ml) was added a solution of (Intermediate 100; 63 mg, 0.30
10 mmol) in DMA (1 mL). The reaction mixture was allowed to stir, under nitrogen, on an ice bath for 10 minutes prior to addition of Bromomethyl cyclobutane (Aldrich; 40 μl , 0.36 mmol). The reaction mixture was stirred on an ice bath for 20 minutes and then warmed to ambient temperature over 1 hour.

A further addition of Sodium hydride (2 mg) and Bromomethyl cyclobutane (20 μl , 0.18
15 mmol) was made and the reaction stirred for a further hour

The reaction mixture was quenched by careful addition of saturated aqueous ammonium chloride (0.5 ml) and the reaction mixture partitioned between DCM(10 mL) and water (10 mL). The organic phase was separated by gravity filtration through a PTFE filter cup and evaporation to dryness gave the title compound as a pale yellow gum (71 mg, 84%)

20 ^1H NMR (400.132 MHz, DMSO- D_6) δ 1.71 - 1.86 (m, 4H), 2.01 (m, 2H), 2.66 (m, 3H), 3.17 (s, 3H), 3.63 (d, 2H), 3.70 (m, 2H), 8.12 (s, 1H); MS m/z 281.3 $[\text{M}+\text{H}]^+$.

Intermediate 103:

10-chloro-6-methyl-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

25 To a solution of 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 1.185 g, 4.31 mmol) in DMA (100 mL) at 0°C, was added methyl iodide (282 μL , 4.53 mmol) followed by sodium hydride (60% oil dispersion, 182 mg, 4.53 mmol) in one portion. The mixture was stirred at 0°C for 4hrs and ice was then added, resulting in a brown sticky precipitate, which was filtered and washed with water. A white solid
30 precipitated from the filtrate, which was filtered off and triturated with diethylether to give the title compound (494mg).

The sticky brown precipitate was dissolved in DCM and suction columned in 2- 5% methanol/dichloromethane to give a yellow oil.

The aqueous filtrate was extracted with DCM and methanol, washed with saturated aqueous brine and evaporated to give a yellow oil which was purified by suction columned as above to
5 give a yellow oil.

Both yellow oils were combined and triturated with diethylether to give the title compound as a white solid (401mg)

^1H NMR (399.9 MHz, DMSO-D6) : δ_{H} : 2.89 (m, 2H), 3.29 (s, 3H), 4.06 (m, 2H), 7.30 (m, 3H), 7.42 (m, 2H), 8.38 (s, 1H); MS m/z 289 $[\text{M}+\text{H}]^+$.

10

Intermediate 104:

10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Methyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-phenyl-amino]propanoate (Intermediate 105; 21.855 g, 64.9 mmol), iron powder (5.44 g, 97.35 mmol) and acetic acid (200 mL) were
15 heated at 80°C for 2hrs and then stirred at room temperature overnight..

The reaction mixture was filtered through celite and the filter cake washed with dichloromethane. The solvent was evaporated and the resultant material was pre-absorbed onto silica with methanol/dichloromethane and then purified by vacuum filtration chromatography eluting with dichloromethane,. diethylether, . ethylacetate and finally. 20%
20 methanol/dichloromethane. Product containing fractions were combined and evaporated To give a brown solid which was triturated with diethylether and then methanol and small % of dichloromethane to give the title compound as an off white solid (2.29 g)

The silica from the filtration column was suspended in 20% methanol/dichloromethane and filtered and washed with a further portion of 20% methanol/dichloromethane. Evaporation
25 afforded a yellow solid which was triturated with methanol and small % of dichloromethane to give the title compound as an off white solid (1.35g)

^1H NMR (399.9 MHz, DMSO-D6) : δ_{H} : 2.89 (m, 2H), 3.98 (m, 2H), 7.32 (m, 3H), 7.42 (m, 2H), 8.01 (s, 1H), 9.90 (s, 1H); MS m/z 275 $[\text{M}+\text{H}]^+$.

Intermediate 105:

Methyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-phenyl-amino]propanoate

To a solution of; 3,4-dichloro-5-nitropyrimidine (Aldrich; 12.59 g, 64.9 mmol) in anhydrous THF (300 mL) at room temperature under a nitrogen atmosphere was added dropwise over 6hrs a solution of Methyl 3-anilinopropanoate (Intermediate 106; 12.795 g, 71.39 mmol) and Hunigs base (13.54 mL, 77.88 mmol) in anhydrous THF (300 mL) The reaction mixture was stirred over night at room temperature.

The solvent was evaporated at 40°C and the residue dissolved in DCM and washed with water and saturated brine. The resulting organic phase was dried over anhydrous sodium sulphate then pre-absorbed onto silica and purified by vacuum filtration chromatography eluting with dichloromethane. Evaporation of product containing fractions afforded the title compound as a dark red oil (24.25g, >100%)

MS m/z 275 [M+H]⁺. Retention time 2.32mins

Intermediate 106:**15 Methyl 3-anilinopropanoate**

Aniline (Acros; 59.89 mL, 657 mmol) , Methylacrylate (Acros; 62.54 mL, 690 mmol) and Glacial acetic acid (15 mL) and were combined and heated at 79°C overnight

The reaction mixture was cooled to room temperature and added to ice water, a solid precipitated and was filtered off and dissolved in dichloromethane aliquot taken and pre-absorbed onto silica and purified by vacuum filtration chromatography eluting with DCM. Product containing fractions were combined and evaporated to give the title compound as a pale yellow sticky solid (14.33 g, 12%)

¹H NMR (399.9 MHz, DMSO-D₆) : δ_H : 2.57 (tr, 2H), 3.29 (tr, 2H), 3.61 (s, 3H), 5.57 (tr, 1H), 6.55 (m, 3H), 7.08 (m, 1H); MS m/z 180 [M+H]⁺.

25

Intermediate 107:**4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide**

3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)-4-nitro-benzamide (2.29 g, 7.67 mmol), iron powder (2.45 g, 43.79 mmol) and ammonium chloride (781 mg, 14.60 mmol) were heated in ethanol (50 mL) and water (18 mL) at reflux for one hour. A few drops of acetic acid were added and heating continued for a further hour. The reaction mixture was cooled,

filtered and the filtrate concentrated. This residue was partitioned between saturated NaHCO_3 (aq.) and DCM. The organic phase was washed with brine, dried with MgSO_4 and concentrated. Column chromatography gave the title compound as an orange crystalline solid. (850mg, 39%)

5 ^1H NMR (399.9 MHz, DMSO-d_6) δ 0.86 (6H, s), 2.16 (2H, s), 2.26 (6H, s), 3.14 (2H, d), 5.83 (2H, s), 6.80 (1H, d), 7.52 - 7.54 (1H, m), 7.72 (1H, d), 8.15 (1H, t); MS m/z 286.16 $[\text{M}+\text{H}]^+$.

Intermediate 108:

3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)-4-nitro-benzamide

10 3-chloro-4-nitro-benzoyl chloride (Intermediate 54; 2.2 g, 10.00 mmol) was dissolved in DCM (20 mL) and N,N-diisopropylethylamine (2.095 mL, 12.00 mmol) added. The mixture was cooled in an ice/water bath and N,N,2,2-tetramethyl-1,3-propanediamine (3.652 mL, 10.00 mmol) in DCM (10 mL) added dropwise. The mixture was allowed to warm to room temperature and stirred for 0.5h. The mixture was washed with brine, 2N NaOH (aq.), dried
15 (MgSO_4) and concentrated. Column chromatography of the residue (2% MeOH/DCM) gave the title compound as a yellow oil 17171/2/1 (2.29g, 77%).

^1H NMR (399.9 MHz, DMSO-d_6) δ 0.89 (6H, s), 2.17 (2H, s), 2.26 (6H, s), 3.21 (2H, d), 7.96 - 7.98 (1H, m), 8.13 (1H, d), 8.18 (1H, d), 8.73 (1H, t); MS m/z 314.21 $[\text{M}+\text{H}]^+$.

Intermediate 109:

10-chloro-2-(2-methoxyethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methoxyethyl)amino]-N-methyl-propanamide (Intermediate 110; 1.12 g, 3.185 mmol) was suspended in dioxane (70 mL), Caesium
25 Carbonate (2.08 g, 6.37 mmol) added and the mixture bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (175 mg, 0.151 mmol) and XANTPHOS (166 mg, 0.287 mmol) were added and the mixture heated to 100 °C for 20 hrs. A further 0.06 equivalent of Tris(dibenzylideneacetone)dipalladium(0) and 0.09 equivalent of XANTPHOS were added and heating continued for a further 2 hrs. The reaction mixture was cooled to room
30 temperature filtered and the filter cake washed with DCM. The filtrate was evaporated and dissolved in DCM and purified on silica eluting with a gradient of 40 – 55% Ethyl Acetate /

iso-hexane then 55% Ethyl Acetate / iso-hexane and finally 70% Ethyl Acetate / iso-hexane. Fractions containing product were combined and evaporated to a yellow solid. Which was purified by base modified reverse phase HPLC to yield the title compound as a white solid (157 mg, 18%)

5 ¹H NMR (399.902 MHz, CDCl₃) δ2.73 (m, 2H), 3.29 (s, 3H), 3.35 (s, 3H), 3.68 (m, 2H), 3.84 (m, 2H), 3.90 (m, 2H), 7.95 (s, 1H); MS m/z 271 [M+H]⁺.

Intermediate 110:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methoxyethyl)amino]-N-methyl-propanamide

10 3-(2-methoxyethylamino)-N-methyl-propanamide (Intermediate 111; 608 mg, 3.79 mmol) 5-Bromo-2,4-dichloropyrimidine (Aldrich; 950 mg, 4.17 mmol), Triethylamine (555 µL, 3.98 mmol), and DCM (5 mL) were combined and stirred over the weekend at room temperature. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution then gravity filtered through a PTFE cup and organic solvents evaporated. The residue was

15 dissolved in DCM and passed through a silica column, eluting with 50% Ethyl Acetate / iso-hexane then 60% Ethyl Acetate / iso-hexane and finally 70% Ethyl Acetate / iso-hexane. Fractions containing product combined and evaporated to a colourless liquid which crystallised under high vacuum to give the title compound as a white solid (1.12 g, 84%)

¹H NMR (399.902 MHz, CDCl₃) δ2.57 (m, 2H), 2.82 (d, 3H), 3.35 (s, 3H), 3.63 (m, 2H), 3.95
20 (m, 2H), 4.01 (m, 2H), 5.80 (s, 1H), 8.20 (s, 1H); MS m/z 353 [M+H]⁺.

Intermediate 111:

3-(2-methoxyethylamino)-N-methyl-propanamide

N-Methylacrylamide (ABCR; 500 mg, 5.87 mmol), 2-Methoxyethylamine (Aldrich; 441 mg, 5.87 mmol), and EtOH (2 mL) were combined and heated in a microwave at 140 °C for 40
25 minutes. The reaction mixture was cooled and added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) then the product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated *in vacuo* to give the the title compound as a clear oil (608 mg, 65%)

¹H NMR (399.902 MHz, CDCl₃) δ2.35 (m, 2H), 2.79 (m, 5H), 2.88 (m, 2H), 3.37 (s, 3H), 3.49 (m, 2H), 7.55 (s, 1H)

Intermediate 112:

10-chloro-2-(1-methoxypropan-2-yl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 318 mg, 1.37 mmol), 2-Amino-1-methoxypropane (152 µl, 1.44 mmol), Triethylamine (382 µl, 2.74 mmol), Titanium Tetra-ethoxide (29 µl, 0.137 mmol) and DCM (5 mL) were combined and stirred at room temperature for 1hr, heated to 40 °C for 3hrs, cooled to room temperature, washed with water and gravity filtered through a PTFE . The organic solution was purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 10 – 50% Ethyl Acetate / iso-hexane. Product containing fractions were combined and evaporated to give the title compound as a clear gum (54 mg, 18%).

¹H NMR (399.902 MHz, CDCl₃) δ1.25 (m, 3H), 2.69 (m, 2H), 3.29 (s, 3H), 3.34 (s, 3H), 3.53 (m, 2H), 3.75 (m, 2H), 4.99 (m, 1H), 7.94 (s, 1H); MS m/z 285 [M+H]⁺.

Intermediate 113:

N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide

5-Methylamino-2,4-Dichloropyrimidine (800 mg, 4.5 mmol) was dissolved in THF (18 mL) and triethylamine (1.88 mL, 13.5 mmol) was added. A solution of 3-chloropropionyl chloride (644 µl, 6.55 mmol) in DCM (2 mL) was added dropwise giving an instantaneous precipitate. The reaction was stirred at room temperature for 30 minutes. The precipitate was filtered off and the filtrate evaporated and the resultant material dissolved in DCM, washed with water, saturated aqueous sodium bicarbonate solution and then gravity filtered through a PTFE cup. The organic solvent was evaporated to give the crude product as a yellow gum which was dissolved in THF (18 mL). Triethylamine (1.8 mL) was added and a further portion of 3-chloropropionyl chloride (215 µl, 2.25 mmol). The reaction was stirred at room temp for 1 hr then worked up as previously to give the title compound as a brown gum (624 mg, 60%) MS m/z 232 [M+H]⁺. Retention Time 1.39mins

Intermediate 114:**5-Methylamino-2,4-Dichloropyrimidine**

To the methylamino-5-uracil (Intermediate 115; 6.81 g, 48.25 mmol) was added
5 triethylamine (13.45 mL, 96.51 mmol) followed by phosphorus oxychloride (67.5 mL, 723
mmol) very slowly. The reaction was heated to reflux for 3 hrs cooled to room temperature
and POCl₃ evaporated and the residues azeotroped with toluene. The residue was diluted
with toluene (100 mL). Ice (200 mL) was added and the mixture stirred for 5 minutes. The
mixture was then neutralised to pH8 with saturated aqueous sodium bicarbonate solution and
10 extracted with toluene (300 mL). The aqueous phase was re-extracted with DCM (5 x 300
mL). The toluene solution was washed with water (100 mL), dried (MgSO₄) and evaporated.
The combined DCM solutions were also washed with water (300 mL), dried (MgSO₄),
combined with the toluene solution and evaporated to a brown gum which was dissolved in
DCM with a little MeOH and chromatographed on silica eluting with a gradient of 0 – 10%
15 Ethyl Acetate / iso-hexane followed by 10% Ethyl Acetate / iso-hexane then 15% Ethyl
Acetate / iso-hexane. Fractions containing impure product were re-chromatographed eluting
with 10% Ethyl Acetate / iso-hexane until the impurity had come off then 15% Ethyl Acetate
/ iso-hexane. Product containing fractions were evaporated to give the title compound as a
cream solid (2.58 g, 30%)
20 ¹H NMR (399.902 MHz, CDCl₃) δ2.98 (d, 3H), 4.35 (s, 1H), 7.90 (s, 1H); MS m/z 175 [M-
H]⁺.

25

Intermediate 115:**Methylamino-5-uracil**

5 Bromo Uracil (Aldrich; 49.66 g, 260 mmol) and 25% Methylamine in Ethanol (Aldrich;
200 mL) were combined and heated in an autoclave at 160 °C for 6 hours.
30 The solution was cooled and evaporated and the residue washed with water, acetone and
diethylether to give the title compound as a white solid (28 g, 70%)

Intermediate 116:**10-chloro-2-(3-furylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-****5 5-one one**

3-Furylmethylamine (Maybridge; 175 mg, 1.8 mmol), N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 347 mg, 1.5 mmol), Triethylamine (420 μ L, 3 mmol), Titanium Tetra-ethoxide (157 μ L, 0.75 mmol) and DCM (5 mL) were combined and stirred at room temp for 1hr, heated at 40 °C overnight then cooled to room temperature. The
10 reaction mixture was washed with water then gravity filtered through a PTFE cup, the aqueous layer containing the titanium emulsion was washed with further DCM (3 x 10 mL) and the combined organic solutiouns gravity filtered through a PTFE cup and solvents evaporated. The residue was dissolved in DCM and purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 10 – 50% Ethyl Acetate /
15 iso-hexane. Product containing fractions were combined and evaporated to give the title compound as a yellow gum (67 mg, 15%)

¹H NMR (399.902 MHz, CDCl₃) δ 2.63 (m, 2H), 3.31 (s, 3H), 3.75 (m, 2H), 4.60 (s, 2H), 6.49 (m, 1H), 7.41 (m, 1H), 7.50 (m, 1H), 8.00 (s, 1H); MS m/z 293 [M+H]⁺.

20 Intermediate 117:**10-chloro-2-cyclopropyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one**

Cyclopropylamine (Aldrich; 150 μ L, 2.18 mmol), N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 337 mg, 1.45 mmol) Triethylamine (404 μ L, 2.9 mmol),
25 Titanium Tetra-ethoxide (152 μ L, 0.725 mmol) and DCM (5 mL) were combined and stirred at room temp for 1hr, heated at 40 °C for 4 hrs then cooled to room temperature. The reaction mixture was washed with water then gravity filtered through a PTFE cup, the aqueous layer containing the titanium emulsion was washed with further DCM (3 x 10 mL) and the combined organic solutiouns gravity filtered through a PTFE cup and solvents evaporated.
30 The residue was dissolved in DCM and purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 10 – 50% Ethyl Acetate / iso-hexane.

Product containing fractions were combined and evaporated to give the title compound as a cream solid (42 mg, 11%)

¹H NMR (399.902 MHz, CDCl₃) δ 0.58 (m, 2H), 0.91 (m, 2H), 2.68 (m, 2H), 2.85 (m, 1H), 3.28 (s, 3H), 3.84 (m, 2H), 8.02 (s, 1H); MS m/z 253 [M+H]⁺.

5

Intermediate 118:**10-chloro-6-methyl-2-(1-methyl-4-piperidyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one**

4-Amino-1-methylpiperidine (Fluorochem; 200 mg, 1.74 mmol), N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 337 mg, 1.45 mmol) Triethylamine (404 μL, 2.9 mmol), Titanium Tetra-ethoxide (152 μL, 0.725 mmol) and DCM (5 mL) were combined and stirred at room temp for 1hr, heated at 40 °C for 3 hrs then cooled to room temperature. The reaction mixture was washed with water then gravity filtered through a PTFE cup, the aqueous layer containing the titanium emulsion was washed with further DCM (3 x 10 mL) and the combined organic solutions gravity filtered through a PTFE cup and solvents evaporated. The residue was dissolved in DCM and purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 0 – 5% 2M ammonia in MeOH / DCM. Product containing fractions were combined and evaporated to give the title compound as a yellow solid (39 mg)

20

Intermediate 119:**4-amino-N-cyclohexyl-3-methoxy-benzamide**

EDAC(7.46 g, 3.90 mmol) was added to a stirred solution of 4-amino-3-methoxy acid (Aldrich; 5 g, 2.9 mmol), cyclohexylamine (Aldrich; 5.13mL, 4.49 mmol) and DMAP (11 g, 9 mmol) in DCM (200 mL) and the reaction mixture was stirred for a 18hrs.under an atmosphere of nitrogen. The mixture was washed with 1M citric acid solution (x3), saturated sodium bicarbonate solution and dried. The solvent was evaporated off and the residue triturated with diethylether to give the title compound as a pink solid (5.3 g, 71%) MS m/z 293 [M+H]⁺.

30

Intermediate 120:

10-chloro-2-cyclopentyl-3,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one.

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-methyl-butanamide (Intermediate 121; 196 mg, 0.52 mmol) was dissolved in 1,4-dioxane (5 mL) and
5 Tris(dibenzylideneacetone)dipalladium(0) 10 mg, 0.02 mmol), XANTPHOS (20 mg, 0.02 mmol) and Caesium Carbonate (247 mg, 0.76 mmol) were added to a microwave reaction vessel which was sealed and irradiated at 150 °C for 30 min. A further addition of Tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.02 mmol) and XANTPHOS (20 mg, 0.02 mmol) was made and the reaction mixture irradiated at 150 °C for 2 hrs.. The cooled
10 reaction mixture was filtered through a pad of celite and the filtrate concentrated down onto silica and purified by flash silica chromatography (companion, 12 g, 0-5% methanol/DCM). Product containing fractions were combined and evaporated to give the title compound as a yellow solid (126 mg, 82%).

¹H NMR (399.902 MHz, CDCl₃) δ 1.34 (d, 3H), 1.44 - 1.95 (m, 8H), 2.63 (dd, 1H), 2.77 (dd, 1H), 3.32 (s, 3H), 3.98 (ddq, 1H), 4.56 (quintet, 1H), 7.94 (s, 1H); MS m/z 295.2 [M+H]⁺.
15

Intermediate 121:**3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-methyl-butanamide**

A stirred solution of 3-(cyclopentylamino)-N-methyl-butanamide (Intermediate 122; 887 mg, 4.80 mmol), 5-bromo-2,4-dichloropyrimidine (1.15 g, 5.04 mmol) and potassium carbonate (1.34 g, 9.60 mmol) in acetone (20 mL) were heated under reflux conditions to 65 °C for 3 days and then at 75 °C for a further 16 hrs.. The solvent was evaporated and the residue taken up in Ethyl Acetate (200 mL) and water (200 mL). The aqueous phase was separated and the organic phase further washed with water (200 mL) and brine (200 mL). The organic phase
25 was evaporated and the residue purified by flash silica chromatography (companion, 40 g, 0-10% MeOH/DCM) followed by base modified preparative HPLC (30-50% gradient) to give the title compound as a yellow solid (117 mg, 6%).

¹H NMR (399.902 MHz, DMSO-d₆) δ 1.29 (d, 3H), 1.36 - 1.51 (m, 2H), 1.65 - 1.93 (m, 6H), 4.03 (quintet, 1H), 4.48 (sextet, 1H), 7.69 (q, 1H), 8.26 (s, 1H), 5 protons obscured in DMSO
30 signal. MS m/z 375.17 [M+H]⁺.

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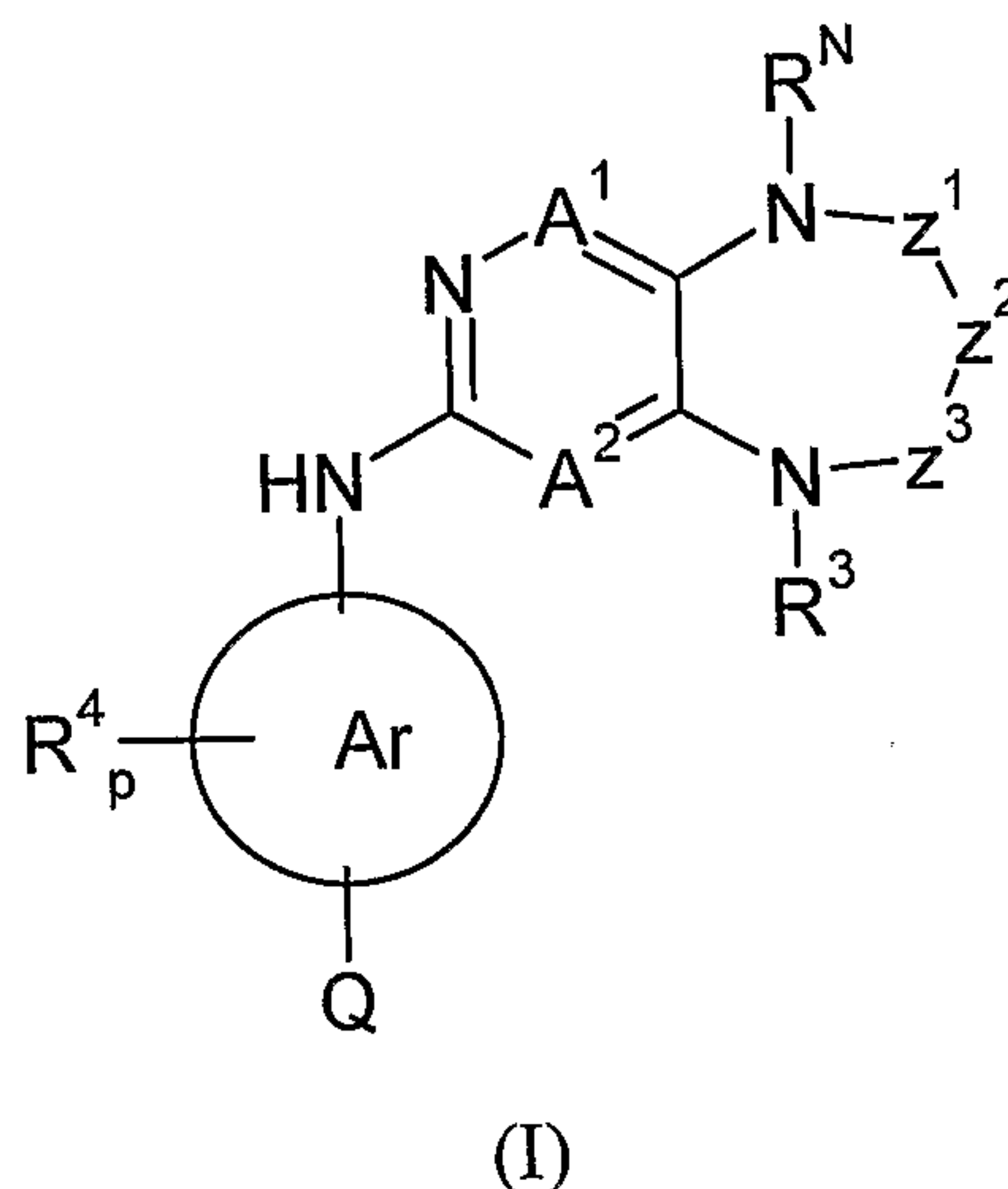
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CLAIMS

1. A compound of formula (I):



wherein

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or an optionally substituted heteroaryl ring comprising 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen or sulphur;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered

heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, $-OH$, $-CN$, $-C=CH$, $-C(=O)NH_2$, $C_{1-3}alkyl$, $C_{1-3}alkylamino$, $C_{1-3}alkylthio$, $C_{1-3}alkyloxy$, $C_{1-3}alkylcarbonyl$, $-CHO$, or $-SO_2Me$

p is 0, 1 or 2;

Q is $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, $-(\text{optionally substituted } C_{1-3}alkyl)_g-NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ or $-(5\text{- or }6\text{-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur})-L_n-R^5_m$;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted $C_{1-6}alkyl$ group, and R^b represents $-L_n-R^5_m$, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted $C_{1-6}alkyl$ group, and R^{b2} represents $-L_n-R^5_m$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted $C_{1-6}alkyl$ group, and R^{b3} represents $-L_n-R^5_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, or R^{a3} and R^{b3} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted $C_{1-6}alkyl$ group, and R^{b4} represents $-L_n-R^5_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted $C_{1-6}alkyl$ group, and R^{b5} represents $-L_n-R^5_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

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R^{a6} represents $-L_n-R^5_m$;

R^{a7} represents $-L_n-R^5_m$;

R^{a8} represents $-L_n-R^5_m$;

R^{a9} represents $-L_n-R^5_m$;

R^{a10} represents $-L_n-R^5_m$;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{7-12} polycycloalkyl group, optionally substituted C_{7-12} polycycloalkenyl group, optionally substituted C_{5-12} spirocycloalkyl group and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatane, optionally substituted oxogranatane and $-NR^8R^9$;

R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group;

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally

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substituted C₆₋₁₄aryl-C₁₋₄alkylsulphonyl, or R⁸ and R⁹ together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

X¹ is O or S;

X² is O, S or H₂;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur; and

A¹, A² each independently represents N or CH;

and wherein

when Z¹ is C=O, Z² is CR^cR^d or NR^e and Z³ is CR¹R²;

R¹, R² each independently represents hydrogen, an optionally substituted C₁₋₆alkyl group or an optionally substituted C₃₋₆cycloalkyl group, or R¹ and R² together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C₁₋₆alkyl group or an optionally substituted C₃₋₆cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C₁₋₆alkyl group or an optionally substituted C₃₋₆cycloalkyl group; or

optionally one of R¹ and R³, or R² and R³, or R¹ and R^c, or R² and R^d, or R¹ and R^e together represent a saturated or unsaturated C₁₋₄alkyl bridge optionally comprising 1 heteroatom;

or when Z² is C=O, Z¹ is CR^{f2}R^{g2} and Z³ is CR¹R²;

R¹, R² each independently represents hydrogen, an optionally substituted C₁₋₆alkyl group or an optionally substituted C₃₋₆cycloalkyl group, or R¹ and R² together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^{f2}, R^{g2} each independently represents hydrogen, an optionally substituted C₁₋₆alkyl group or an optionally substituted C₃₋₆cycloalkyl group, or R^{f2} and R^{g2} together with

the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or optionally one of R^1 and R^3 , or R^2 and R^3 together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

or when Z^3 is $C=O$, Z^2 is $CR^{c3}R^{d3}$ or NR^{e3} and Z^1 is $CR^{f3}R^{g3}$;

R^{c3} , R^{d3} each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^{c3} and R^{d3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^{e3} represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group;

R^{f3} , R^{g3} each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^{f3} and R^{g3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^{c3} and R^{f3} , or R^{d3} and R^{g3} , or R^{e3} and R^{f3} together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom

or when Z^1 is CR^fR^g , Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2 ;

R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group;

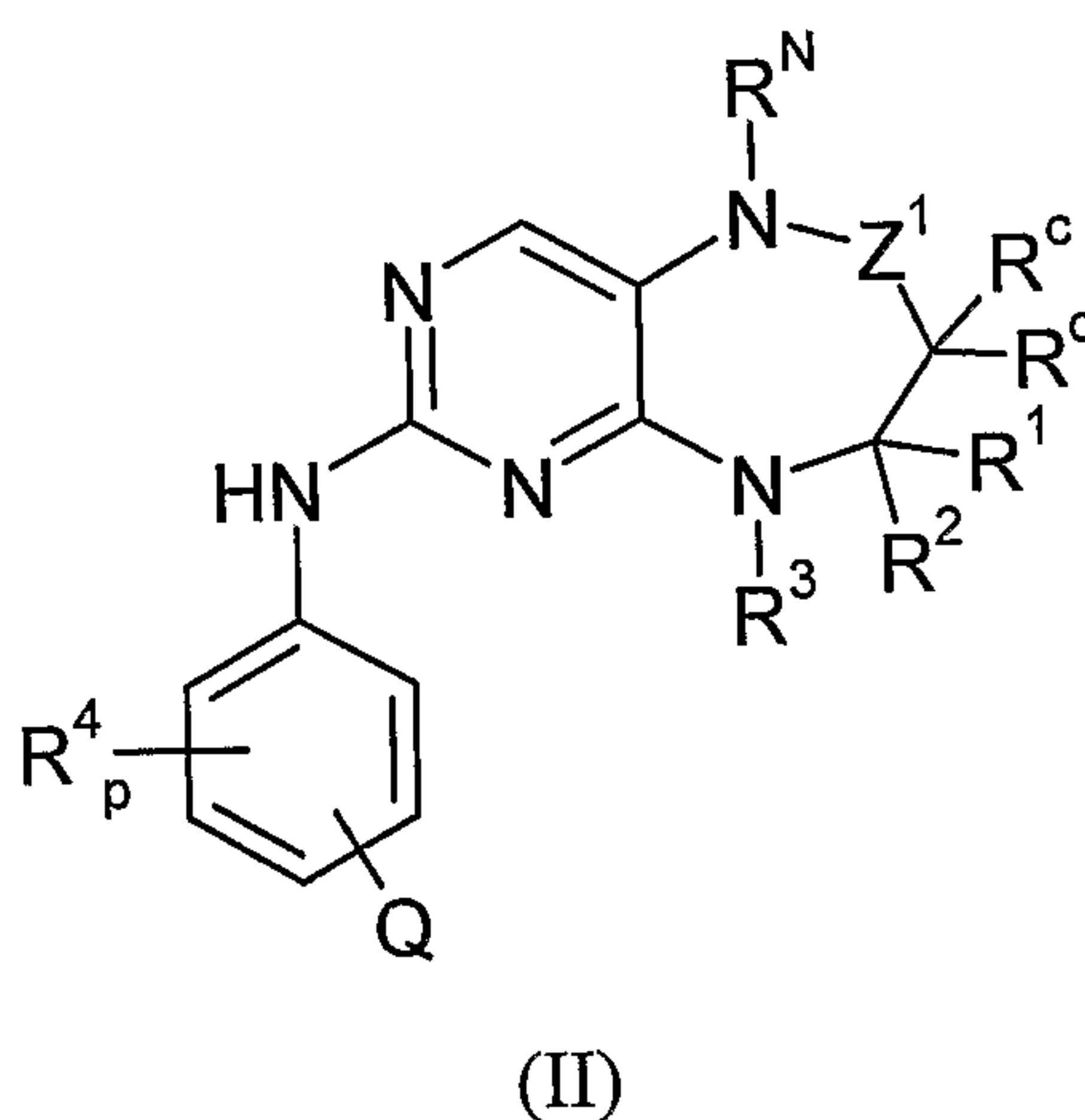
R^f , R^g each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^f and R^g together with the

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carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d , or R^1 and R^{e3} together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom,

or pharmacologically acceptable salts thereof.

2. A compound of formula (II):



wherein

R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an

optionally substituted C₅₋₁₂spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R¹ and R³, or R² and R³, or R¹ and R^c, or R² and R^d together represent a saturated or unsaturated C₁₋₄alkyl bridge optionally comprising 1 heteroatom;

R⁴ each independently represent -CN, hydroxy, -NR⁶R⁷, -NR⁶SO₂R⁷, halogen, an optionally substituted C₁₋₆alkyl group, an optionally substituted C₃₋₇cycloalkyl group, an optionally substituted C₂₋₆alkenyl group, an optionally substituted C₂₋₆alkynyl group, an optionally substituted C₁₋₅alkyloxy group, an optionally substituted C₃₋₆cycloalkyloxy group, an optionally substituted C₂₋₅alkenyloxy group, an optionally substituted C₂₋₅alkynyloxy group, an optionally substituted C₁₋₆alkythio group, an optionally substituted C₁₋₆alkylsulphoxo group or an optionally substituted C₁₋₆alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, -NH₂, -OH, -CN, -C=CH, -C(=O)NH₂, C₁₋₃alkyl, C₁₋₃alkylamino, C₁₋₃alkylthio, C₁₋₃alkyloxy, C₁₋₃alkylcarbonyl, -CHO, or -SO₂Me;

p is 0, 1 or 2;

Q is -C(=X¹)-NR^aR^b, -S(O)₂-NR^{a2}R^{b2}, -(optionally substituted C₁₋₃alkyl)_g-NR^{a3}R^{b3}, -S(O)_k-R^{a8}, -C(=X²)-OR^{a9}, -OR^{a10} or -(5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur)-L_n-R⁵_m;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted C₁₋₆alkyl group, and R^b represents -L_n-R⁵_m, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b2} represents $-L_n-R^5_m$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b3} represents $-L_n-R^5_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, or R^{a3} and R^{b3} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b4} represents $-L_n-R^5_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C_{1-6} alkyl group, and R^{b5} represents $-L_n-R^5_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a6} represents $-L_n-R^5_m$;

R^{a7} represents $-L_n-R^5_m$;

R^{a8} represents $-L_n-R^5_m$;

R^{a9} represents $-L_n-R^5_m$;

R^{a10} represents $-L_n-R^5_m$;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;
n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl,

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optionally substituted sulfoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

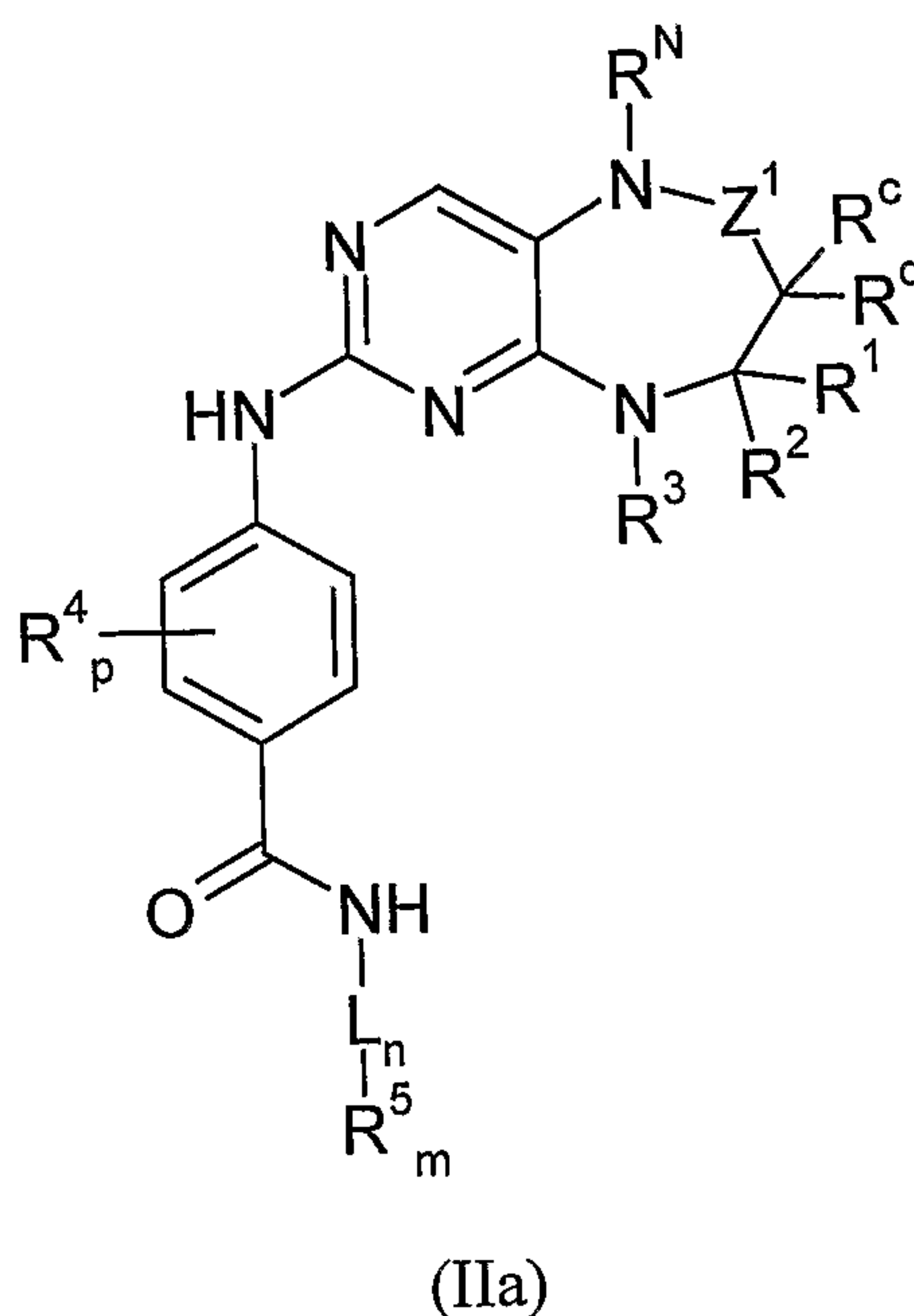
R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group;

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and Z^1 is $C=O$ or CR^fR^g wherein R^f , R^g each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms, or pharmacologically acceptable salts thereof.

3. A compound according to Claim 1 or 2 wherein R^N represents C_{1-3} alkyl.
4. A compound according to any one of Claims 1 to 3 wherein R^N represents methyl or ethyl.
5. A compound according to any one of Claims 1 to 4 wherein Q represents $-C(=X^1)-NR^aR^b$, wherein X^1 is O, or $-CH_2-NR^{a3}R^{b3}$.

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6. A compound of formula (IIa):



wherein

R^1 , R^2 each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally

substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, $-OH$, $-CN$, $-C=CH$, $-C(=O)NH_2$, C_{1-3} alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{1-3} alkyloxy, C_{1-3} alkylcarbonyl, $-CHO$, or $-SO_2Me$;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted

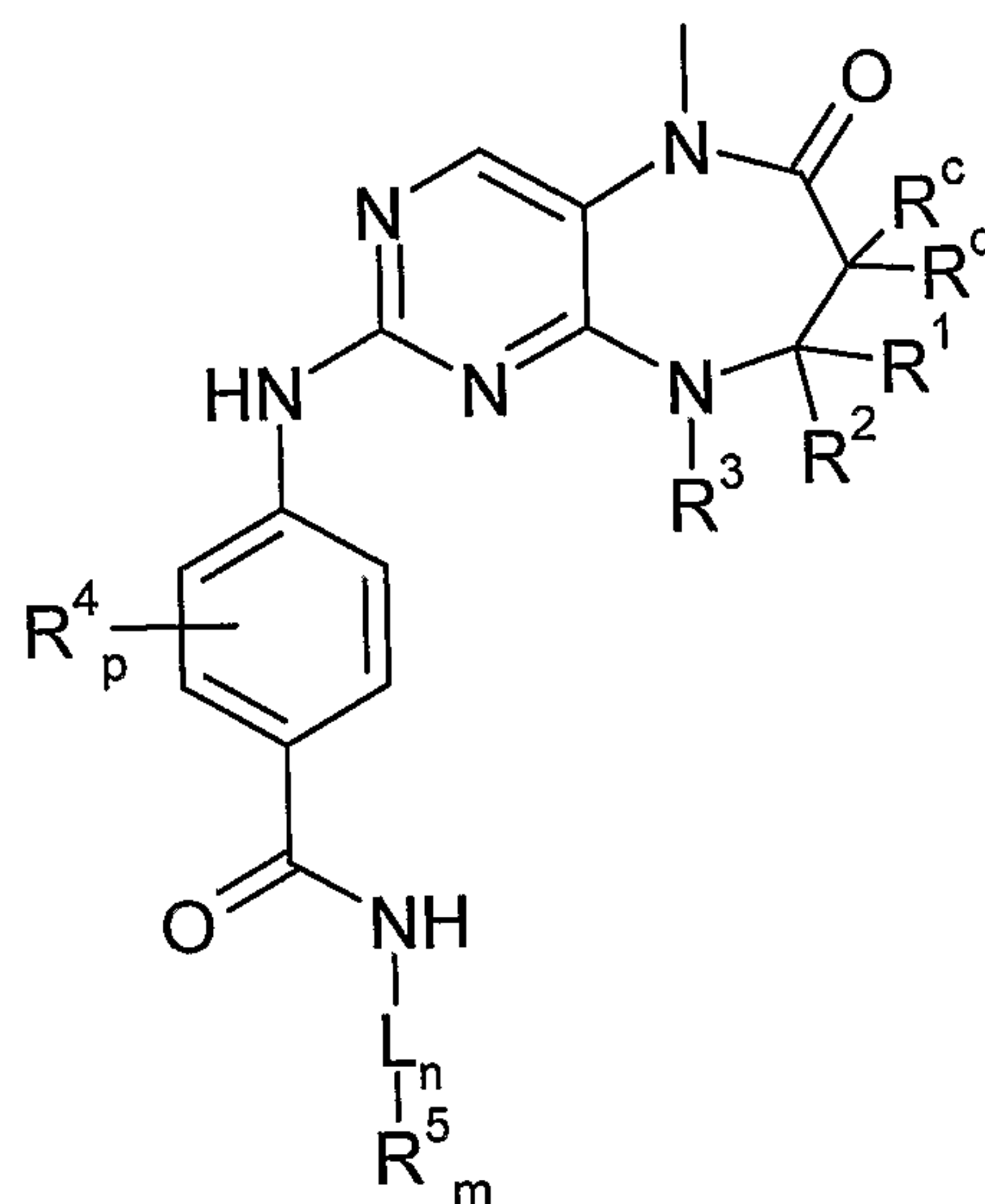
azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group;

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and Z^1 is $C=O$ or CR^fR^g wherein R^f , R^g each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms, or pharmacologically acceptable salts thereof.

7. A compound according to Claim 6 wherein Z^1 is $C=O$ or CH_2 .
8. A compound of formula (III):

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(III)

wherein

R^1 , R^2 each independently represents hydrogen or an optionally substituted C_{1-6} alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

m is 1 or 2;

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group; and

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms, or pharmacologically acceptable salt thereof.

9. A compound according to any one of Claims 6 to 8 wherein R^1 and R^2 are hydrogen.
10. A compound according to Claim 9 wherein one of R^c or R^d is hydrogen.
11. A compound according to Claim 10 wherein one of R^c or R^d is hydrogen and the other is methyl.
12. A compound according to Claim 9 wherein R^c and R^d are methyl.
13. A compound according to Claim 9 wherein R^c and R^d together represent an ethylene bridge.
14. A compound according to Claim 9 wherein R^c and R^d may be identical or different and represent hydrogen or a C_1 - C_6 alkyl group optionally substituted by one or more substituents selected from C_{1-3} alkyloxy, C_{1-3} alkylthio, C_{1-3} alkyl-S(O)₂, C_{1-3} alkylamino and di-(C_{1-3} alkyl)amino.

15. A compound according to any one of Claims 1 to 14 wherein R^3 represents cyclopentyl or cyclohexyl.
16. A compound according to any one of Claims 1 to 15 wherein when p is 1, R^4 represents methoxy, methyl, ethoxy, chlorine or fluorine.
17. A compound according to any one of Claims 1 to 15 wherein when p is 2, each R^4 may be the same or different and selected from methoxy, methyl, ethoxy, ethyl, propargyloxy, chlorine or fluorine.
18. A compound according to any one of Claims 1 to 15 wherein when p is 2 and when each R^4 is adjacent, both R^4 together with the aromatic ring atoms to which they are attached form a 4- to 7-member unsaturated ring optionally comprising 1 to 2 heteroatoms.
19. A compound according to any one of Claims 1 to 18 wherein when n is 1, L represents an optionally substituted C_{2-10} alkyl or an optionally substituted C_{3-12} cycloalkyl linker.
20. A compound according to Claim 19 wherein when n is 1, L represents cyclohexyl, $-C(CH_3)_2-CH_2-$ or $-CH_2-C(CH_3)_2-CH_2-$.
21. A compound according to any one of Claims 1 to 20 wherein n is 0.
22. A compound according to any one of Claims 1 to 21 wherein m is 1 and R^5 represents hydrogen, $-NR^8R^9$ or a piperidinyl, morpholinyl, pyrrolidinyl, sulphoxomorpholiny, piperazinyl, thiomorpholinyl, tropenyl, granatanyl, oxogranatanyl or azacycloheptyl each optionally substituted by one or more groups as defined for R^8 .
23. A compound according to Claim 22 wherein R^5 represents a piperidinyl, pyrrolidinyl, or granatanyl each optionally substituted by one or more groups as defined for R^8 .

24. A compound according to Claims 22 or 23 wherein R^8 represents methyl, ethyl or propyl, and/or R^9 represents methyl, ethyl or propyl.

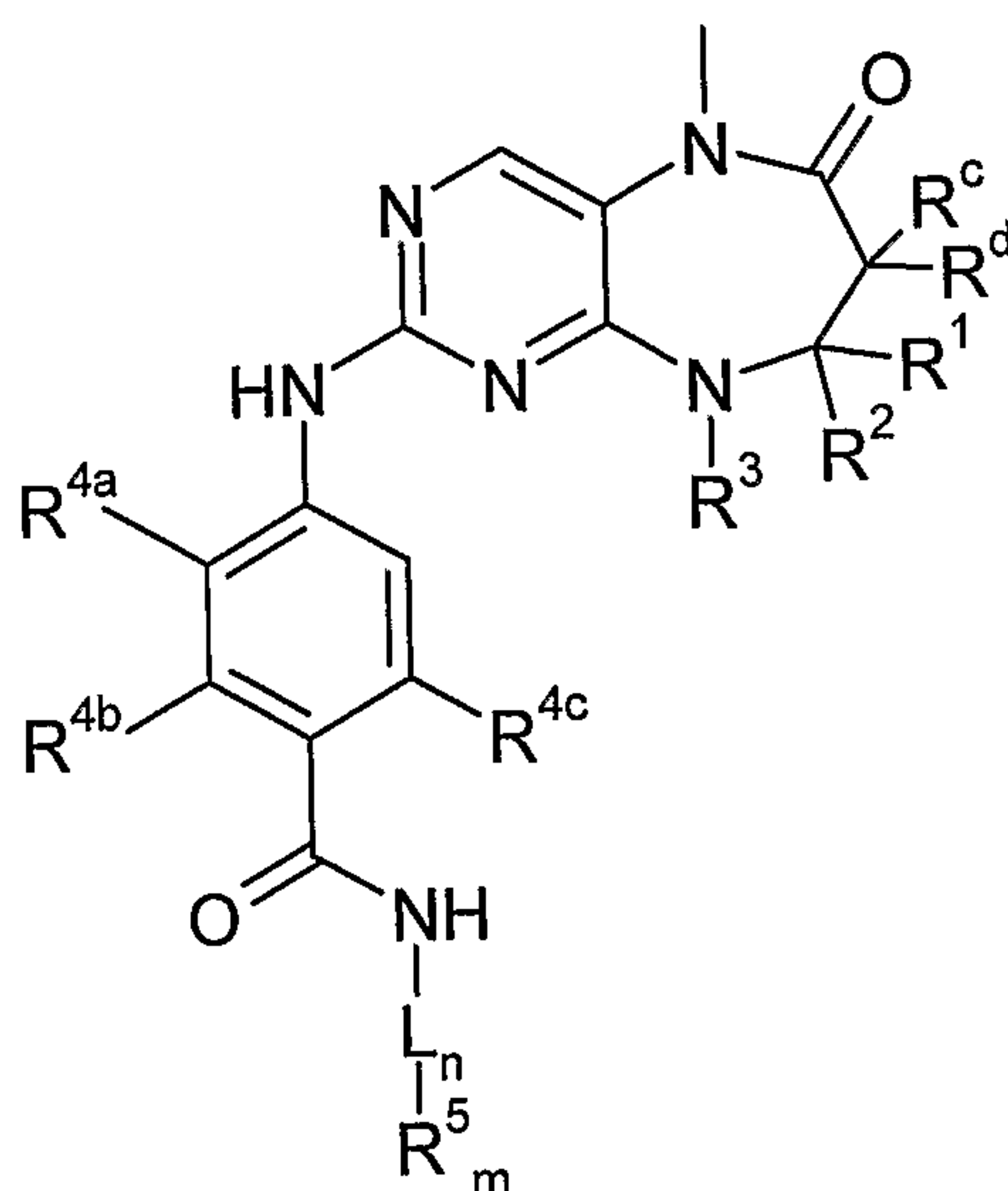
25. A compound according to Claim 8 wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl or optionally substituted C_{6-14} aryl group; p is 0 or 1; R^4 represents OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2 , F, Cl, Br, O-propargyl, O-butynyl, CN, SMe, NMe₂, CONH₂, ethynyl, propynyl, butynyl or allyl; L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes hydrogen or a group, which is bound to L via a carbon atom, selected from among $-NR^8R^9$, piperidinyl, piperazinyl, pyrrolidinyl, piperazinylcarbonyl, tropenyl, morpholinyl, granatanyl, oxogranatanyl and azacycloheptyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent hydrogen, C_{1-6} alkyl, $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, $-C_{1-4}$ alkyl- C_{6-14} aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4} alkyloxycarbonyl, C_{6-14} arylcarbonyl, C_{1-4} alkylcarbonyl, C_{6-14} arylmethyloxycarbonyl, C_{6-14} arylsulphonyl, C_{1-4} alkylsulphonyl or C_{6-14} aryl- C_{1-4} alkylsulphonyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

26. A compound according to Claim 25 wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and piperidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

27. A compound according to Claim 25 wherein wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

28. A compound according to Claim 25 wherein wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

29. A compound of formula (IIIa):



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(IIIa)

wherein

R^1 , R^2 each independently represents hydrogen or an optionally substituted C_{1-6} alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c , R^d each independently represents hydrogen, an optionally substituted C_{1-6} alkyl group or an optionally substituted C_{3-6} cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12} alkyl group, an optionally substituted C_{2-12} alkenyl group, an optionally substituted C_{2-12} alkynyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-12} cycloalkyl group, an optionally substituted C_{3-12} cycloalkenyl group, an optionally substituted C_{7-12} polycycloalkyl group, an optionally substituted C_{7-12} polycycloalkenyl group, an optionally substituted C_{5-12} spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3 , or R^2 and R^3 , or R^1 and R^c , or R^2 and R^d together represent a saturated or unsaturated C_{1-4} alkyl bridge optionally comprising 1 heteroatom;

R^{4a} , R^{4b} , R^{4c} each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-5} alkyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{2-5} alkenyloxy group, an optionally substituted C_{2-5} alkynyloxy group, an optionally substituted C_{1-6} alkythio group, an optionally substituted C_{1-6} alkylsulphoxo group or an optionally substituted C_{1-6} alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally

substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is the number of $R^{4a, 4b, 4c}$ groups that are not hydrogen and is selected from 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{2-4}$ alkyl- C_{6-14} aryl, optionally substituted $-C_{6-14}$ aryl- C_{1-4} alkyl, optionally substituted C_{3-12} cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms; n is 0 or 1;

m is 1 or 2;

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6 , R^7 each independently represents hydrogen or an optionally substituted C_{1-4} alkyl group; and

R^8 , R^9 each independently represents hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted $-C_{1-4}$ alkyl- C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted $-C_{1-4}$ alkyl- C_{6-14} aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4} alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14} arylcarbonyl, optionally substituted C_{1-4} alkylcarbonyl, optionally substituted C_{6-14} arylmethyloxycarbonyl, optionally substituted C_{6-14} arylsulphonyl, optionally substituted C_{1-4} alkylsulphonyl, optionally substituted C_{6-14} aryl- C_{1-4} alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,

or pharmacologically acceptable salt thereof.

30. A compound according to Claim 29 wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and piperidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

31. A compound according to Claim 29 wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

32. A compound according to Claim 29 wherein R^3 represents an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10} alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8 ; R^8 , R^9 each independently represent C_{1-6} alkyl; R^1 , R^2 are hydrogen; R^c , R^d are each independently selected from hydrogen, Me, or

Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH₂O bridge, or pharmacologically acceptable salts thereof.

33. A compound according to any one of Claims 25, 26, 27, 28, 30, 31 or 32 wherein R³ represents cyclopentyl or cyclohexyl.

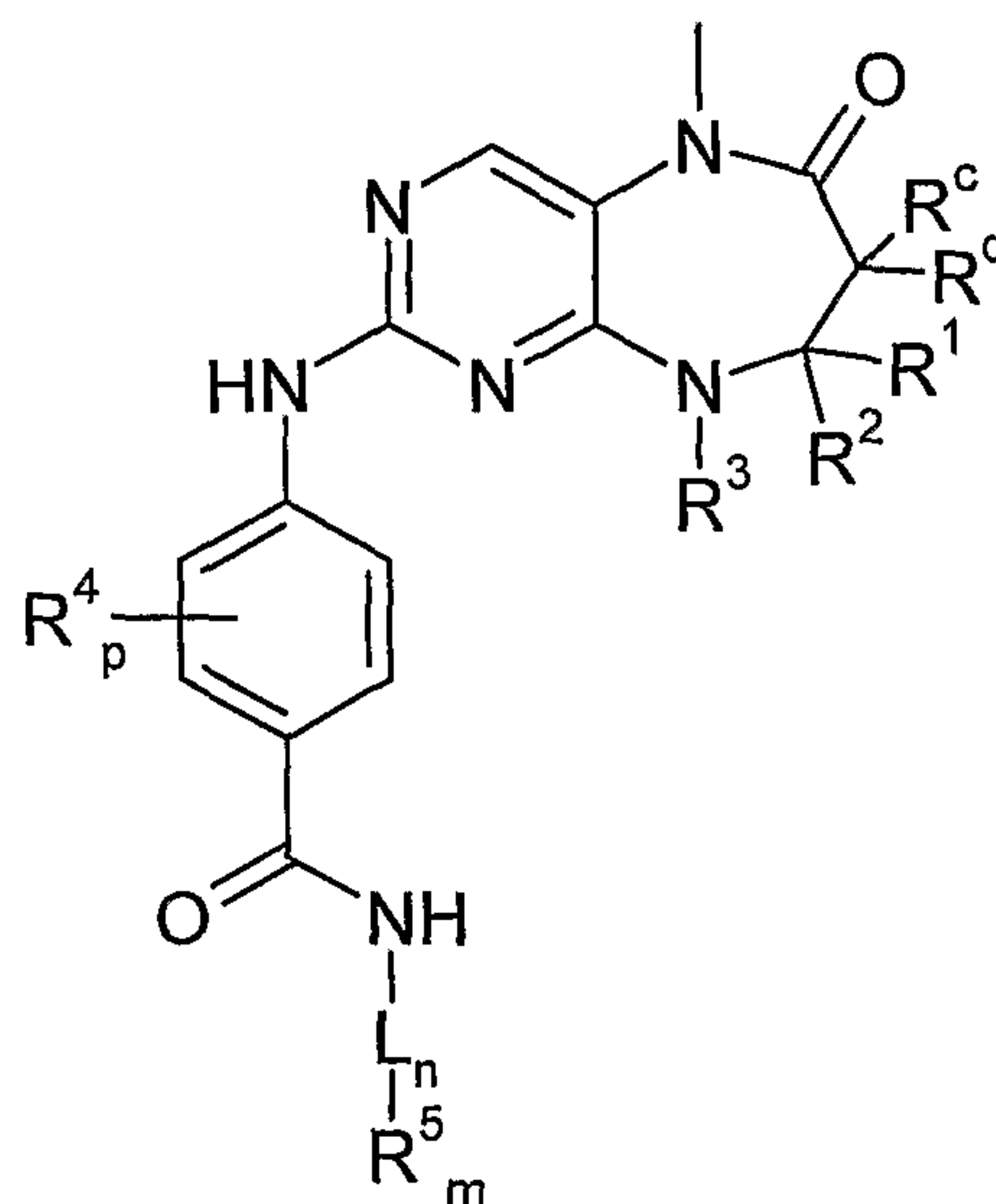
34. A compound according to Claims 33 wherein R⁸ represents methyl, ethyl or propyl, and/or R⁹ represents methyl, ethyl or propyl.

35. A compound selected from any one of the Examples or pharmacologically acceptable salts thereof.

36. A compound selected from any one of Examples 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451, 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453, or pharmacologically acceptable salts thereof.

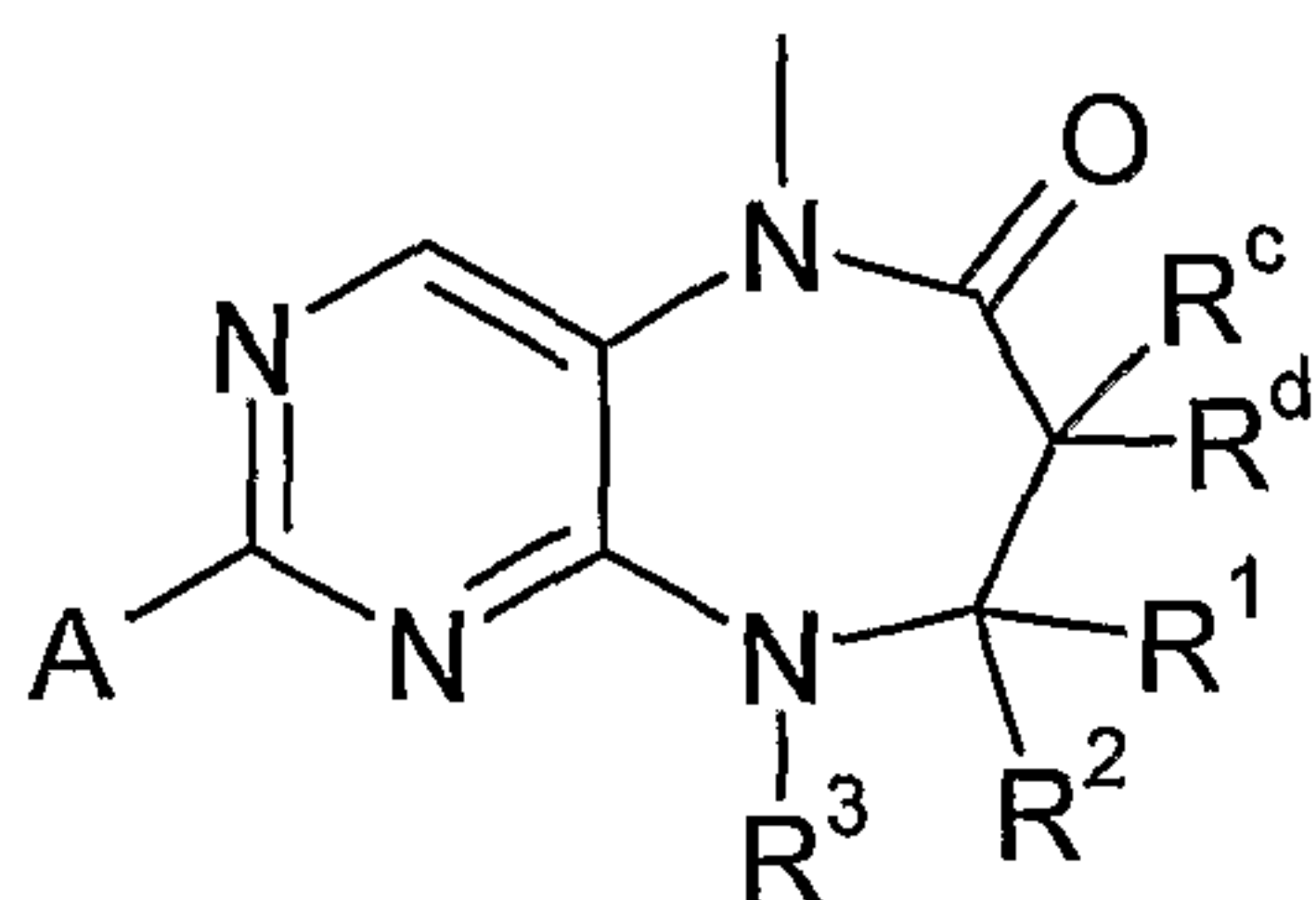
37. A compound selected from any one of Examples 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453, or pharmacologically acceptable salts thereof.

38. A process for preparing a compound of general formula (III),



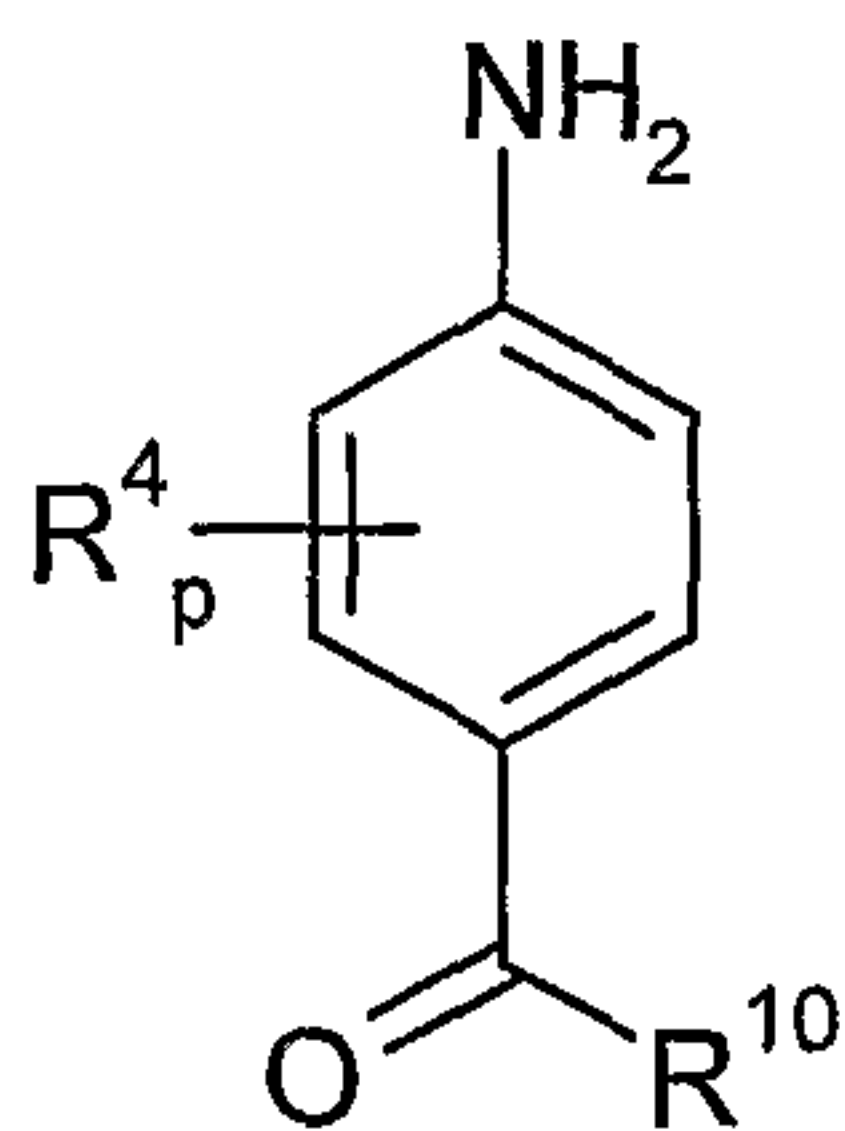
wherein R^1 - R^5 , R^c , R^d , m , n , p and L are as hereinbefore defined,
comprising reacting a compound of general formula (IV)

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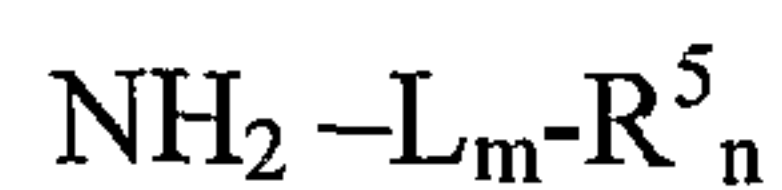
(IV)

wherein R^1 - R^3 are as hereinbefore defined and A is a leaving group,
with an optionally substituted compound of general formula (V):



(V)

wherein p and R^4 are as hereinbefore defined; and R^{10} denotes OH, $NH-L_m-R_n^5$, OMe, OEt,
and when R^{10} denotes OH, OMe or OEt optionally after previous hydrolysis of the ester group $-COR^{10}$, reacting with an amine of general formula (VI):

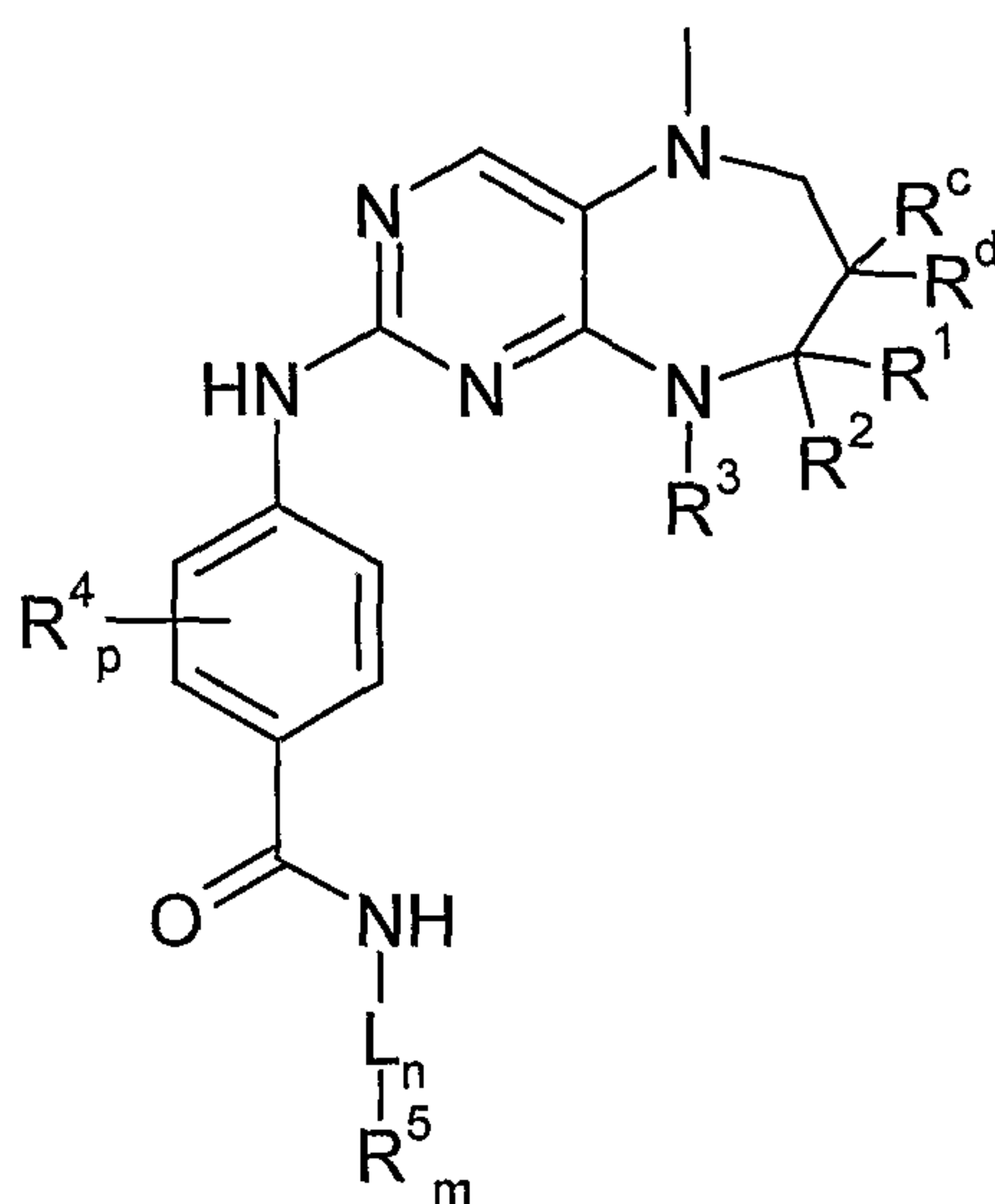


(VI)

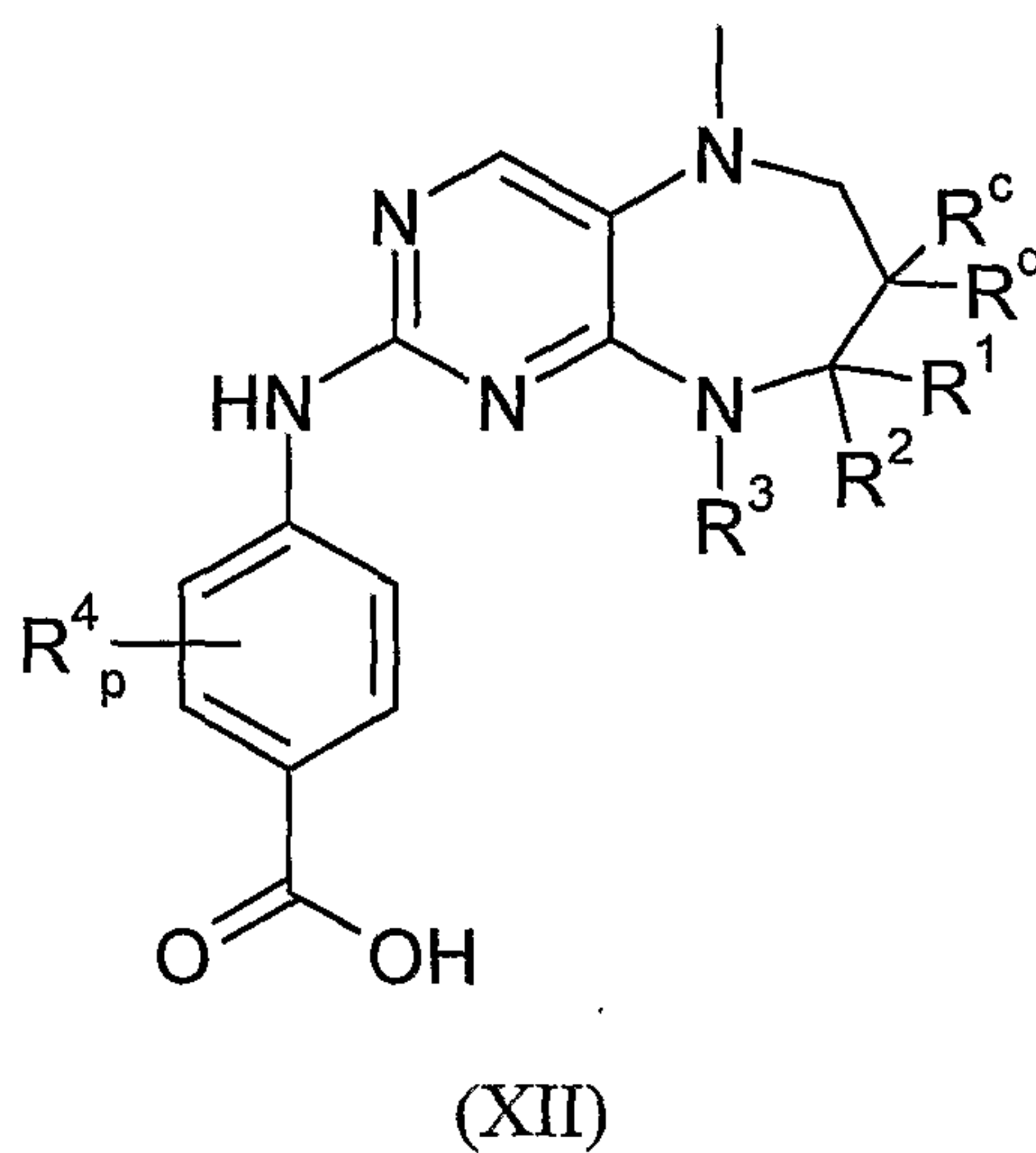
wherein R^5 is as hereinbefore defined,
to give a compound of formula (III).

39. A process for preparing a compound of general formula (XI),

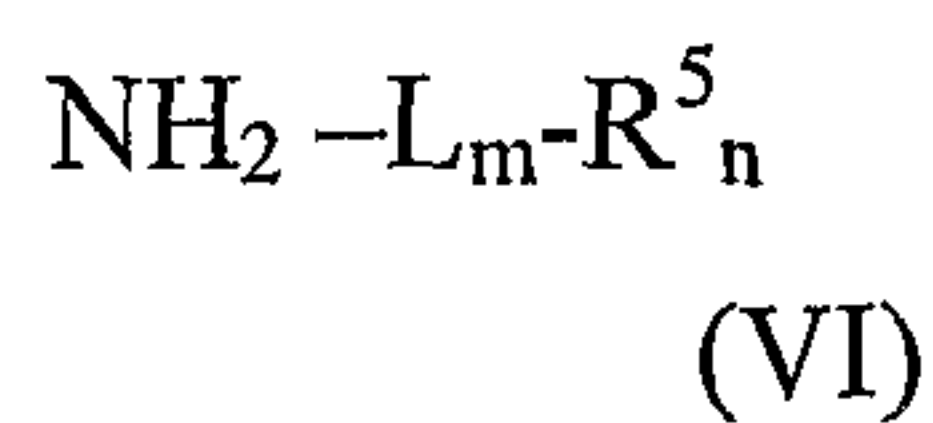
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wherein R^1 - R^5 , R^c , R^d , m , n , p and L are as hereinbefore defined,
comprising reacting a compound of general formula (XII)



with an amine of general formula (VI):



wherein L and R^5 are as hereinbefore defined.

40. A pharmaceutical composition comprising a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one claims 1 to 37 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

41. A process for the preparation of a pharmaceutical composition as claimed in claim 40 which comprises mixing a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as defined in any one of claim 1 to 37 with a pharmaceutically acceptable adjuvant, diluent or carrier.

42. A compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 37 for use in therapy.

43. Use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 37 in the manufacture of a medicament for the treatment of cancer.

44. Use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one claims 1 to 37 in the manufacture of a medicament for modulating polo-like kinas (Plk) activity.

45. A method of treating cancer which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 37.

46. A method of modulating polo-like kinase (Plk) activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one claims 1 to 37.

