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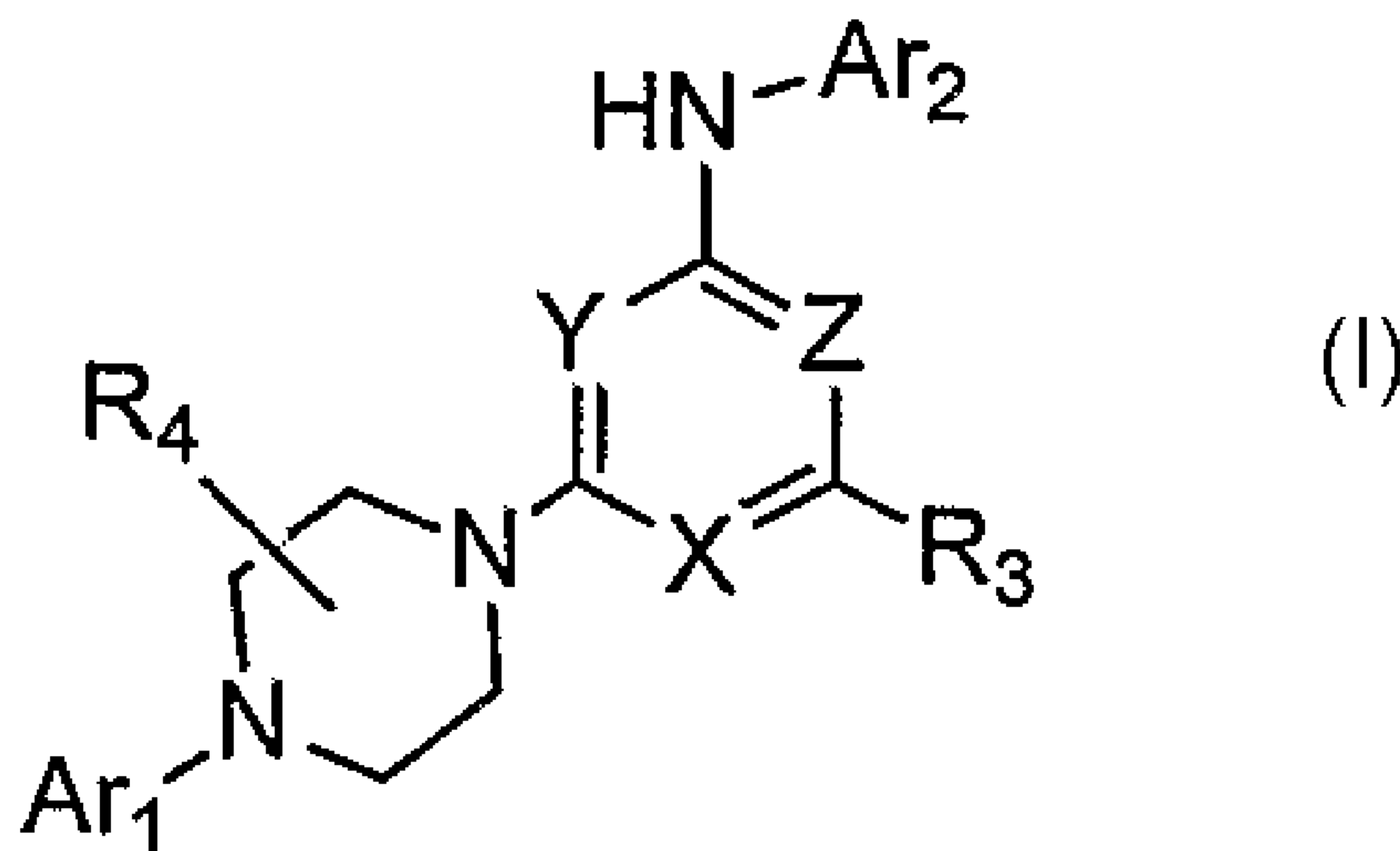
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(54) Titre : ANALOGUES DE DIARYLAMINE HETEROCYCLIQUES SUBSTITUES

(54) Title: SUBSTITUTED HETEROCYCLIC DIARYLAMINE ANALOGUES



(57) **Abrégé/Abstract:**

Substituted heterocyclic diarylamine analogues of Formula I are provided: wherein X, Y and Z are independently N or optionally substituted C, and other variables are as described in the specification. Such compounds are ligands that may be used to modulate specific receptor activity in vivo or in vitro, and are particularly useful in the treatment of conditions associated with pathological receptor activation in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor localization studies.



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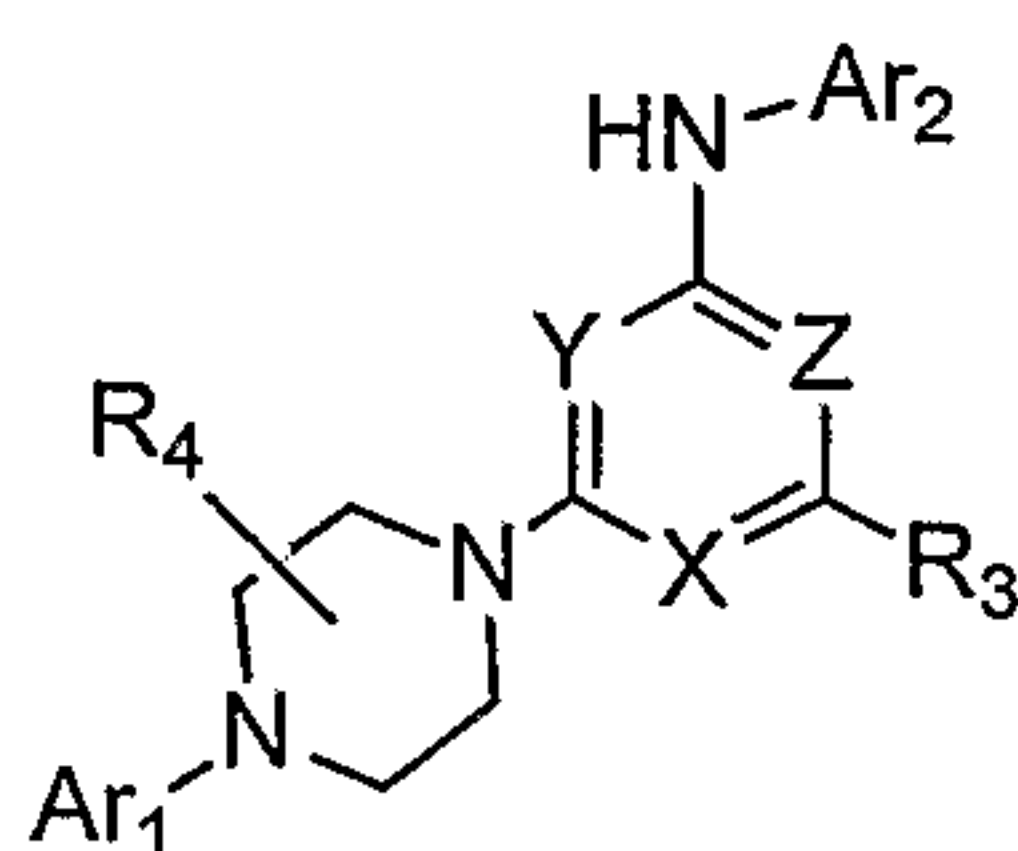
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(54) Title: SUBSTITUTED HETEROCYCLIC DIARYLAMINE ANALOGUES



(I)

(57) Abstract: Substituted heterocyclic diarylamine analogues of Formula I are provided: wherein X, Y and Z are independently N or optionally substituted C, and other variables are as described in the specification. Such compounds are ligands that may be used to modulate specific receptor activity *in vivo* or *in vitro*, and are particularly useful in the treatment of conditions associated with pathological receptor activation in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor localization studies.

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SUBSTITUTED HETEROCYCLIC DIARYLAMINE ANALOGUES

FIELD OF THE INVENTION

5 This invention relates generally to substituted heterocyclic diarylamine analogues that are modulators of capsaicin receptors, and to the use of such compounds for treating conditions related to capsaicin receptor activation. The invention further relates to the use such compounds as probes for detecting and localizing capsaicin receptors.

10 BACKGROUND OF THE INVENTION

 Pain perception, or nociception, is mediated by the peripheral terminals of a group of specialized sensory neurons, termed "nociceptors." A wide variety of physical and chemical stimuli induce activation of such neurons in mammals, leading to recognition of a potentially harmful stimulus. Inappropriate or excessive activation of nociceptors, however, can result in
15 debilitating acute or chronic pain.

 Neuropathic pain involves pain signal transmission in the absence of stimulus, and typically results from damage to the nervous system. In most instances, such pain is thought to occur because of sensitization in the peripheral and central nervous systems following initial damage to the peripheral system (*e.g.*, via direct injury or systemic disease).
20 Neuropathic pain is typically burning, shooting and unrelenting in its intensity and can sometimes be more debilitating than the initial injury or disease process that induced it.

 Existing treatments for neuropathic pain are largely ineffective. Opiates, such as morphine, are potent analgesics, but their usefulness is limited because of adverse side effects, such as physical addictiveness and withdrawal properties, as well as respiratory
25 depression, mood changes, and decreased intestinal motility with concomitant constipation, nausea, vomiting, and alterations in the endocrine and autonomic nervous systems. In addition, neuropathic pain is frequently non-responsive or only partially responsive to conventional opioid analgesic regimens. Treatments employing the N-methyl-D-aspartate antagonist ketamine or the alpha(2)-adrenergic agonist clonidine can reduce acute or chronic
30 pain, and permit a reduction in opioid consumption, but these agents are often poorly tolerated due to side effects.

 Topical treatment with capsaicin has been used to treat chronic and acute pain, including neuropathic pain. Capsaicin is a pungent substance derived from the plants of the Solanaceae family (which includes hot chili peppers) and appears to act selectively on the

small diameter afferent nerve fibers (A-delta and C fibers) that are believed to mediate pain. The response to capsaicin is characterized by persistent activation of nociceptors in peripheral tissues, followed by eventual desensitization of peripheral nociceptors to one or more stimuli. From studies in animals, capsaicin appears to trigger C fiber membrane depolarization by opening cation selective channels for calcium and sodium.

Similar responses are also evoked by structural analogues of capsaicin that share a common vanilloid moiety. One such analogue is resiniferatoxin (RTX), a natural product of *Euphorbia* plants. The term vanilloid receptor (VR) was coined to describe the neuronal membrane recognition site for capsaicin and such related irritant compounds. The capsaicin response is competitively inhibited (and thereby antagonized) by another capsaicin analog, capsazepine, and is also inhibited by the non-selective cation channel blocker ruthenium red. These antagonists bind to VR with no more than moderate affinity (typically with K_i values of no lower than 140 μ M).

Rat and human vanilloid receptors have been cloned from dorsal root ganglion cells. The first type of vanilloid receptor to be identified is known as vanilloid receptor type 1 (VR1), and the terms "VR1" and "capsaicin receptor" are used interchangeably herein to refer to rat and/or human receptors of this type, as well as mammalian homologs. The role of VR1 in pain sensation has been confirmed using mice lacking this receptor, which exhibit no vanilloid-evoked pain behavior, and impaired responses to heat and inflammation. VR1 is a nonselective cation channel with a threshold for opening that is lowered in response to elevated temperatures, low pH, and capsaicin receptor agonists. For example, the channel usually opens at temperatures higher than about 45°C. Opening of the capsaicin receptor channel is generally followed by the release of inflammatory peptides from neurons expressing the receptor and other nearby neurons, increasing the pain response. After initial activation by capsaicin, the capsaicin receptor undergoes a rapid desensitization via phosphorylation by cAMP-dependent protein kinase.

Because of their ability to desensitize nociceptors in peripheral tissues, VR1 agonist vanilloid compounds have been used as topical anesthetics. However, agonist application may itself cause burning pain, which limits this therapeutic use. Recently, it has been reported that VR1 antagonists, including nonvanilloid compounds, are also useful for the treatment of pain (*see* PCT International Application Publication Number WO 02/08221, which published January 31, 2002).

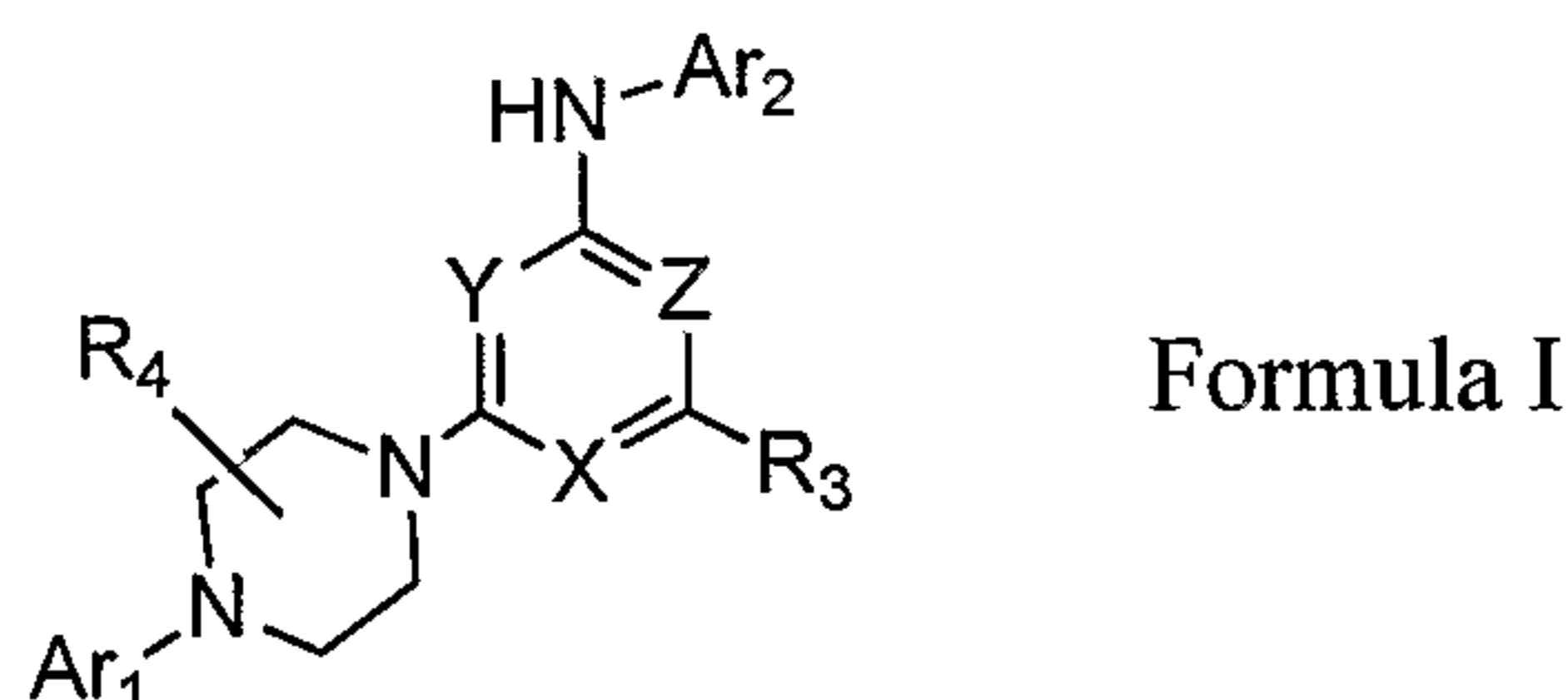
Thus, compounds that interact with VR1, but do not elicit the initial painful sensation of VR1 agonist vanilloid compounds, are desirable for the treatment of chronic and acute

pain, including neuropathic pain. Antagonists of this receptor are particularly desirable for the treatment of pain, as well as conditions such as tear gas exposure, itch and urinary tract conditions such as urinary incontinence and overactive bladder. The present invention fulfills this need, and provides further related advantages.

5

SUMMARY OF THE INVENTION

The present invention provides compounds that modulate, preferably inhibit, VR1 activation. Within certain aspects, compounds provided herein are substituted heterocyclic diarylamine analogues of Formula I:



10 or are a pharmaceutically acceptable form thereof. Within Formula I:

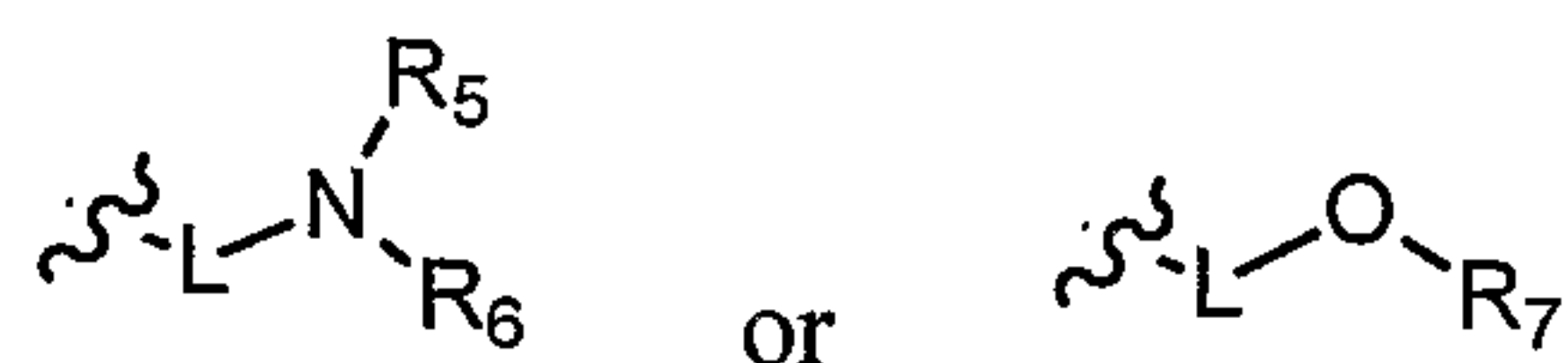
Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is optionally substituted, or more preferably substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

20 X, Y and Z are independently optionally substituted carbon (preferably CR_x) or N; preferably at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, halogen, optionally substituted C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

- 25 (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
 (ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;
 and
 (iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

5 (a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

10 R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is optionally substituted, preferably with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl,

15 C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

20 R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl.

Within certain aspects, VR1 modulators as described herein exhibit a K_i of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in a capsaicin receptor binding assay and/or have an EC₅₀ or IC₅₀ value of no greater than 1
25 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in an assay for determination of capsaicin receptor antagonist activity.

In certain embodiments, VR1 modulators as described herein are VR1 antagonists and exhibit no detectable agonist activity in an *in vitro* assay of capsaicin receptor activation.

Within certain aspects, VR1 modulators as described herein are labeled with a
30 detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

Within certain aspects, VR1 modulators and pharmaceutically acceptable forms thereof as described herein are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one VR1 modulator as described herein (*i.e.*, a compound as provided herein or a pharmaceutically acceptable form thereof) in combination with a physiologically acceptable carrier or excipient.

5 Within further aspects, methods are provided for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell (*e.g.*, neuronal) expressing a capsaicin receptor with a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein. Such contact may occur *in vivo* or *in vitro*.

10 Methods are further provided for inhibiting binding of vanilloid ligand to a capsaicin receptor. Within certain such aspects, the inhibition takes place *in vitro*. Such methods comprise contacting a capsaicin receptor with at least one VR1 modulator as described herein, under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to the capsaicin receptor. Within other such aspects, the capsaicin receptor is in a patient. Such methods comprise contacting cells expressing a capsaicin receptor in a patient
15 with at least one VR1 modulator as described herein in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

20 The present invention further provides methods for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

Within other aspects, methods are provided for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

25 Methods are further provided for treating itch, urinary incontinence, overactive bladder, cough and/or hiccup in a patient, comprising administering to a patient suffering from one or more of the foregoing conditions a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

30 The present invention further provides methods for promoting weight loss in an obese patient, comprising administering to an obese patient a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

Within further aspects, the present invention provides methods for determining the presence or absence of capsaicin receptor in a sample, comprising: (a) contacting a sample with a VR1 modulator as described herein under conditions that permit binding of the VR1

modulator to capsaicin receptor; and (b) detecting a level of the VR1 modulator bound to capsaicin receptor.

The present invention also provides packaged pharmaceutical preparations, comprising: (a) a pharmaceutical composition as described herein in a container; and (b)
5 instructions for using the composition to treat one or more conditions responsive to capsaicin receptor modulation, such as pain, itch, urinary incontinence, overactive bladder, cough, hiccup and/or obesity.

In yet another aspect, the invention provides methods of preparing the compounds disclosed herein, including the intermediates.

10 These and other aspects of the present invention will become apparent upon reference to the following detailed description.

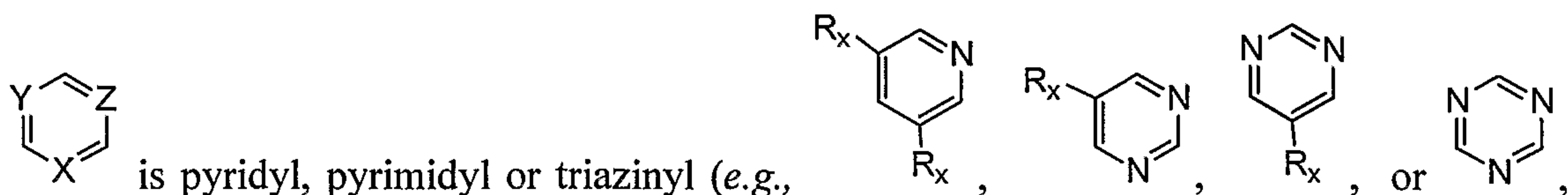
DETAILED DESCRIPTION

As noted above, the present invention provides substituted heterocyclic diarylamine
15 analogues. Such modulators may be used *in vitro* or *in vivo*, to modulate (preferably inhibit) capsaicin receptor activity in a variety of contexts.

TERMINOLOGY

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise
20 specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in *Z*- and *E*- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric
25 forms. Certain compounds are described herein using a general formula that includes variables ((*e.g.*, R_1 - R_4 , A, B, Z). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The term "substituted heterocyclic diarylamine analogue," as used herein,
30 encompasses all compounds of Formula I, as well as compounds of other Formulas provided herein (including any enantiomers, racemates and stereoisomers) and pharmaceutically acceptable forms of such compounds. For example, compounds in which the core ring



each of which is optionally substituted as described herein) are specifically included within the definition of substituted heterocyclic diarylamine analogues.

"Pharmaceutically acceptable forms" of the compounds recited herein are pharmaceutically acceptable salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates and prodrugs of such compounds. As used herein, a pharmaceutically acceptable salt is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile, is preferred.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound of Formula I, or other formula provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include

compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved to the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C₁-C₈alkyl), from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. "C₀-C₄alkyl" refers to a bond or an alkyl group having 1, 2, 3 or 4 carbon atoms; "C₀-C₆alkyl" refers to a single covalent bond (C₀) or a C₁-C₆alkyl group; "C₀-C₈alkyl" refers to a single covalent bond or a C₁-C₈alkyl group. In some instances herein, a substituent of an alkyl group is specifically indicated. For example, "cyanoC₁-C₄alkyl" refers to a C₁-C₄alkyl group that has at least one CN substituent. The term "alkylene" refers to a divalent alkyl group. That is, an alkylene group is an alkyl group that is bonded to two additional non-hydrogen residues, such as a one carbon methylene group in methylene dichloride (Cl-CH₂-Cl).

Similarly, "alkenyl" refers to straight or branched chain alkene groups. Alkenyl groups include C₂-C₈alkenyl, C₂-C₆alkenyl and C₂-C₄alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C₂-C₈alkynyl, C₂-C₆alkynyl and C₂-C₄alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a saturated cyclic group in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. If substituted, any ring carbon atom may be bonded to any indicated substituent, such as halogen, cyano, C₁-C₈alkyl, C₁-C₈alkoxy, or C₂-C₈alkanoyl.

A "cycloalkyl" is a saturated cyclic group in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Certain cycloalkyl groups are C₃-C₇cycloalkyl, in which the ring contains from 3 to 7 ring members.

By "alkoxy," as used herein, is meant an alkyl group as described above attached via an oxygen bridge. Alkoxy groups include C₁-C₆alkoxy and C₁-C₄alkoxy groups, which have from 1 to 6 or 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy,
 5 hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy are specific alkoxy groups.

Similarly, "alkylthio" refers to an alkyl, alkenyl or alkynyl group as described above attached via a sulfur bridge. Preferred alkoxy and alkylthio groups are those in which an alkyl group is attached via the heteroatom bridge.

"Alkylsulfonyl" refers to groups of the formula $-(SO_2)-alkyl$, in which the sulfur atom
 10 is the point of attachment. Alkylsulfonyl groups include C₁-C₆alkylsulfonyl and C₁-C₄alkylsulfonyl groups, which have from 1 to 6 or 1 to 4 carbon atoms, respectively. Methylsulfonyl is one representative alkylsulfonyl group.

"Alkylsulfonamido" refers to groups of the formula $-(SO_2)-N(R)_2$, in which the sulfur atom is the point of attachment and each R is independently hydrogen or alkyl. The term
 15 "mono- or di-(C₁-C₆alkyl)sulfonamido" refers to such groups in which one R is C₁-C₆alkyl and the other R is hydrogen or an independently chosen C₁-C₆alkyl.

The term "oxo," as used herein, refers to a keto (C=O) group. An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of $-CH_2-$ to $-C(=O)-$. It will be apparent that substitution of an aromatic carbon atom with an oxo group destroys the
 20 aromaticity.

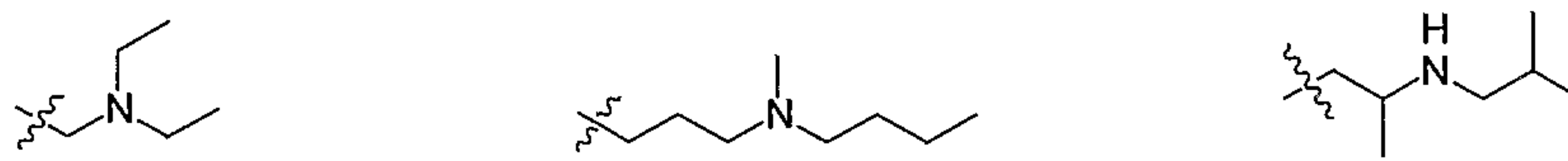
The term "alkanoyl" refers to an acyl group in a linear or branched arrangement (*e.g.*, $-(C=O)-alkyl$), where attachment is through the carbon of the keto group. Alkanoyl groups include C₂-C₈alkanoyl, C₂-C₆alkanoyl and C₂-C₄alkanoyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively. "C₁alkanoyl" refers to $-(C=O)-H$, which (along
 25 with C₂-C₈alkanoyl) is encompassed by the term "C₁-C₈alkanoyl." Ethanoyl is C₂alkanoyl.

An "alkanone" is a ketone group in which carbon atoms are in a linear or branched alkyl arrangement. "C₃-C₈alkanone," "C₃-C₆alkanone" and "C₃-C₄alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C₃ alkanone group has the structure $-CH_2-(C=O)-CH_3$.

30 Similarly, "alkyl ether" refers to a linear or branched ether substituent. Alkyl ether groups include C₂-C₈alkyl ether, C₂-C₆alkyl ether and C₂-C₄alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C₂ alkyl ether group has the structure $-CH_2-O-CH_3$.

"Alkylamino" refers to a secondary or tertiary amine having the general structure —NH—alkyl or —N(alkyl)(alkyl), wherein each alkyl may be the same or different. Such groups include, for example, mono- and di-(C₁-C₈alkyl)amino groups, in which each alkyl may be the same or different and may contain from 1 to 8 carbon atoms, as well as mono- and di-(C₁-C₆alkyl)amino groups and mono- and di-(C₁-C₄alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkyl group (*i.e.*, a group having the general structure -alkyl-NH-alkyl or -alkyl-N(alkyl)(alkyl)) in which each alkyl is selected independently. Such groups include, for example, mono- and di-(C₁-C₈alkyl)aminoC₁-C₈alkyl, mono- and di-(C₁-C₆alkyl)aminoC₁-C₆alkyl and mono- and di-(C₁-C₄alkyl)aminoC₁-C₄alkyl, in which each alkyl may be the same or different. "Mono- or di-(C₁-C₆alkyl)aminoC₀-C₆alkyl" refers to a mono- or di-(C₁-C₆alkyl)amino group linked via a direct bond or a C₁-C₆alkyl group. The following are representative alkylaminoalkyl groups:



The term "aminocarbonyl" refers to an amide group (*i.e.*, -(C=O)NH₂). "Mono- or di-(C₁-C₈alkyl)aminocarbonyl" is an aminocarbonyl group in which one or both of the hydrogen atoms is replaced with C₁-C₈alkyl. If both hydrogen atoms are so replaced, the C₁-C₈alkyl groups may be the same or different.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

A "haloalkyl" is a branched, straight-chain or cyclic alkyl group, substituted with 1 or more halogen atoms (*e.g.*, "C₁-C₈haloalkyl" groups have from 1 to 8 carbon atoms; "C₁-C₆haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "C₁-C₈haloalkoxy" groups have 1 to 8 carbon atoms.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

A "heteroatom," as used herein, is oxygen, sulfur or nitrogen.

A "heterocycloalkyl" is a saturated cyclic group in which at least one ring atom is a heteroatom. Heterocycloalkyl groups include, for example, morpholinyl, thiomorpholinyl, and tetrahydropyranyl.

A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocyclic ring. Unless otherwise specified, each carbocyclic ring within a carbocycle may be saturated, partially saturated or aromatic. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings, carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (*i.e.*, C₃-C₈); C₅-C₇ rings are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain representative carbocycles are cycloalkyl (*i.e.*, groups that comprise saturated and/or partially saturated rings, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of any of the foregoing, such as cyclohexenyl), as well as aromatic groups (*i.e.*, groups that contain at least one aromatic carbocyclic ring, such as phenyl, benzyl, naphthyl, phenoxy, benzoxy, phenylethanonyl, fluorenyl, indanyl and 1,2,3,4-tetrahydro-naphthyl. Carbon atoms present within a carbocyclic ring may, of course, be further bonded to zero, one or two hydrogen atoms and/or any of a variety of ring substituents, such as hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkylthio, amino, mono- or di-(C₁-C₈alkyl)amino, C₃-C₇cycloalkylC₀-C₄alkyl, haloC₁-C₈alkyl, haloC₁-C₈alkoxy, aminoC₁-C₈alkyl, hydroxyC₁-C₈alkyl, C₁-C₈alkanoyl, C₁-C₈alkoxycarbonyl, -COOH, -C(=O)NH₂, mono- or di-(C₁-C₈alkyl)carboxamido, -S(O₂)NH₂, and/or mono- or di-(C₁-C₈alkyl)sulfonamido.

Certain carbocycles recited herein include C₆-C₁₀arylC₀-C₆alkyl groups (*i.e.*, groups in which a carbocyclic group comprising at least one aromatic ring is linked via a direct bond or a C₁-C₆alkyl group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via C₁-C₆alkyl, preferably via C₁-C₄alkyl. Phenyl groups linked via a direct bond or alkyl group may be designated phenylC₀-C₆alkyl (*e.g.*, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl).

A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1-4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 5 to 7 ring members are recited in certain embodiments), and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Heterocycles may be

optionally substituted at nitrogen and/or carbon atoms with a variety of substituents, such as those described above for carbocycles. Unless otherwise specified, a heterocycle may be a heterocycloalkyl group (*i.e.*, each ring is saturated or partially saturated) or a heteroaryl group (*i.e.*, at least one ring within the group is aromatic). A heterocyclic group may generally be
 5 linked via any ring or substituent atom, provided that a stable compound results. N-linked heterocyclic groups are linked via a component nitrogen atom. A "heterocycleC₀-C₈alkyl" is a heterocyclic group linked via a direct bond or C₁-C₈alkyl group. A (3- to 10-membered heterocycle)C₁-C₆alkyl is a heterocyclic group having from 3 to 10 ring members linked via a C₁-C₆alkyl group

10 Heterocyclic groups include, for example, acridinyl, azepanyl, azocinyl, benzimidazolyl, benzimidazoliny, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolylcarbazolyl, benztetrazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dihydrofuro[2,3-b]tetrahydrofuran, dihydroisoquinolinyl,
 15 dihydrotetrahydrofuranyl, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, dithiazinyl, furanyl, furazanyl, imidazoliny, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indolinyl, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenaziny, phenothiazinyl,
 20 phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidinyl, piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridooxazolyl, pyridothiazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolidonyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl,
 25 thianthrenyl, thiazolyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, thiophenyl, thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, xanthenyl and any of the foregoing that are substituted with from 1 to 4 substituents as described above.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety
 30 such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded,

and such that a chemically stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Such optional substituents include, for example, hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkylthio, amino, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈haloalkyl, C₁-C₈haloalkoxy, C₁-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, -COOH, -CONH₂, mono- or di-(C₁-C₈alkyl)aminocarbonyl, -SO₂NH₂, and/or mono or di(C₁-C₈alkyl)sulfonamido, as well as carbocyclic and heterocyclic groups. Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents).

The terms "VR1" and "capsaicin receptor" are used interchangeably herein to refer to a type 1 vanilloid receptor. Unless otherwise specified, these terms encompass both rat and human VR1 receptors (*e.g.*, GenBank Accession Numbers AF327067, AJ277028 and NM_018727; sequences of certain human VR1 cDNAs are provided in SEQ ID NOs:1-3, and the encoded amino acid sequences shown in SEQ ID NOs:4 and 5, of U.S. Patent No. 6,482,611), as well as homologs thereof found in other species.

A "VR1 modulator," also referred to herein as a "modulator," is a compound that modulates VR1 activation and/or VR1-mediated signal transduction. VR1 modulators specifically provided herein are compounds of Formula I and pharmaceutically acceptable forms of compounds of Formula I. A VR1 modulator may be a VR1 agonist or antagonist. A modulator binds with "high affinity" if the K_i at VR1 is less than 1 micromolar, preferably less than 100 nanomolar, 10 nanomolar or 1 nanomolar. A representative assay for determining K_i at VR1 is provided in Example 5, herein.

A modulator is considered an "antagonist" if it detectably inhibits vanilloid ligand binding to VR1 and/or VR1-mediated signal transduction (using, for example, the representative assay provided in Example 6); in general, such an antagonist inhibits VR1 activation with a IC₅₀ value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar or 1 nanomolar within the assay provided in

Example 6. VR1 antagonists include neutral antagonists and inverse agonists. In certain embodiments, capsaicin receptor antagonists provided herein are not vanilloids.

An "inverse agonist" of VR1 is a compound that reduces the activity of VR1 below its basal activity level in the absence of added vanilloid ligand. Inverse agonists of VR1 may also inhibit the activity of vanilloid ligand at VR1, and/or may also inhibit binding of vanilloid ligand to VR1. The ability of a compound to inhibit the binding of vanilloid ligand to VR1 may be measured by a binding assay, such as the binding assay given in Example 5. The basal activity of VR1, as well as the reduction in VR1 activity due to the presence of VR1 antagonist, may be determined from a calcium mobilization assay, such as the assay of Example 6.

A "neutral antagonist" of VR1 is a compound that inhibits the activity of vanilloid ligand at VR1, but does not significantly change the basal activity of the receptor (*i.e.*, within a calcium mobilization assay as described in Example 6 performed in the absence of vanilloid ligand, VR1 activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists of VR1 may inhibit the binding of vanilloid ligand to VR1.

As used herein a "capsaicin receptor agonist" or "VR1 agonist" is a compound that elevates the activity of the receptor above the basal activity level of the receptor (*i.e.*, enhances VR1 activation and/or VR1-mediated signal transduction). Capsaicin receptor agonist activity may be identified using the representative *in vitro* assay of capsaicin receptor agonism provided in Example 6. In general, such an agonist has an EC₅₀ value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar within the assay provided in Example 6. In certain embodiments, capsaicin receptor agonists provided herein are not vanilloids.

A "vanilloid" is capsaicin or any capsaicin analogue that comprises a phenyl ring with two oxygen atoms bound to adjacent ring carbon atoms (one of which carbon atom is located *para* to the point of attachment of a third moiety that is bound to the phenyl ring). A vanilloid is a "vanilloid ligand" if it binds to VR1 with a K_i (determined as described herein) that is no greater than 10 μM. Vanilloid ligand agonists include capsaicin, olvanil, N-arachidonoyl-dopamine and resiniferatoxin (RTX). Vanilloid ligand antagonists include capsazepine and iodo-resiniferatoxin.

A "capsaicin receptor modulatory amount" is an amount that, upon administration to a patient, achieves a concentration of VR1 modulator at a capsaicin receptor within the patient

that is sufficient to alter the binding of vanilloid ligand to VR1 *in vitro* (using the assay provided in Example 5) and/or VR1-mediated signal transduction (using an assay provided in Example 6). The capsaicin receptor may be present, for example, in a body fluid such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine.

5 A "therapeutically effective amount" is an amount that, upon administration, is sufficient to provide detectable patient relief from a condition being treated. Such relief may be detected using any appropriate criteria, including alleviation of one or more symptoms such as pain.

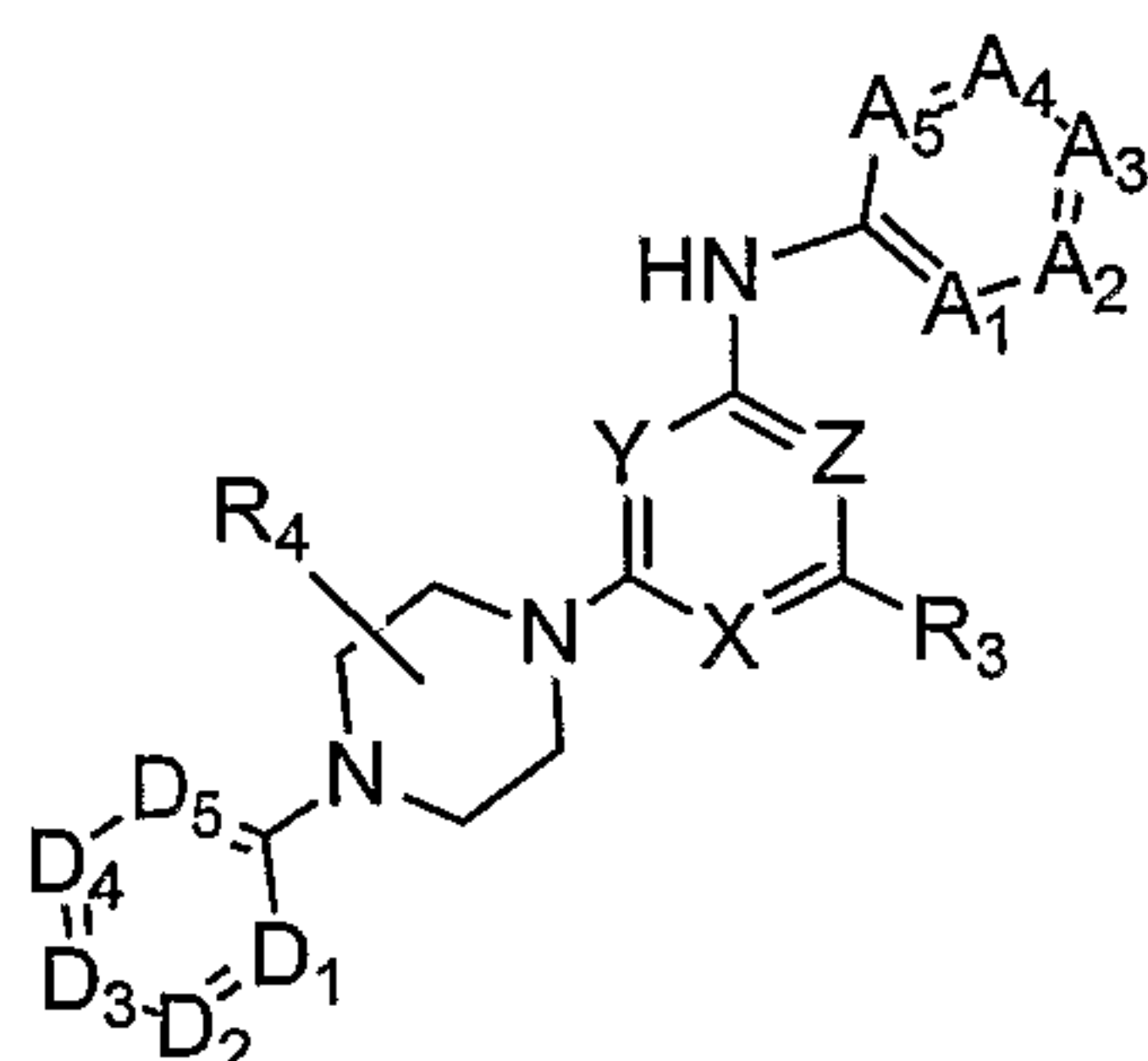
A "patient" is any individual treated with a VR1 modulator as provided herein.
10 Patients include humans, as well as other animals such as companion animals (*e.g.*, dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to capsaicin receptor modulation (*e.g.*, pain, exposure to vanilloid ligand, itch, urinary incontinence, overactive bladder, respiratory disorders, cough and/or hiccup), or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic).

15 VR1 MODULATORS

As noted above, the present invention provides VR1 modulators that may be used in a variety of contexts, including in the treatment of pain (*e.g.*, neuropathic or peripheral nerve-mediated pain); exposure to capsaicin; exposure to acid, heat, light, tear gas air pollutants, pepper spray or related agents; respiratory conditions such as asthma or chronic obstructive
20 pulmonary disease; itch; urinary incontinence or overactive bladder; cough or hiccup; and/or obesity. VR1 modulators may also be used within *in vitro* assays (*e.g.*, assays for receptor activity), as probes for detection and localization of VR1 and as standards in ligand binding and VR1-mediated signal transduction assays.

VR1 modulators provided herein are substituted heterocyclic diarylamine analogues
25 that detectably modulate the binding of capsaicin to VR1 at nanomolar (*i.e.*, submicromolar) concentrations, preferably at subnanomolar concentrations, more preferably at concentrations below 100 picomolar, 20 picomolar, 10 picomolar or 5 picomolar. Such modulators are preferably not capsaicin analogs (*i.e.*, they do not comprise a phenyl ring with two oxygen atoms bound to adjacent ring carbons). Preferred modulators are VR1 antagonists and have
30 no detectable agonist activity in the assay described in Example 6. In certain embodiments, such modulators further bind with high affinity to VR1, and do not substantially inhibit activity of human EGF receptor tyrosine kinase.

The present invention is based, in part, on the discovery that small molecules having the general Formula I, above, (as well as pharmaceutically acceptable forms thereof) are highly active modulators of VR1 activity. Within certain embodiments, compounds provided herein are substituted heterocyclic diarylamine analogues of Formula Ia:



Formula Ia

5 or are a pharmaceutically acceptable form thereof. Within Formula Ia:

A₁, A₂, A₃, A₄ and A₅ are independently CR₂ or N;

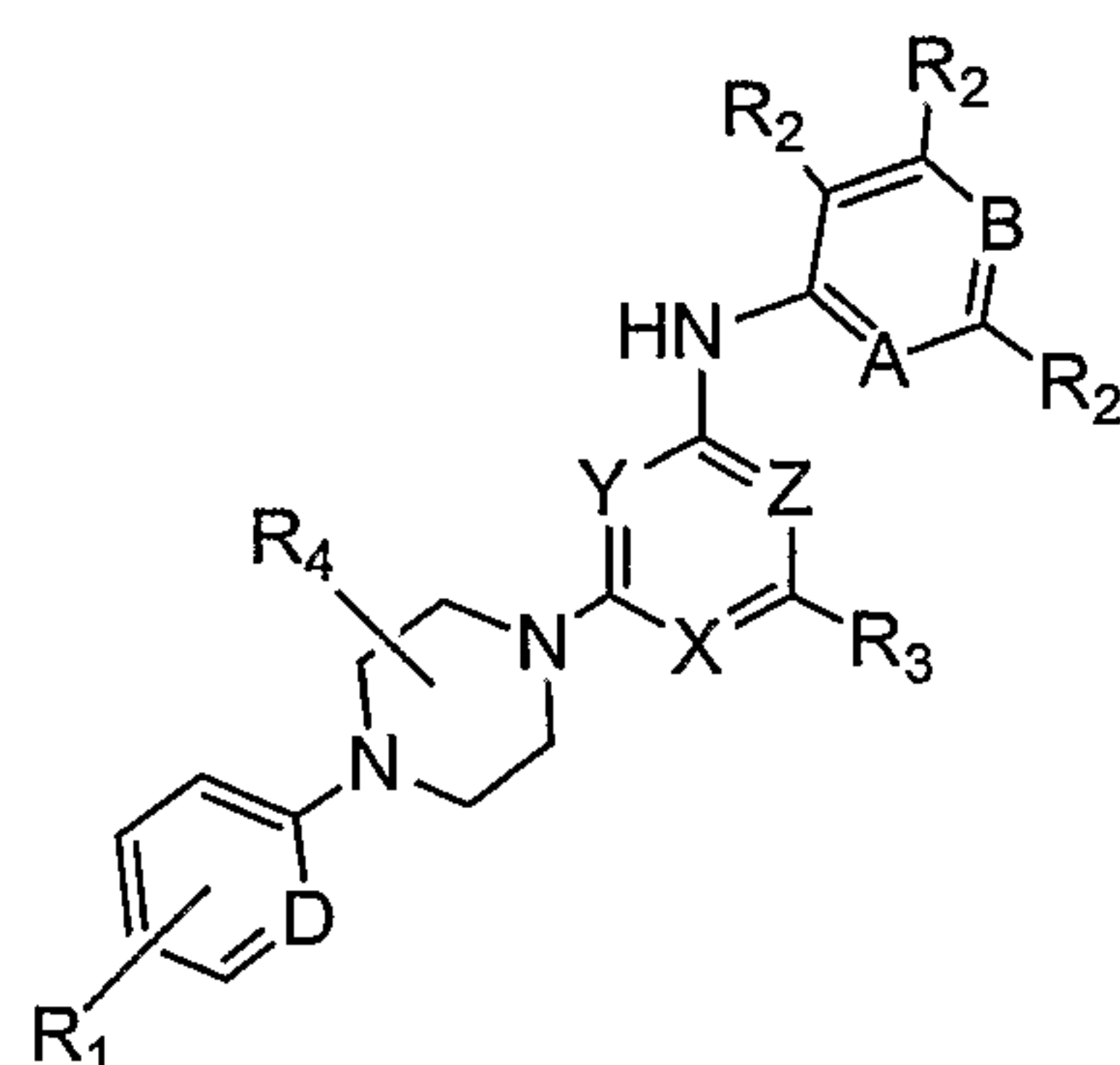
D₁, D₂, D₃, D₄ and D₅ are independently CR_d or N, wherein each R_d is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, -COOH, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, nitro, halogen, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₁-C₆alkoxycarbonyl, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl; or
- (ii) taken together with an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen, oxo and C₁-C₆alkyl; and

X, Y, Z, R₃ and R₄ are as described for Formula I.

Within further embodiments, compounds provided herein are substituted heterocyclic diarylamine analogues of Formula Ib:



Formula Ib

or are a pharmaceutically acceptable form thereof. Within Formula Ib:

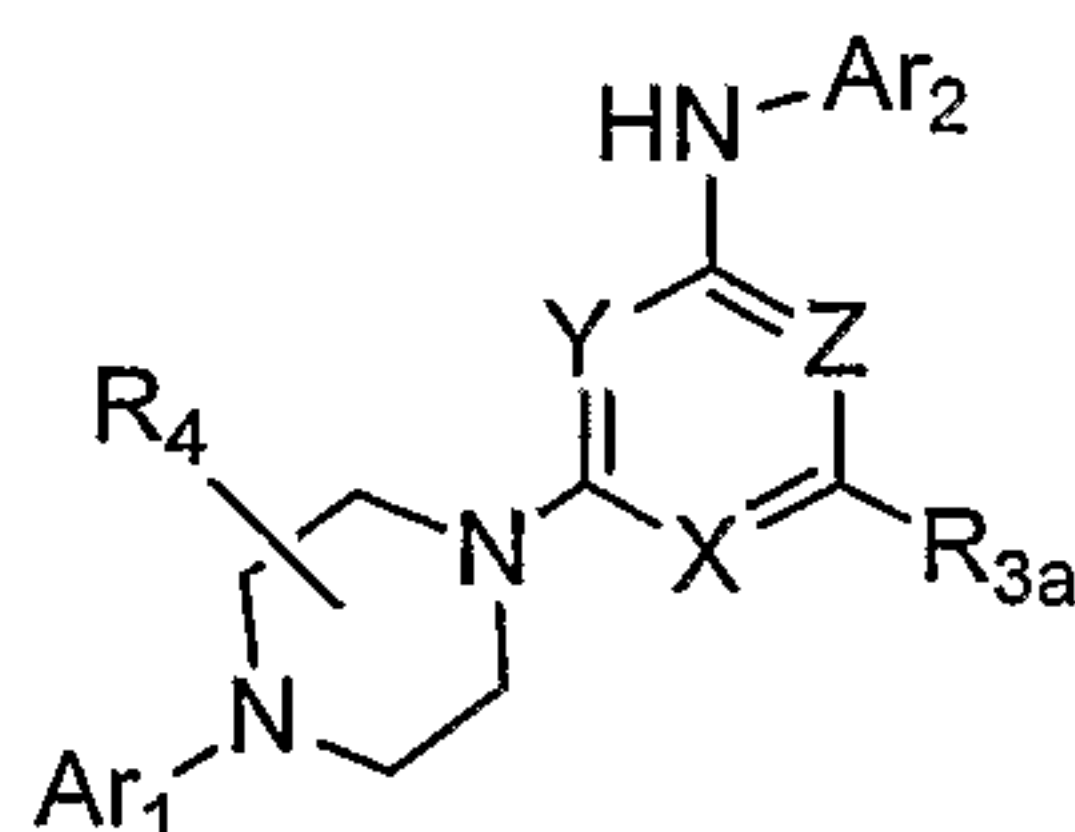
A and B are independently CR₂ or N;

D is CH or N;

X, Y, Z, R₃ and R₄ are as described for Formula I;

- 5 R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, -COOH, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; and
- 10 Each R₂ is as described for Formula Ia.

Within further embodiments, compounds provided herein are substituted heterocyclic diarylamine analogues of Formula Ic:

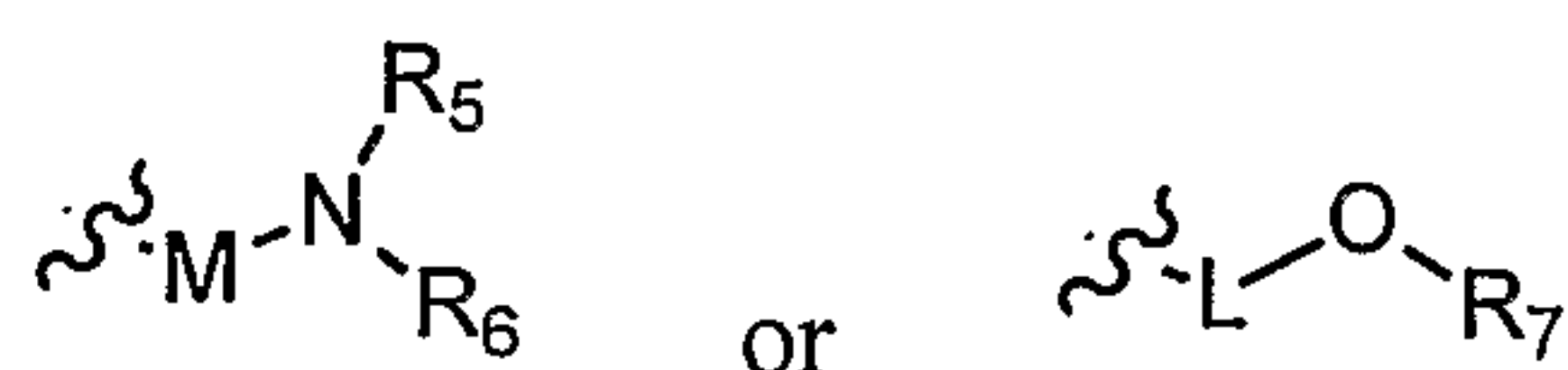


Formula Ic

or are a pharmaceutically acceptable form thereof. Within Formula Ic:

Ar₁, Ar₂, X, Y, Z and R₄ are as described for Formula I: and

- 15 R_{3a} is selected from:
- (i) hydroxy, halogen and C₁-C₆haloalkyl;
 - (ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl; and
 - (iii) groups of the formula



20

wherein

L is a single covalent bond or C₁-C₆alkylene;

M is C₁-C₆alkyl;

R₅ and R₆ are:

5 (a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to M to form a 5- to 7-membered heterocycloalkyl; or

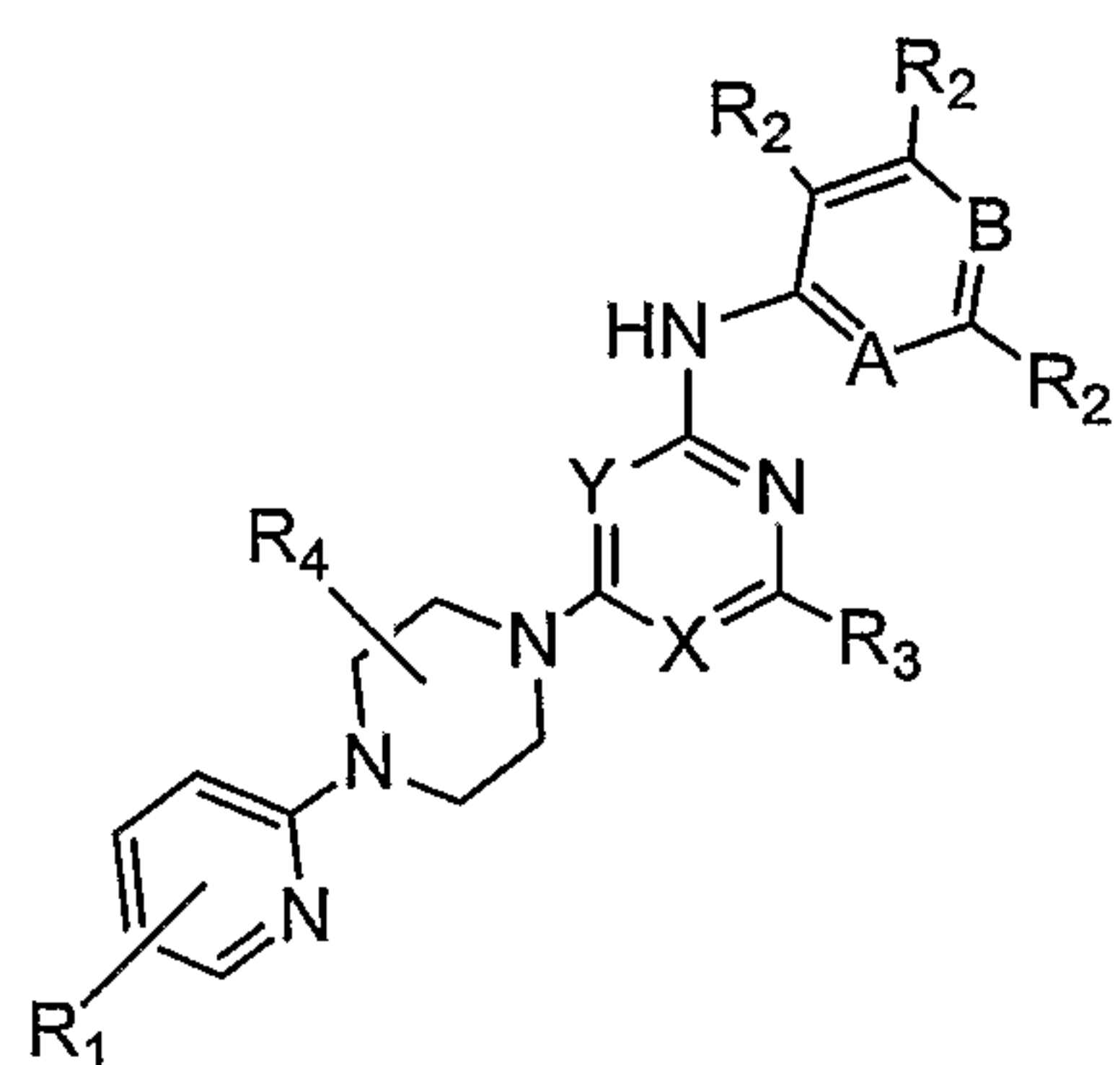
(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

10 R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

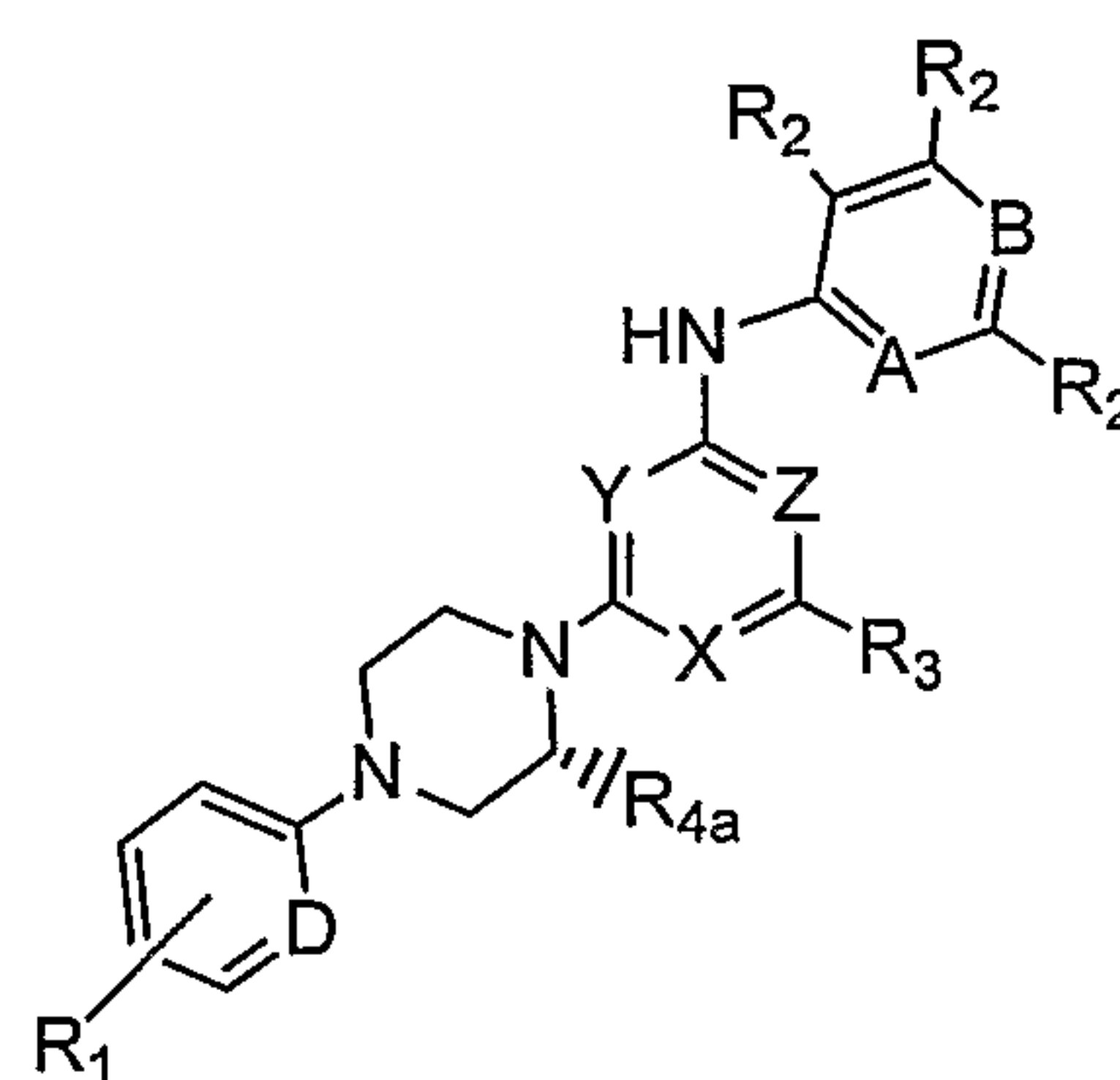
15 wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl.

20 In certain embodiments of Formulas I and Ic, Ar₁ has at least one non-hydrogen substituent; preferably one such substituent is located *ortho* to the point of attachment. In other words, if Ar₁ is phenyl, a non-hydrogen substituent is located at the 2 position, and if Ar₁ is pyridine-2-yl, a non-hydrogen substituent is located at the 3 position. Representative *ortho* substituents include, for example, fluoro, chloro, cyano, methyl, trifluoromethyl and methylsulfonyl.

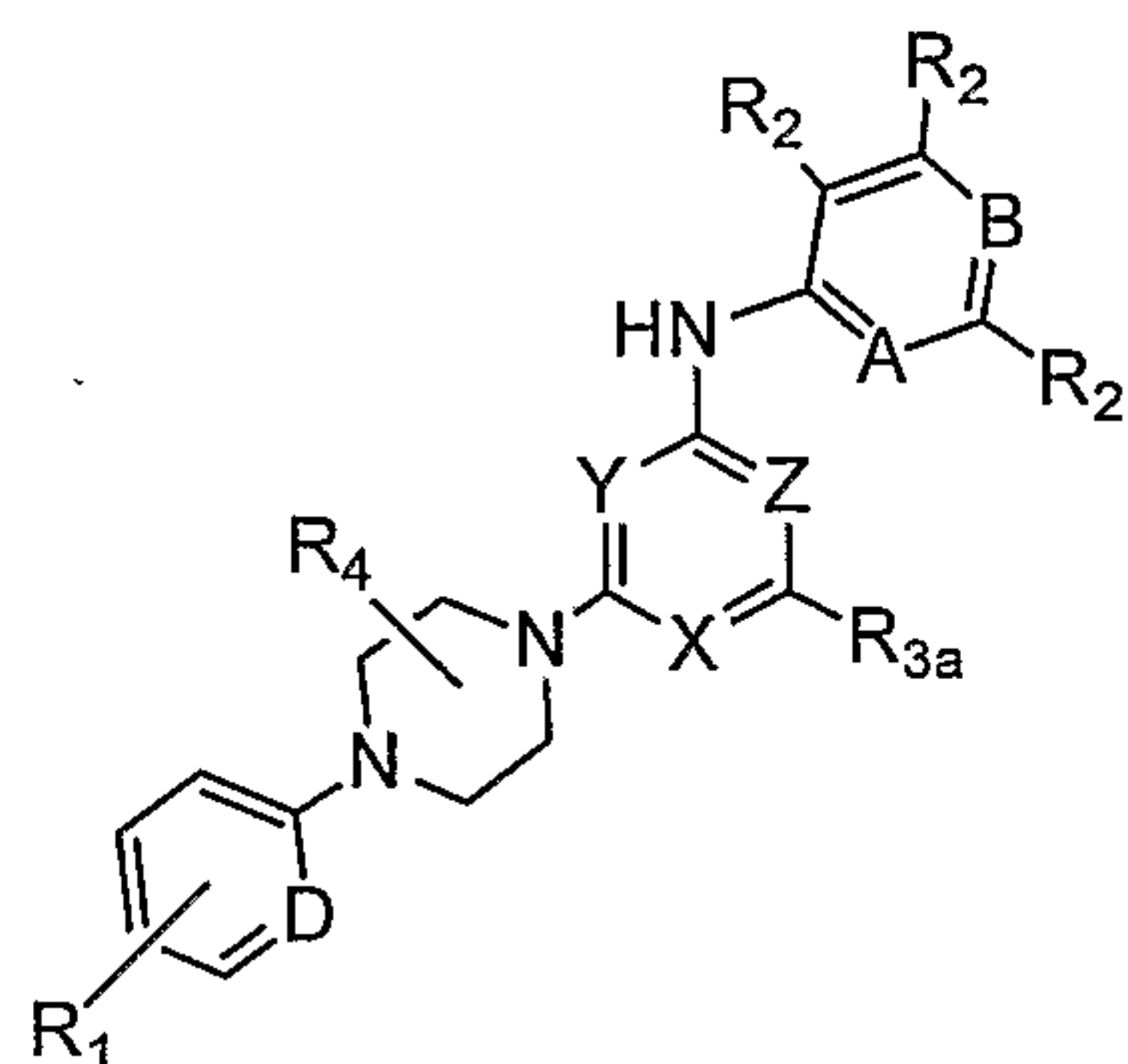
25 Within still further embodiments, certain VR1 modulators provided herein further satisfy one or more of Formulas II, III and IV, or are a pharmaceutically acceptable form thereof, in which R₄, X, Y and Z are as described for Formula I; R₁, A, B and D are as described for Formula Ib (in certain embodiments, A, D, X and/or Y are independently CH or N), and the remaining variables are as indicated below:



Formula II



Formula III



Formula IV

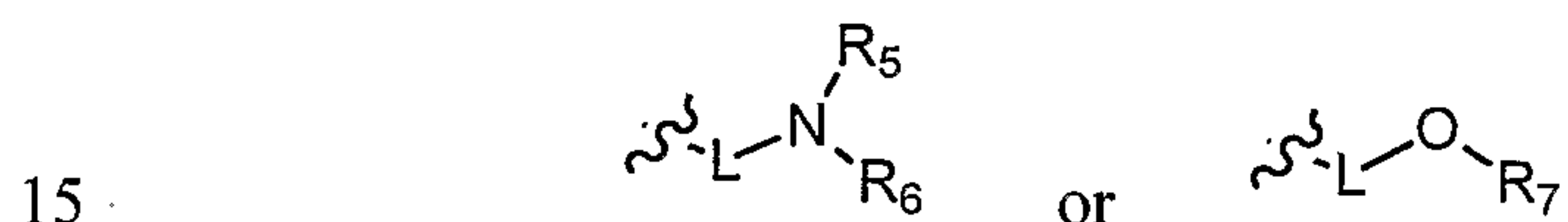
Within Formula II:

Each R_2 is as described above, preferably each R_2 is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C_1 - C_6 haloalkyl, C_2 - C_6 alkyl ether, C_2 - C_6 alkanoyl, C_3 - C_6 alkanone, mono- and di- $(C_1$ - C_6 alkyl)amino C_0 - C_4 alkyl, C_1 - C_6 alkylsulfonyl, mono- and di- $(C_1$ - C_6 alkyl)sulfonamido and mono- and di- $(C_1$ - C_6 alkyl)aminocarbonyl; or
- (ii) taken together with an adjacent R_2 to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen, oxo and C_1 - C_6 alkyl; and

R_3 is as described above, preferably R_3 is selected from:

- (i) hydrogen, hydroxy, halogen and C_1 - C_6 haloalkyl;
- (ii) C_1 - C_6 alkyl, $(C_3$ - C_8 cycloalkyl) C_0 - C_4 alkyl, phenyl C_0 - C_4 alkyl and pyridyl C_0 - C_4 alkyl;
- and
- (iii) groups of the formula



wherein

L is a single covalent bond or C_1 - C_6 alkylene;

R_5 and R_6 are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl, such that neither R₅ nor R₆ is phenyl or pyridyl if L is a bond; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl.

Within Formula III, R₂ and R₃ are as described for Formula Ib; and R_{4a} is methyl or C₁haloalkyl.

Within Formula IV, R₂ is as described for Formula Ib and R_{3a} is as described for Formula Ic.

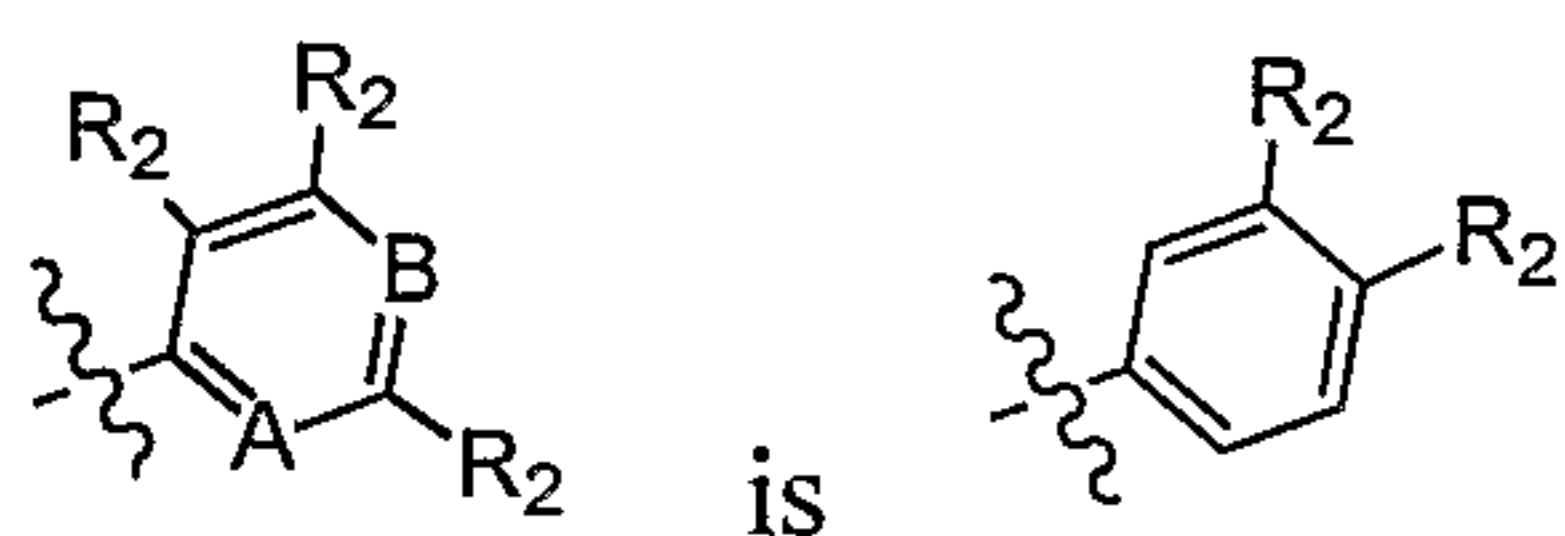
In certain embodiments of Formulas Ib, III and IV, D is N.

In certain embodiments of Formulas Ib, II, III and IV, the variable R₁ represents from 0 to 2 substituents independently chosen from halogen, amino, cyano, -COOH, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido. Within certain such compounds, at least one substituent represented by R₁ is located *ortho* to the point of attachment (*e.g.*, R₁ may represent a single substituent that is located at the *ortho* position). Representative such R₁ groups include, for example, halogen, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)sulfonamido; in certain such compounds, R₁ is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl. Within further such compounds, at least one substituent is located *para* to the point of attachment. Representative such R₁ groups include, for example, halogen, amino, hydroxy, cyano, -COOH, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄hydroxyalkyl, and C₁-C₄haloalkyl.

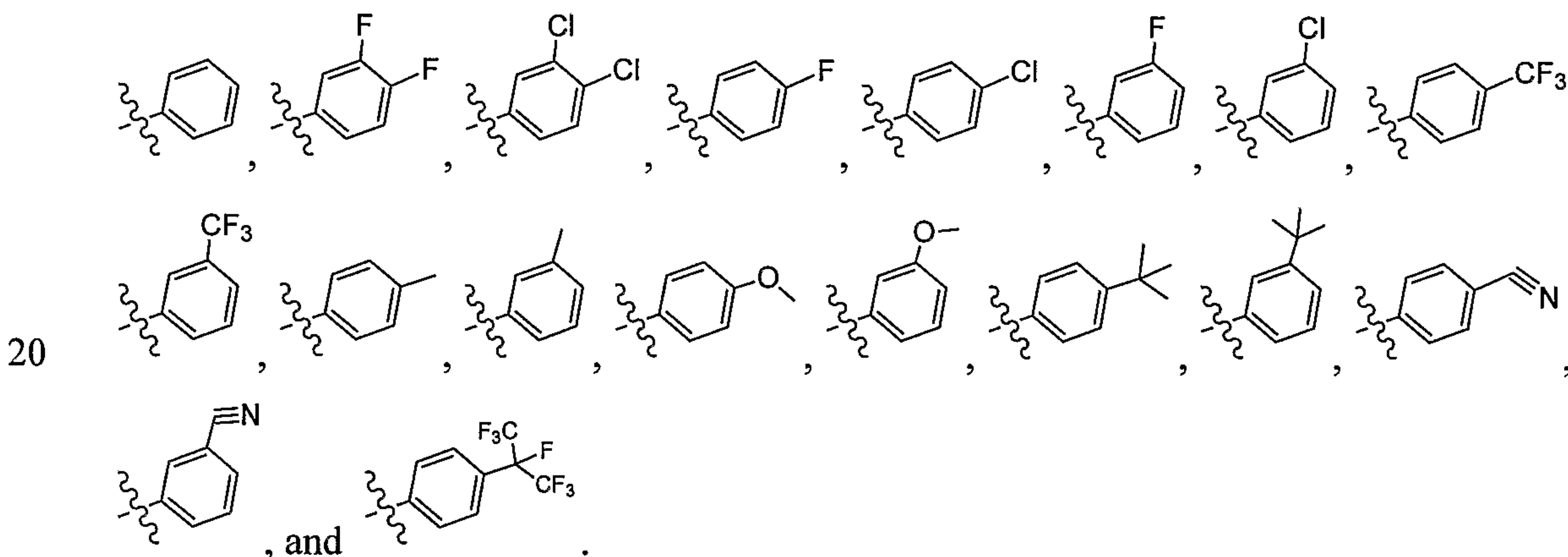
Certain such compounds have two substituents represented by R_1 , one of which is located *ortho* to the point of attachment and the other of which is located *para* to the point of attachment.

Each R_2 , within certain compounds of Formulas Ia, Ib, III and IV is independently
 5 chosen from hydrogen, amino, cyano, halogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkyl ether, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 cyanoalkyl, C_1 - C_6 alkylsulfonyl and mono- and di- $(C_1$ - C_6 alkyl)sulfonamido. Representative such R_2 include, for example, hydrogen, amino, cyano, chloro, fluoro, *t*-butyl and trifluoromethyl. For certain compounds of Formula II, R_2 is independently chosen from hydrogen, amino, cyano,
 10 halogen, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl and mono- and di- $(C_1$ - C_6 alkyl)sulfonamido.

In certain embodiments of Formulas Ib, II, III and IV, the variable B is CR_2 . In further such compounds, A is CH and B is CR_2 . For example, the group:



is within certain such compounds. Representative such groups include, for example: phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, *para*-tolyl, *meta*-tolyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-*tert*-butylphenyl, 3-*tert*-butylphenyl, 4-cyanophenyl, 3-cyanophenyl, and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl, as shown below:

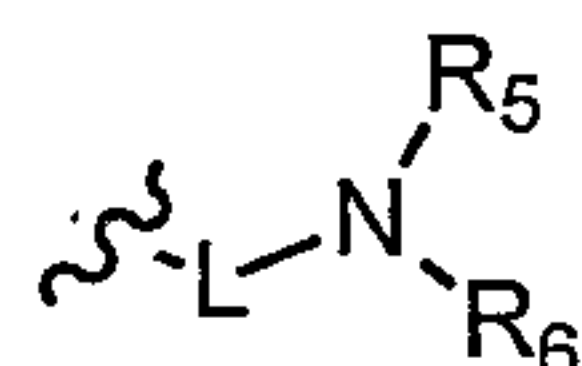


In certain compounds of Formulas Ia, Ib, II, III and IV, at least one R_2 is not hydrogen; in certain embodiments, 1, 2 or 3 R_2 groups are not hydrogen.

In certain embodiments of Formulas I, Ia, Ib, Ic, III and IV, the variable Z is N. For
 25 example, compounds provided herein include those in which (a) Z and X are N and Y is CR_x ; (b) Z and Y are N and X is CR_x ; (c) Z is N and X and Y are CR_x ; or (d) X, Y and Z are each

N. In other embodiments, X and Y are N and Z is CR_x. Similarly, for Formula II, compounds provided herein include those in which (a) X is N and Y is CR_x; (b) Y is N and X is CR_x; (c) X and Y are CR_x; or (d) X and Y are N. In certain compounds, each R_x is independently hydrogen, methyl or cyano.

5 R₃, in certain embodiments of Formulas I, Ia, Ib, II and III, is a group of the formula:



wherein:

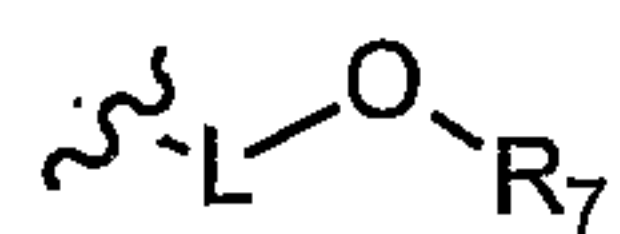
L is a single covalent bond or C₁-C₄alkylene; and

R₅ and R₆ are:

- 10 (a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or
 (b) taken together to form a 5- to 7-membered heterocycloalkyl;
 each of which alkyl, alkenyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, oxo, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₄alkyl)amino.
- 15 Such R₃ groups include, for example, mono- and di-(C₁-C₄alkyl)aminoC₀-C₂alkyl, pyrrolidinylC₀-C₂alkyl, morpholinylC₀-C₂alkyl, piperidinylC₀-C₂alkyl, piperazinylC₀-C₂alkyl and azepanylC₀-C₂alkyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, cyano, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₆alkyl)amino, and preferably each of which is substituted
- 20 with from 0 to 2 substituents independently chosen from halogen, cyano, amino, hydroxy and C₁-C₄alkyl.

In other embodiments, R₃ is $\sim\sim\sim\text{L}-\text{O}-\text{R}_7$, wherein L is a single covalent bond or C₁-C₄alkylene; and R₇ is hydrogen, C₁-C₆alkyl or phenylC₀-C₆alkyl, wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, cyano, amino, C₁-C₄alkyl, C₁-C₆haloalkyl and C₁-C₆alkoxy. Such R₃ groups include, for example, C₁-C₄alkyl ether and benzyloxy, each of which is optionally substituted with chlorine, fluorine or trifluoromethyl.

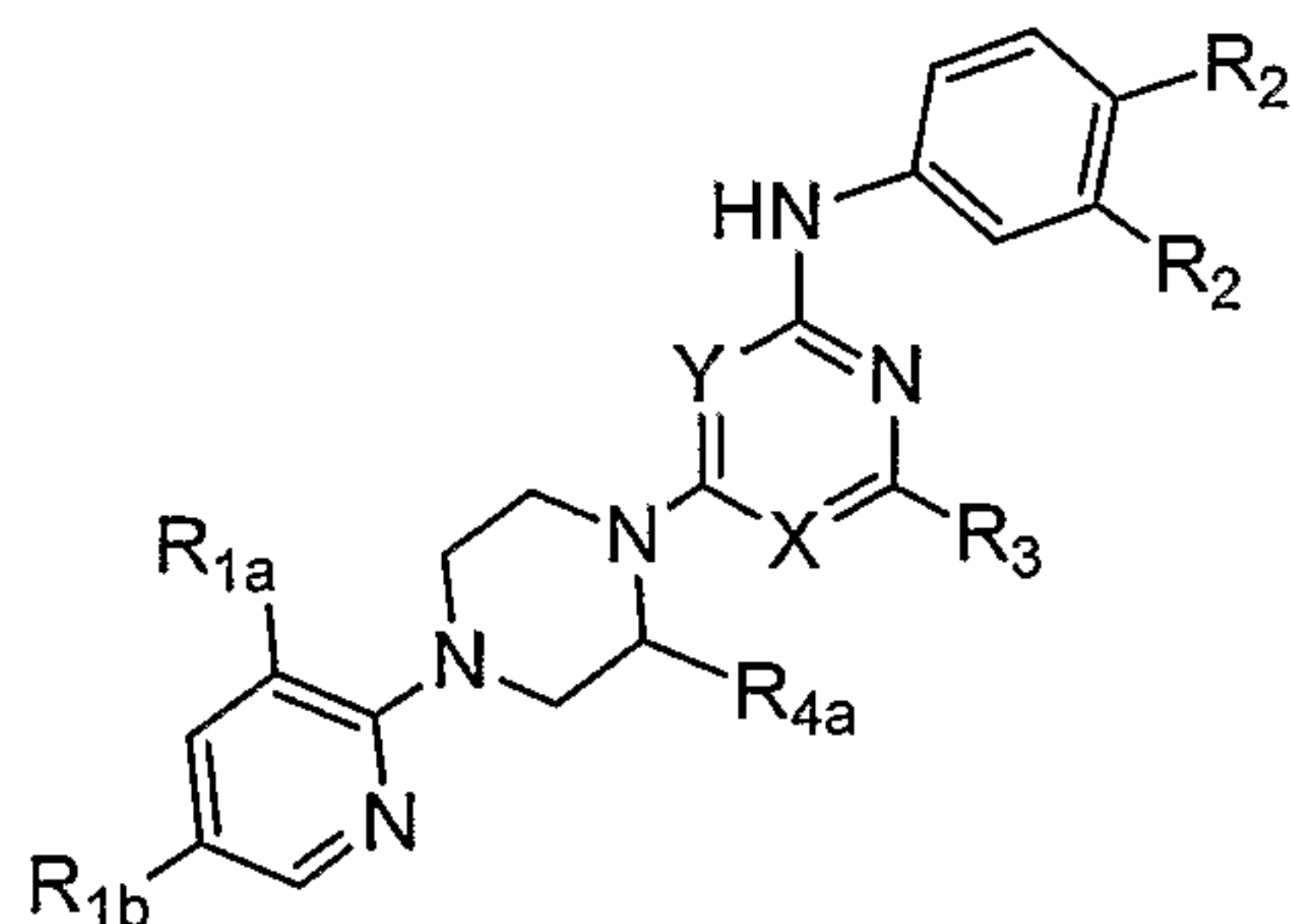
R_{3a}, in certain embodiments of Formulas Ic and IV, is a group of the formula:



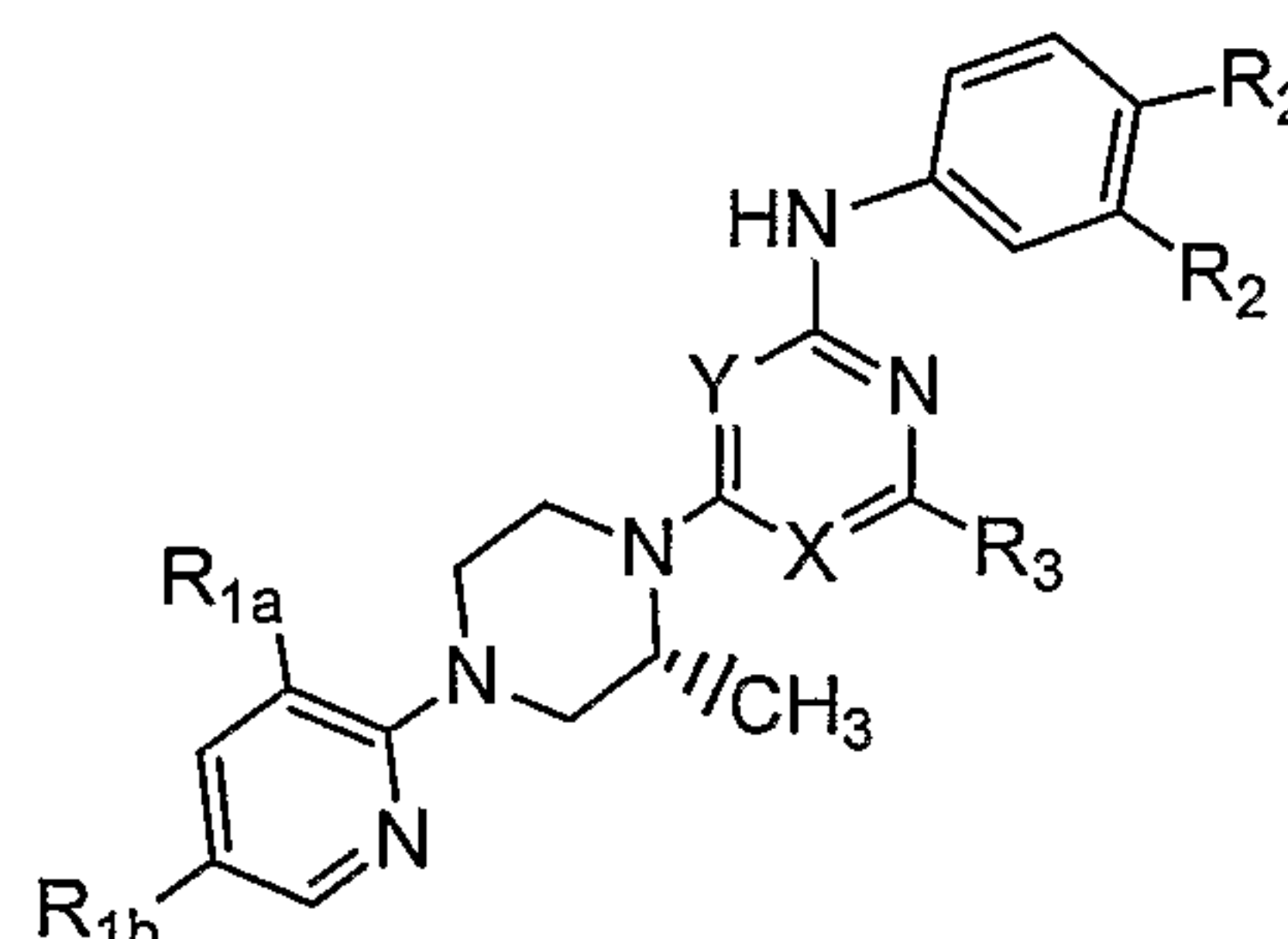
30 as described above. Such R_{3a} groups include, for example, C₂-C₆alkyl ether and benzyloxy, optionally substituted with chlorine, fluorine or trifluoromethyl. In other embodiments, R_{3a} is halogen, C₁-C₆alkyl or (C₃-C₈cycloalkyl)C₀-C₄alkyl.

R₄, in certain compounds of Formulas I, Ia, Ib, Ic, II and IV, represents one substituent, such as a methyl group, located at the 2-position of the piperazine group. The carbon to which such a substituent is attached may, but need not, be chiral, with the R isomer generally preferred.

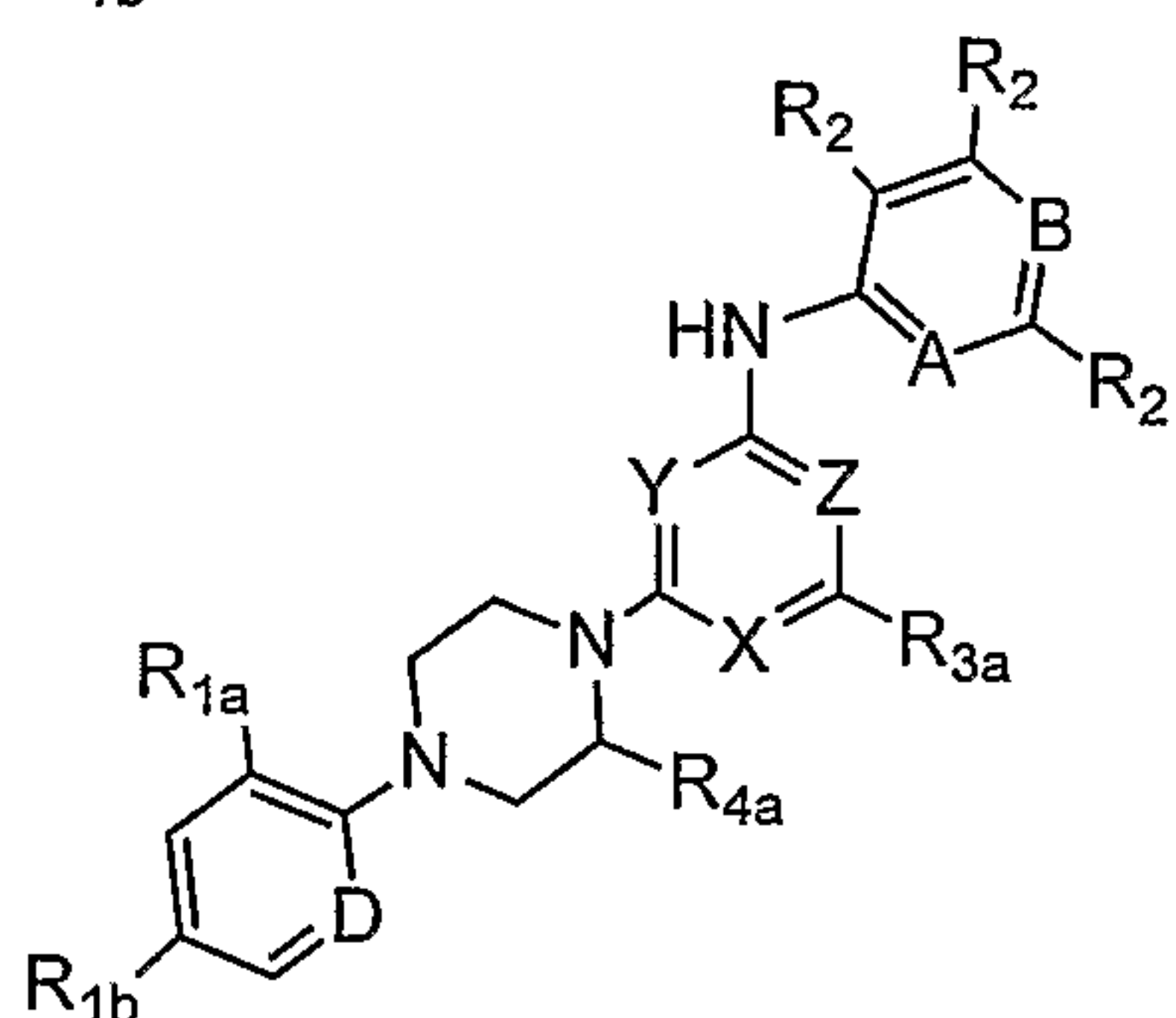
- 5 Within certain embodiments of Formulas II, III and IV, compounds provided herein satisfy Formula IIa, IIIa or IVa, respectively. Variables in each of these formulas are as described for Formulas II, III and IV, respectively, except that R_{4a} of Formula IIa and IVa is hydrogen, methyl, CHO or C₁haloalkyl (preferably hydrogen or methyl); R_{1a} is halogen, hydroxy, amino, cyano, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- or di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)sulfonamido, or mono- or di-(C₁-C₆alkyl)aminocarbonyl; and R_{1b} is hydrogen, halogen, amino, hydroxy, cyano, -COOH, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₆hydroxyalkyl or C₁-C₄haloalkyl. Preferably, R_{1a} is halogen, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)sulfonamido; and R_{1b} is hydrogen, halogen, amino, hydroxy, cyano, -COOH, aminocarbonyl, C₁-C₂alkyl, C₁-C₂alkoxy, C₁-C₂hydroxyalkyl or C₁-C₂haloalkyl



Formula IIa



Formula IIIa



Formula IVa

- 20 Within certain embodiments of Formulas IIa-IVa, R_{1a} is fluoro, chloro, cyano, methyl or trifluoromethyl. For certain compounds of Formula IIa, each R₂ is independently chosen from hydrogen, halogen, cyano and C₁-C₄haloalkyl. For certain compounds of Formula IIIa and IVa, each R₂ is independently chosen from hydrogen, halogen, cyano, C₁-C₄alkyl, C₁-

C₄alkoxy and C₁-C₄haloalkyl. R₃, for certain compounds of Formulas IIa and IIIa, is mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, pyrrolidinylC₀-C₂alkyl, morpholinylC₀-C₂alkyl, piperidinylC₀-C₂alkyl, piperazinylC₀-C₂alkyl, C₂-C₆alkyl ether or benzyloxyC₀-C₂alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, cyano, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₆alkyl)amino. R_{3a}, for certain compounds of Formula IVa, is halogen, C₁-C₆alkyl or (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₂-C₆alkyl ether or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, cyano and C₁-C₄haloalkyl.

Representative compounds provided herein include, but are not limited to, those specifically described in Examples 1-3. It will be apparent that the specific compounds recited therein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a pharmaceutically acceptable form, such as a hydrate or acid addition salt.

Substituted heterocyclic diarylamine analogues provided herein detectably alter (modulate) VR1 activity, as determined using an *in vitro* VR1 ligand binding assay and/or a functional assay such as a calcium mobilization assay, dorsal root ganglion assay or *in vivo* pain relief assay. References herein to a "VR1 ligand binding assay" are intended to refer to a standard *in vitro* receptor binding assay such as that provided in Example 5, and a "calcium mobilization assay" (also referred to herein as a "signal transduction assay") may be performed as described in Example 6. Briefly, to assess binding to VR1, a competition assay may be performed in which a VR1 preparation is incubated with labeled (*e.g.*, ¹²⁵I or ³H) compound that binds to VR1 (*e.g.*, a capsaicin receptor agonist such as RTX) and unlabeled test compound. Within the assays provided herein, the VR1 used is preferably mammalian VR1, more preferably human or rat VR1. The receptor may be recombinantly expressed or naturally expressed. The VR1 preparation may be, for example, a membrane preparation from HEK293 or CHO cells that recombinantly express human VR1. Incubation with a compound that detectably modulates vanilloid ligand binding to VR1 results in a decrease or increase in the amount of label bound to the VR1 preparation, relative to the amount of label bound in the absence of the compound. This decrease or increase may be used to determine the K_i at VR1 as described herein. In general, compounds that decrease the amount of label bound to the VR1 preparation within such an assay are preferred.

As noted above, compounds that are VR1 antagonists are preferred within certain embodiments. IC₅₀ values for such compounds may be determined using a standard *in vitro*

VR1-mediated calcium mobilization assay, as provided in Example 6. Briefly, cells expressing capsaicin receptor are contacted with a compound of interest and with an indicator of intracellular calcium concentration (*e.g.*, a membrane permeable calcium sensitivity dye such as Fluo-3 or Fura-2 (both of which are available, for example, from Molecular Probes, Eugene, OR), each of which produce a fluorescent signal when bound to Ca^{++}). Such contact is preferably carried out by one or more incubations of the cells in buffer or culture medium comprising either or both of the compound and the indicator in solution. Contact is maintained for an amount of time sufficient to allow the dye to enter the cells (*e.g.*, 1-2 hours). Cells are washed or filtered to remove excess dye and are then contacted with a vanilloid receptor agonist (*e.g.*, capsaicin, RTX or olvanil), typically at a concentration equal to the EC_{50} concentration, and a fluorescence response is measured. When agonist-contacted cells are contacted with a compound that is a VR1 antagonist the fluorescence response is generally reduced by at least 20%, preferably at least 50% and more preferably at least 80%, as compared to cells that are contacted with the agonist in the absence of test compound. The IC_{50} for VR1 antagonists provided herein is preferably less than 1 micromolar, less than 100 nM, less than 10 nM or less than 1 nM.

In other embodiments, compounds that are capsaicin receptor agonists are preferred. Capsaicin receptor agonist activity may generally be determined as described in Example 6. When cells are contacted with 1 micromolar of a compound that is a VR1 agonist, the fluorescence response is generally increased by an amount that is at least 30% of the increase observed when cells are contacted with 100 nM capsaicin. The EC_{50} for VR1 agonists provided herein is preferably less than 1 micromolar, less than 100 nM or less than 10 nM.

VR1 modulating activity may also, or alternatively, be assessed using a cultured dorsal root ganglion assay as provided in Example 9 and/or an *in vivo* pain relief assay as provided in Example 10. Compounds provided herein preferably have a statistically significant specific effect on VR1 activity within one or more functional assays provided herein.

Within certain embodiments, VR1 modulators provided herein do not substantially modulate ligand binding to other cell surface receptors, such as EGF receptor tyrosine kinase or the nicotinic acetylcholine receptor. In other words, such modulators do not substantially inhibit activity of a cell surface receptor such as the human epidermal growth factor (EGF) receptor tyrosine kinase or the nicotinic acetylcholine receptor (*e.g.*, the IC_{50} or IC_{40} at such a receptor is preferably greater than 1 micromolar, and most preferably greater than 10 micromolar). Preferably, a modulator does not detectably inhibit EGF receptor activity or

nicotinic acetylcholine receptor activity at a concentration of 0.5 micromolar, 1 micromolar or more preferably 10 micromolar. Assays for determining cell surface receptor activity are commercially available, and include the tyrosine kinase assay kits available from Panvera (Madison, WI).

5 Preferred VR1 modulators provided herein are non-sedating. In other words, a dose of VR1 modulator that is twice the minimum dose sufficient to provide analgesia in an animal model for determining pain relief (such as a model provided in Example 10, herein) causes only transient (*i.e.*, lasting for no more than $\frac{1}{2}$ the time that pain relief lasts) or preferably no statistically significant sedation in an animal model assay of sedation (using the
10 method described by Fitzgerald et al. (1988) *Toxicology* 49(2-3):433-9). Preferably, a dose that is five times the minimum dose sufficient to provide analgesia does not produce statistically significant sedation. More preferably, a VR1 modulator provided herein does not produce sedation at intravenous doses of less than 25 mg/kg (preferably less than 10 mg/kg) or at oral doses of less than 140 mg/kg (preferably less than 50 mg/kg, more preferably less
15 than 30 mg/kg).

If desired, VR1 modulators provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective concentrations of the compound to be achieved at oral doses of less than 140 mg/kg,
20 preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred VR1 modulator is nontoxic when a capsaicin receptor modulatory amount is administered to a subject), side effects (a preferred VR1 modulator produces side effects comparable to placebo when a therapeutically effective amount of the
25 compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred VR1 modulator exhibits an *in vitro* half-life that is equal to an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable for VR1 modulators used to treat pain by modulating CNS VR1
30 activity such that total daily oral doses as described above provide such modulation to a therapeutically effective extent, while low brain levels of VR1 modulators used to treat peripheral nerve mediated pain may be preferred (*i.e.*, such doses do not provide brain (*e.g.*, CSF) levels of the compound sufficient to significantly modulate VR1 activity). Routine assays that are well known in the art may be used to assess these properties, and identify

superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously).
5 Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 7, herein.

As noted above, preferred VR1 modulators provided herein are nontoxic. In general,
10 the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally
15 satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, and (4) does not cause substantial release of liver enzymes.

As used herein, a VR1 modulator that "does not substantially inhibit cellular ATP production" is a compound that satisfies the criteria set forth in Example 8, herein. In other
20 words, cells treated as described in Example 8 with 100 μ M of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A VR1 modulator that "does not significantly prolong heart QT intervals" is a
25 compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of twice the minimum dose yielding a therapeutically effective *in vivo* concentration. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of
30 heart QT intervals. By "statistically significant" is meant results varying from control at the $p < 0.1$ level or more preferably at the $p < 0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A VR1 modulator "does not cause substantial liver enlargement" if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with twice the minimum dose that yields

a therapeutically effective *in vivo* concentration results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result
5 in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a VR1 modulator "does not promote substantial release of liver enzymes" if
10 administration of twice the minimum dose yielding a therapeutically effective *in vivo* concentration does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternatively, a VR1 modulator "does not promote substantial release of
15 liver enzymes" if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) equivalent to two-fold the minimum *in vivo* therapeutic concentration of the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no
20 detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the minimum *in vivo* therapeutic concentration of the compound.

In other embodiments, certain preferred VR1 modulators do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity,
25 CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the minimum therapeutically effective *in vivo* concentration.

Certain preferred VR1 modulators are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral
30 micronucleus assay or the like) at a concentration equal to the minimum therapeutically effective *in vivo* concentration. In other embodiments, certain preferred VR1 modulators do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, VR1 modulators provided herein may be isotopically-labeled or radiolabeled. For example, compounds recited in Formulas I-III may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF VR1 MODULATORS

Substituted heterocyclic diarylamine analogues may generally be prepared using standard synthetic methods. Starting materials are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of Schemes 1-4 may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Each variable in the following schemes refers to any group consistent with the description of the compounds provided herein.

In the Schemes and Examples provided herein, certain definitions are as follows:

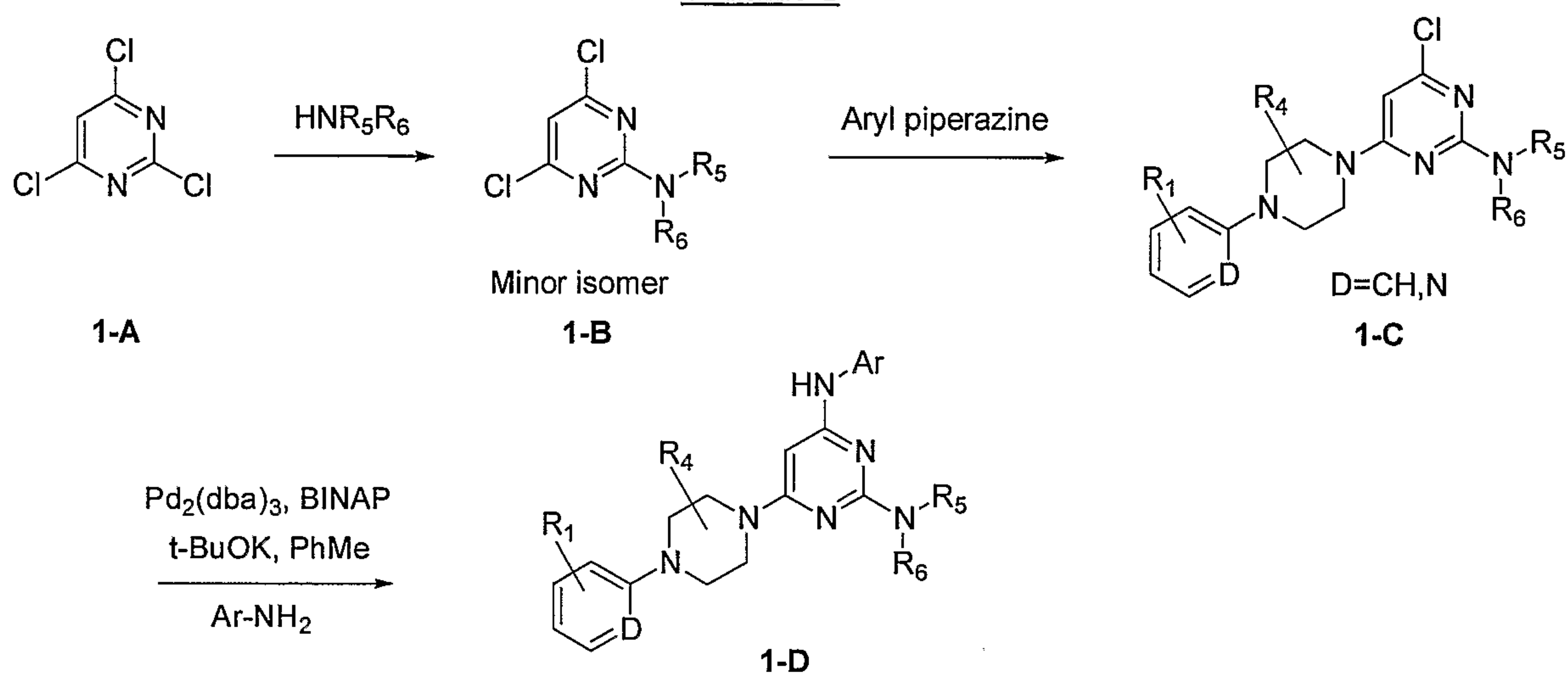
Ar	an optionally substituted aromatic 6-membered ring
Aryl piperazine	piperazine substituted at the 4-position with an optionally substituted 6-membered aromatic ring, and optionally substituted with R_4 at the 2, 3, 5 and/or 6 position of the piperazine
25 BINAP	(<i>rac</i>)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Et_3N	triethylamine
MS	mass spectrometry
(M+1)	mass + 1
EtOAc	ethyl acetate
30 EtOH	ethanol
$\text{Pd}_2(\text{dba})_3$	tris[dibenzylideneacetone]di-palladium
Ph	phenyl
t-BuOK	Potassium <i>tert</i> -butoxide

THF

tetrahydrofuran

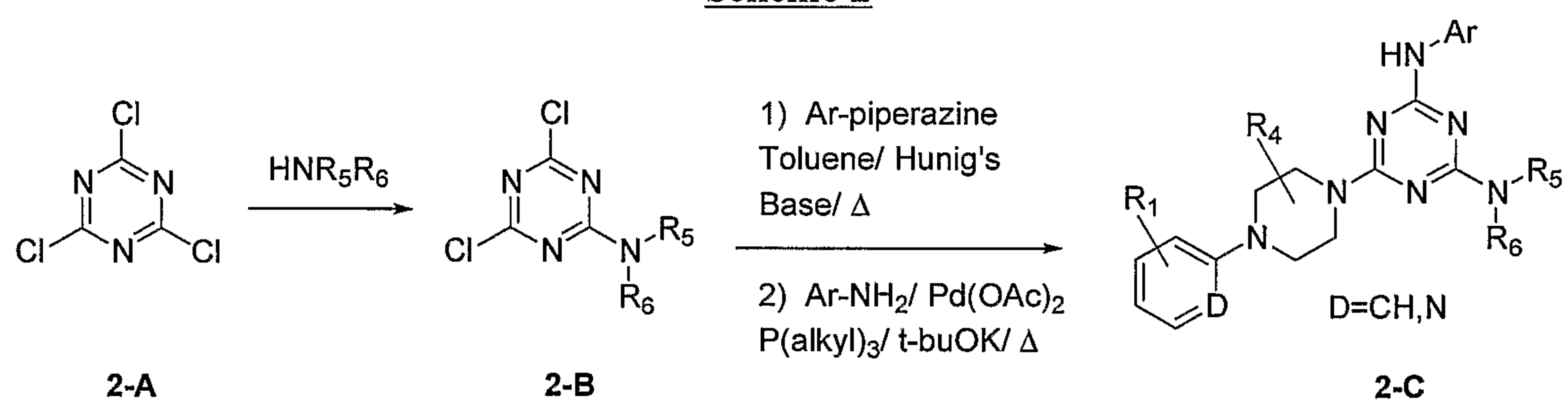
TLC

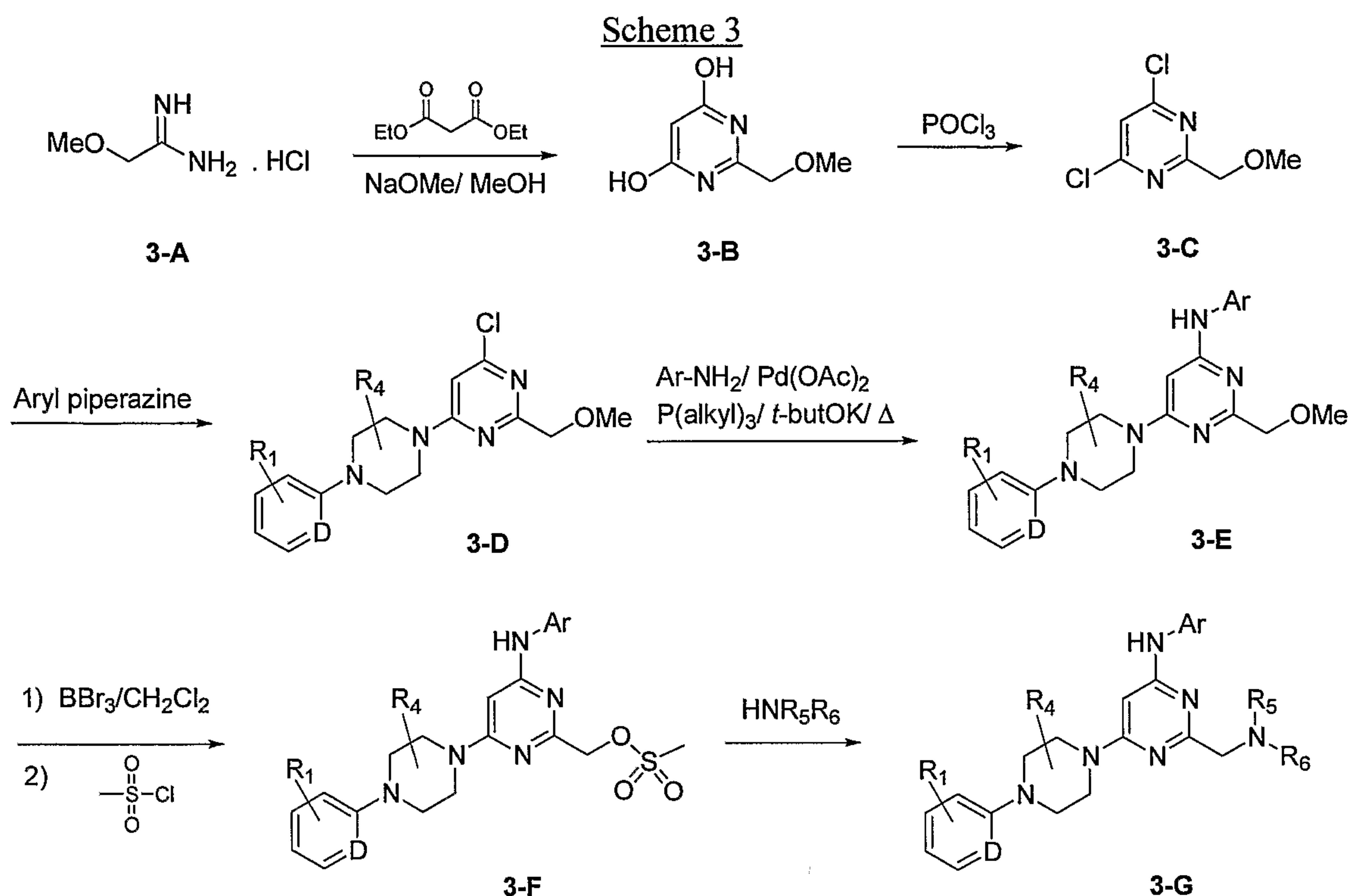
thin layer chromatography

Scheme 1

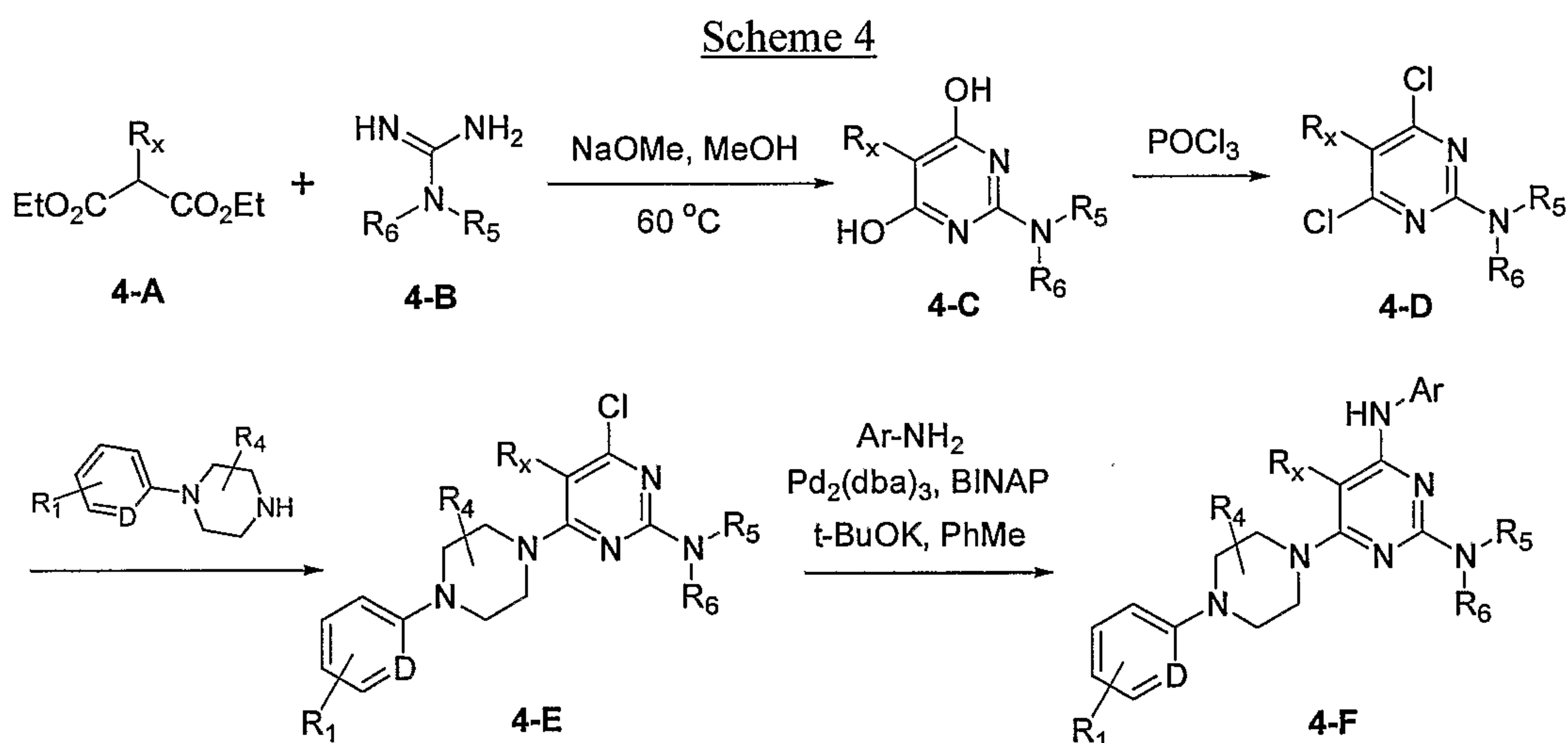
5

10

Scheme 2



5



10 In certain embodiments, a VR1 modulator may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers

15 include asymmetric synthesis and resolution of the racemates. Resolution of the racemates

can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (e.g., ^{14}C), hydrogen (e.g., ^3H), sulfur (e.g., ^{35}S), or iodine (e.g., ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more VR1 modulators, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (e.g., neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate. Formulation for topical administration may be preferred for certain conditions (e.g., in the treatment of skin conditions such as burns

or itch). Formulation for direct administration into the bladder (intravesicular administration) may be preferred for treatment of urinary incontinence and overactive bladder.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, 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 partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard

paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions 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
5 by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

10 Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil), a mineral oil (*e.g.*, liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*,
15 sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more
20 demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery.
25 Topical vehicles include water; organic solvents such as alcohols (*e.g.*, ethanol or isopropyl alcohol) or glycerin; glycols (*e.g.*, butylene, isoprene or propylene glycol); aliphatic alcohols (*e.g.*, lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides,
30 sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling

agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as
5 hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. The physical appearance and viscosity of such pharmaceutically acceptable forms
10 can be governed by the presence and amount of emulsifier(s) and viscosity adjuster(s) present in the formulation. Solids are generally firm and non-pourable and commonly are formulated as bars or sticks, or in particulate form; solids can be opaque or transparent, and optionally can contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final
15 product. Creams and lotions are often similar to one another, differing mainly in their viscosity; both lotions and creams may be opaque, translucent or clear and often contain emulsifiers, solvents, and viscosity adjusting agents, as well as moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Gels can be prepared with a range of viscosities, from thick
20 or high viscosity to thin or low viscosity. These formulations, like those of lotions and creams, may also contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Liquids are thinner than creams, lotions, or gels and often do not contain emulsifiers. Liquid topical products often contain solvents, emulsifiers,
25 moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product.

Suitable emulsifiers for use in topical formulations include, but are not limited to, ionic emulsifiers, cetearyl alcohol, non-ionic emulsifiers like polyoxyethylene oleyl ether, PEG-40 stearate, cetareth-12, cetareth-20, cetareth-30, cetareth alcohol, PEG-100
30 stearate and glyceryl stearate. Suitable viscosity adjusting agents include, but are not limited to, protective colloids or non-ionic gums such as hydroxyethylcellulose, xanthan gum, magnesium aluminum silicate, silica, microcrystalline wax, beeswax, paraffin, and cetyl palmitate. A gel composition may be formed by the addition of a gelling agent such as chitosan, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyquaterniums,

hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate. Suitable surfactants include, but are not limited to, nonionic, amphoteric, ionic and anionic surfactants. For example, one or more of dimethicone copolyol, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, lauramide DEA, cocamide DEA, and cocamide MEA, oleyl betaine, cocamidopropyl phosphatidyl PG-dimonium chloride, and ammonium laureth sulfate may be used within topical formulations. Suitable preservatives include, but are not limited to, antimicrobials such as methylparaben, propylparaben, sorbic acid, benzoic acid, and formaldehyde, as well as physical stabilizers and antioxidants such as vitamin E, sodium ascorbate/ascorbic acid and propyl gallate. Suitable moisturizers include, but are not limited to, lactic acid and other hydroxy acids and their salts, glycerin, propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol, petrolatum, isostearyl neopentanoate and mineral oils. Suitable fragrances and colors include, but are not limited to, FD&C Red No. 40 and FD&C Yellow No. 5. Other suitable additional ingredients that may be included a topical formulation include, but are not limited to, abrasives, absorbents, anti-caking agents, anti-foaming agents, anti-static agents, astringents (*e.g.*, witch hazel, alcohol and herbal extracts such as chamomile extract), binders/excipients, buffering agents, chelating agents, film forming agents, conditioning agents, propellants, opacifying agents, pH adjusters and protectants.

20 An example of a suitable topical vehicle for formulation of a gel is: hydroxypropylcellulose (2.1%); 70/30 isopropyl alcohol/water (90.9%); propylene glycol (5.1%); and Polysorbate 80 (1.9%). An example of a suitable topical vehicle for formulation as a foam is: cetyl alcohol (1.1%); stearyl alcohol (0.5%); Quaternium 52 (1.0%); propylene glycol (2.0%); Ethanol 95 PGF3 (61.05%); deionized water (30.05%); P75 hydrocarbon
25 propellant (4.30%). All percents are by weight.

Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing. Controlled release vehicles can also be used.

30 A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The modulator, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be

employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Modulators may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that 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.

Pharmaceutical compositions may be formulated as sustained release formulations (*i.e.*, a formulation such as a capsule that effects a slow release of modulator following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In addition to or together with the above modes of administration, a modulator may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Modulators are generally administered in a capsaicin receptor modulatory amount, and preferably a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated

and the particular mode of administration. Dosage units will generally contain between from about 10 µg to about 500 mg of an active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating conditions responsive to VR1 modulation (*e.g.*, treatment of exposure to vanilloid ligand, pain, itch, obesity or urinary incontinence). Packaged pharmaceutical compositions may include a container holding a therapeutically effective amount of at least one VR1 modulator as described herein and instructions (*e.g.*, labeling) indicating that the contained composition is to be used for treating a condition responsive to VR1 modulation in the patient.

10 METHODS OF USE

VR1 modulators provided herein may be used to alter activity and/or activation of capsaicin receptors in a variety of contexts, both *in vitro* and *in vivo*. Within certain aspects, VR1 antagonists may be used to inhibit the binding of vanilloid ligand agonist (such as capsaicin and/or RTX) to capsaicin receptor *in vitro* or *in vivo*. In general, such methods comprise the step of contacting a capsaicin receptor with a capsaicin receptor modulatory amount of one or more VR1 modulators provided herein, in the presence of vanilloid ligand in aqueous solution and under conditions otherwise suitable for binding of the ligand to capsaicin receptor. The capsaicin receptor may be present in solution or suspension (*e.g.*, in an isolated membrane or cell preparation), or in a cultured or isolated cell. Within certain embodiments, the capsaicin receptor is expressed by a neuronal cell present in a patient, and the aqueous solution is a body fluid. Preferably, one or more VR1 modulators are administered to an animal in an amount such that the analogue is present in at least one body fluid of the animal at a therapeutically effective concentration that is 1 micromolar or less; preferably 500 nanomolar or less; more preferably 100 nanomolar or less, 50 nanomolar or less, 20 nanomolar or less, or 10 nanomolar or less. For example, such compounds may be administered at a dose that is less than 20 mg/kg body weight, preferably less than 5 mg/kg and, in some instances, less than 1 mg/kg.

Also provided herein are methods for modulating, preferably reducing, the signal-transducing activity (*i.e.*, the calcium conductance) of a cellular capsaicin receptor. Such modulation may be achieved by contacting a capsaicin receptor (either *in vitro* or *in vivo*) with a capsaicin receptor modulatory amount of one or more VR1 modulators provided herein under conditions suitable for binding of the modulator(s) to the receptor. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or in a cell

within a patient. For example, the cell may be a neuronal cell that is contacted *in vivo* in an animal. Alternatively, the cell may be an epithelial cell, such as a urinary bladder epithelial cell (urothelial cell) or an airway epithelial cell that is contacted *in vivo* in an animal. Modulation of signal transducing activity may be assessed by detecting an effect on calcium ion conductance (also referred to as calcium mobilization or flux). Modulation of signal transducing activity may alternatively be assessed by detecting an alteration of a symptom (e.g., pain, burning sensation, broncho-constriction, inflammation, cough, hiccup, itch, urinary incontinence or overactive bladder) of a patient being treated with one or more VR1 modulators provided herein.

VR1 modulator(s) provided herein are preferably administered to a patient (e.g., a human) orally or topically, and are present within at least one body fluid of the animal while modulating VR1 signal-transducing activity. Preferred VR1 modulators for use in such methods modulate VR1 signal-transducing activity *in vitro* at a concentration of 1 nanomolar or less, preferably 100 picomolar or less, more preferably 20 picomolar or less, and *in vivo* at a concentration of 1 micromolar or less, 500 nanomolar or less, or 100 nanomolar or less in a body fluid such as blood.

The present invention further provides methods for treating conditions responsive to VR1 modulation. Within the context of the present invention, the term "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). A condition is "responsive to VR1 modulation" if it is characterized by inappropriate activity of a capsaicin receptor, regardless of the amount of vanilloid ligand present locally, and/or if modulation of capsaicin receptor activity results in alleviation of the condition or a symptom thereof. Such conditions include, for example, symptoms resulting from exposure to VR1-activating stimuli, pain, respiratory disorders such as asthma and chronic obstructive pulmonary disease, itch, urinary incontinence, overactive bladder, cough, hiccup, and obesity, as described in more detail below. Such conditions may be diagnosed and monitored using criteria that have been established in the art. Patients may include humans, domesticated companion animals and livestock, with dosages as described above.

Treatment regimens may vary depending on the compound used and the particular condition to be treated. However, for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage regimen of 2 times

daily is more preferred, with once a day dosing particularly preferred. For the treatment of acute pain, a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Patients experiencing symptoms resulting from exposure to capsaicin receptor-activating stimuli include individuals with burns caused by heat, light, tear gas or acid and those whose mucous membranes are exposed (*e.g.*, via ingestion, inhalation or eye contact) to capsaicin (*e.g.*, from hot peppers or in pepper spray) or a related irritant such as acid, tear gas or air pollutants. The resulting symptoms (which may be treated using VR1 modulators, especially antagonists, provided herein) may include, for example, pain, broncho-constriction and inflammation.

Pain that may be treated using the VR1 modulators provided herein may be chronic or acute and includes, but is not limited to, peripheral nerve-mediated pain (especially neuropathic pain). Compounds provided herein may be used in the treatment of, for example, postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache (dental pain), denture pain, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome and/or bilateral peripheral neuropathy. Additional neuropathic pain conditions include causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve), neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (*e.g.*, those mentioned above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia), surgery-related pain, musculoskeletal pain, AIDS-related neuropathy, MS-related neuropathy, and spinal cord

injury-related pain. Headache, including headaches involving peripheral nerve activity, such as sinus, cluster (*i.e.*, migranous neuralgia) and some tension headaches and migraine, may also be treated as described herein. For example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient. Further pain conditions that can be treated as described herein include "burning mouth syndrome," labor pains, Charcot's pains, intestinal gas pains, menstrual pain, acute and chronic back pain (*e.g.*, lower back pain), hemorrhoidal pain, dyspeptic pains, angina, nerve root pain, homotopic pain and heterotopic pain – including cancer associated pain (*e.g.*, in patients with bone cancer), pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma associated pain (*e.g.*, post-surgical pain, pain from cuts, bruises and broken bones, and burn pain). Additional pain conditions that may be treated as described herein include pain associated with inflammatory bowel disease, irritable bowel syndrome and/or inflammatory bowel disease.

Within certain aspects, VR1 modulators provided herein may be used for the treatment of mechanical pain. As used herein, the term "mechanical pain" refers to pain other than headache pain that is not neuropathic or a result of exposure to heat, cold or external chemical stimuli. Mechanical pain includes physical trauma (other than thermal or chemical burns or other irritating and/or painful exposures to noxious chemicals) such as post-surgical pain and pain from cuts, bruises and broken bones; toothache, denture pain; nerve root pain; osteoarthritis; rheumatoid arthritis; fibromyalgia; meralgia paresthetica; back pain; cancer-associated pain; angina; carpal tunnel syndrome; and pain resulting from bone fracture, labor, hemorrhoids, intestinal gas, dyspepsia, and menstruation.

Itching conditions that may be treated include psoriatic pruritis, itch due to hemodialysis, allergic pruritus, and itching associated with vulvar vestibulitis, contact dermatitis, insect bites and skin allergies. Urinary tract conditions that may be treated as described herein include urinary incontinence (including overflow incontinence, urge incontinence and stress incontinence), as well as overactive or unstable bladder conditions (including detrusor hyperflexia of spinal origin and bladder hypersensitivity). In certain such treatment methods, VR1 modulator is administered via a catheter or similar device, resulting in direct injection of VR1 modulator into the bladder. Compounds provided herein may also be used as anti-tussive agents (to prevent, relieve or suppress coughing) and for the treatment of hiccup, and to promote weight loss in an obese patient.

Within other aspects, VR1 modulators provided herein may be used within combination therapy for the treatment of conditions involving inflammatory components. Such conditions include, for example, autoimmune disorders and pathologic autoimmune responses known to have an inflammatory component including, but not limited to, arthritis
5 (especially rheumatoid arthritis), psoriasis, Crohn's disease, lupus erythematosus, irritable bowel syndrome, tissue graft rejection, and hyperacute rejection of transplanted organs. Other such conditions include trauma (*e.g.*, injury to the head or spinal cord), cardio- and cerebo-vascular disease and certain infectious diseases.

Within such combination therapy, a VR1 modulator is administered to a patient along
10 with an anti-inflammatory agent. The VR1 modulator and anti-inflammatory agent may be present in the same pharmaceutical composition, or may be administered separately in either order. Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF)
15 receptor antagonists, anti-TNF alpha antibodies, anti-C5 antibodies, and interleukin-1 (IL-1) receptor antagonists. Examples of NSAIDs include, but are not limited to ibuprofen (*e.g.*, ADVIL™, MOTRIN™), flurbiprofen (ANSAID™), naproxen or naproxen sodium (*e.g.*, NAPROSYN, ANAPROX, ALEVE™), diclofenac (*e.g.*, CATAFLAM™, VOLTAREN™), combinations of diclofenac sodium and misoprostol (*e.g.*, ARTHROTEC™), sulindac
20 (CLINORIL™), oxaprozin (DAYPRO™), diflunisal (DOLOBID™), piroxicam (FELDENE™), indomethacin (INDOCIN™), etodolac (LODINE™), fenoprofen calcium (NALFON™), ketoprofen (*e.g.*, ORUDIS™, ORUVAIL™), sodium nabumetone (RELAFEN™), sulfasalazine (AZULFIDINE™), tolmetin sodium (TOLECTIN™), and hydroxychloroquine (PLAQUENIL™). A particular class of NSAIDs consists of compounds
25 that inhibit cyclooxygenase (COX) enzymes, such as celecoxib (CELEBREX™) and rofecoxib (VIOXX™). NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates (TRILISATE™), and salsalate (DISALCID™), as well as corticosteroids such as cortisone (CORTONE™ acetate), dexamethasone (*e.g.*, DECADRON™), methylprednisolone (MEDROL™) prednisolone
30 (PRELONE™), prednisolone sodium phosphate (PEDIAPRED™), and prednisone (*e.g.*, PREDNICEN-M™, DELTASONE™, STERAPRED™).

Suitable dosages for VR1 modulator within such combination therapy are generally as described above. Dosages and methods of administration of anti-inflammatory agents can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In

certain embodiments, the combination administration of a VR1 modulator with an anti-inflammatory agent results in a reduction of the dosage of the anti-inflammatory agent required to produce a therapeutic effect. Thus, preferably, the dosage of anti-inflammatory agent in a combination or combination treatment method of the invention is less than the
5 maximum dose advised by the manufacturer for administration of the anti-inflammatory agent without combination administration of a VR1 antagonist. More preferably this dosage is less than $\frac{3}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably, less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent(s) when
10 administered without combination administration of a VR1 antagonist. It will be apparent that the dosage amount of VR1 antagonist component of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the anti-inflammatory agent component of the combination.

In certain preferred embodiments, the combination administration of a VR1
15 modulator with an anti-inflammatory agent is accomplished by packaging one or more VR1 modulators and one or more anti-inflammatory agents in the same package, either in separate containers within the package or in the same contained as a mixture of one or more VR1 antagonists and one or more anti-inflammatory agents. Preferred mixtures are formulated for oral administration (*e.g.*, as pills, capsules, tablets or the like). In certain embodiments, the
20 package comprises a label bearing indicia indicating that the one or more VR1 modulators and one or more anti-inflammatory agents are to be taken together for the treatment of an inflammatory pain condition. A highly preferred combination is one in which the anti-inflammatory agent(s) include at least one COX-2 specific cyclooxygenase enzyme inhibitor such as valdecoxib (BEXTRA®), lumiracoxib (PREXIGE™), etoricoxib (ARCOXIA®),
25 celecoxib (CELEBREX®) and/or rofecoxib (VIOXX®).

Within further aspects, VR1 modulators provided herein may be used in combination with one or more additional pain relief medications. Certain such medications are also anti-inflammatory agents, and are listed above. Other such medications are narcotic analgesic agents, which typically act at one or more opioid receptor subtypes (*e.g.*, μ , κ and/or δ),
30 preferably as agonists or partial agonists. Such agents include opiates, opiate derivatives and opioids, as well as pharmaceutically acceptable salts and hydrates thereof. Specific examples of narcotic analgesics include, within preferred embodiments, alfentanyl, alphaprodine, anileridine, bezitramide, buprenorphine, codeine, diacetyldihydromorphine, diacetylmorphine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin,

hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphan, levorphanol, meperidine, metazocine, methadone, methorphan, metopon, morphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, paregoric, pentazocine, pethidine, phenazocine, piminodine, propoxyphene, racemethorphan, racemorphan, thebaine and pharmaceutically acceptable salts and hydrates of the foregoing agents.

Other examples of narcotic analgesic agents include acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alpracetilmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, butorphanol, clonitazene, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiamubutene, dioxaphetyl butyrate, dipipanone, drotebanol, ethanol, ethylmethylthiambutene, etonitazene, etorphine, etoxeridine, furethidine, hydromorphenol, hydroxypethidine, ketobemidone, levomoramide, levophenacymorphan, methyl-desorphine, methyldihydromorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, naloxone, nalbuypine, naltrexone, nicocodeine, nicomorphine, noracymethadol, norlevorphanol, normethadone, normorphine, norpipanone, pentazocaine, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine, proheptazone, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts and hydrates thereof.

Further specific representative analgesic agents include, for example: TALWIN® Nx and DEMEROL® (both available from Sanofi Winthrop Pharmaceuticals; New York, NY); LEVO-DROMORAN®; BUPRENEX® (Reckitt & Coleman Pharmaceuticals, Inc.; Richmond, VA); MSIR® (Purdue Pharma L.P.; Norwalk, CT); DILAUDID® (Knoll Pharmaceutical Co.; Mount Olive, NJ); SUBLIMAZE®; SUFENTA® (Janssen Pharmaceutica Inc.; Titusville, NJ); PERCOCET®, NUBAIN® and NUMORPHAN® (all available from Endo Pharmaceuticals Inc.; Chadds Ford, PA) HYDROSTAT® IR, MS/S and MS/L (all available from Richwood Pharmaceutical Co. Inc; Florence, KY), ORAMORPH® SR and ROXICODONE® (both available from Roxanne Laboratories; Columbus OH) and STADOL® (Bristol-Myers Squibb; New York, NY). Still further analgesic agents include CB2-receptor agonists, such as AM1241, and compounds that bind to the $\alpha 2\delta$ subunit, such as Neurontin (Gabapentin) and pregabalin.

Suitable dosages for VR1 modulator within such combination therapy are generally as described above. Dosages and methods of administration of other pain relief medications can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a VR1 modulator with one or more additional pain medications results in a reduction of the dosage of each therapeutic agent required to produce a therapeutic effect (*e.g.*, the dosage of one or both agent may be less than $\frac{3}{4}$, less than $\frac{1}{2}$, less than $\frac{1}{4}$ or less than 10% of the maximum dose listed above or advised by the manufacturer). In certain preferred embodiments, the combination administration of a VR1 modulator with one or more additional pain relief medications is accomplished by packaging one or more VR1 modulators and one or more additional pain relief medications in the same package, as described above.

Modulators that are VR1 agonists may further be used, for example, in crowd control (as a substitute for tear gas) or personal protection (*e.g.*, in a spray formulation) or as pharmaceutical agents for the treatment of pain, itch, urinary incontinence or overactive bladder via capsaicin receptor desensitization. In general, compounds for use in crowd control or personal protection are formulated and used according to conventional tear gas or pepper spray technology.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of capsaicin receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). Compounds may also be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to capsaicin receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize capsaicin receptors in living subjects. For example, a VR1 modulator may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may

be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of capsaicin receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of capsaicin receptor in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

Modulators provided herein may also be used within a variety of well known cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby isolating, capsaicin receptors (*e.g.*, isolating receptor-expressing cells) *in vitro*. Within one preferred embodiment, a modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

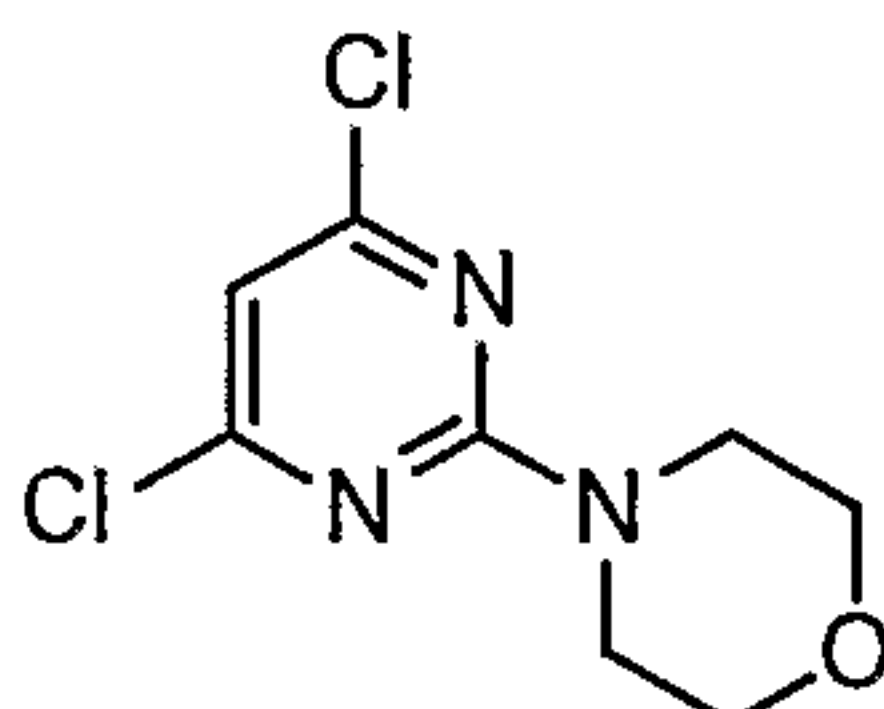
20 EXAMPLES

EXAMPLE 1

Preparation of (4-Fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine

This Example illustrates the preparation of the representative substituted heterocyclic diarylamine analogue (4-fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine.

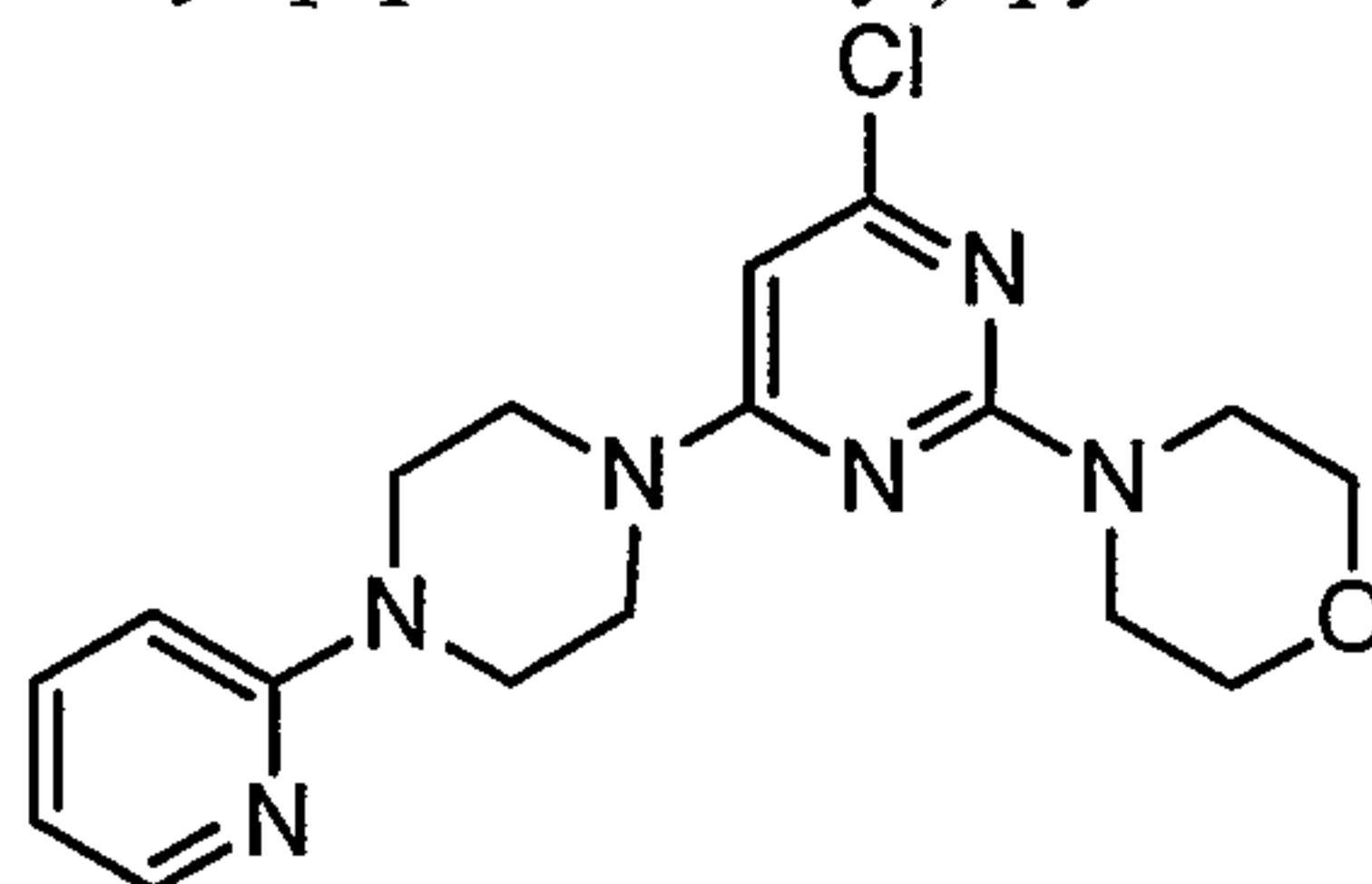
1. 6-morpholino-2,4-dichloropyrimidine



To an ice-cold solution containing 2,4,6-trichloropyrimidine (8 g, 44 mmol) in methanol (80 mL) and NaHCO₃ (10 g) add slowly and dropwise a methanolic solution (20 mL) of morpholine (4 mL, 46 mmol). Allow the mixture to warm to 25°C and stir overnight.

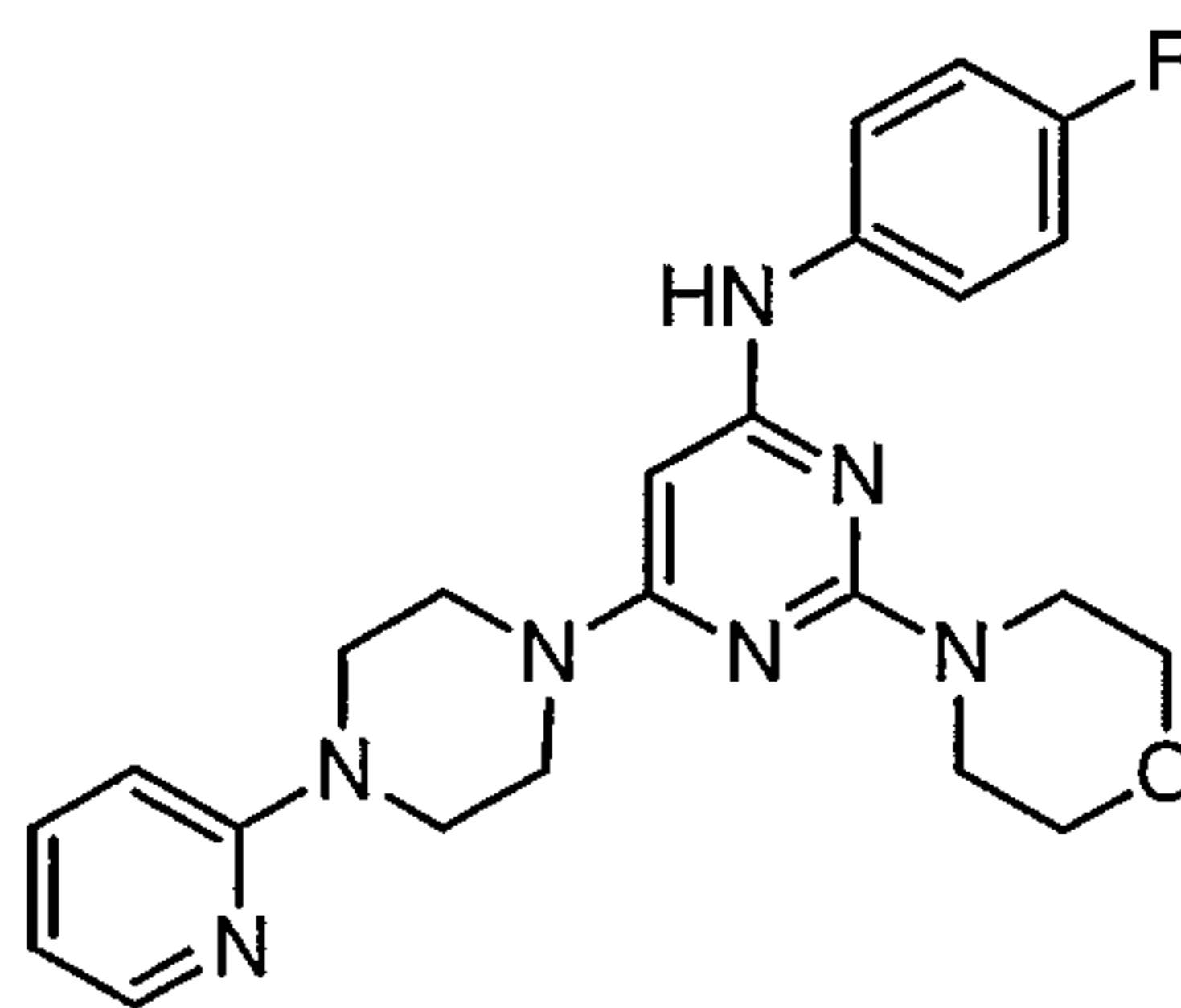
Dilute with water, vigorously stir for 1 hour, and filter to give a white crystalline solid as a mixture of regioisomers. Carefully recrystallize from toluene to give 6-morpholino-2,4-dichloropyrimidine. Concentrate the mother liquor and carefully recrystallize from EtOH to give 4,6-dichloro-2-morpholinopyrimidine.

5 2. 4-[4-Chloro-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-morpholine



To a rubber-septum-capped vial containing 4,6-dichloro-2-morpholinopyrimidine (0.2 M in dioxane, 0.25 mL) and 1-pyridin-2-yl-piperazine (0.2 M in dioxane, 0.28 mL) add aqueous K₃PO₄ (0.5 M, 0.125 mL). Heat the mixture at 90°C for 24 hours. Cool the mixture and concentrate under reduced pressure. Partition between ethyl acetate and water, dry (Na₂SO₄) the organic layer and concentrate under reduced pressure. Filter the crude product through a pad of silica gel (1:1 ethyl acetate/hexanes) and remove the solvent under reduced pressure to give the title compound.

15 3. (4-Fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine



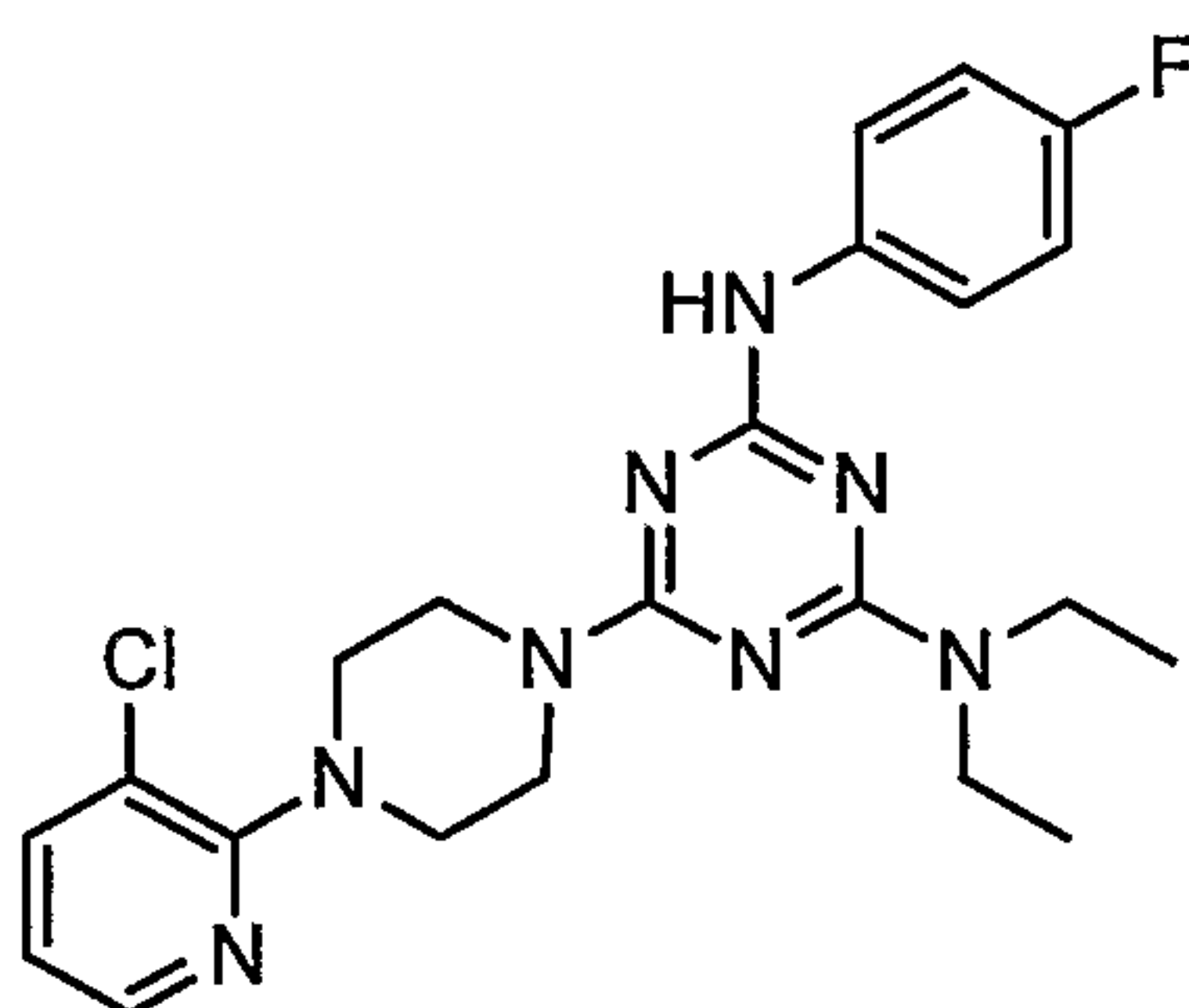
To a de-gassed mixture of 4-[4-chloro-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-morpholine (134 mg, 0.258 mmol), 4-fluoroaniline (32 mg, 0.284 mmol), and 1M (THF) potassium *tert*-butoxide (0.516 mmol), in dioxane (4mL) under nitrogen, add Pd(OAc)₂ (0.01 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.013 mmol). Stir the mixture at 80°C for 16 hours, concentrate and extract with EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and purify by preparative TLC (1:3 hexanes/EtOAc) to give (4-fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine. LCMS M+1 = 436.3

EXAMPLE 2

Preparation of Additional Representative Compounds

This Example illustrates the preparation of additional representative substituted heterocyclic diarylamine analogues.

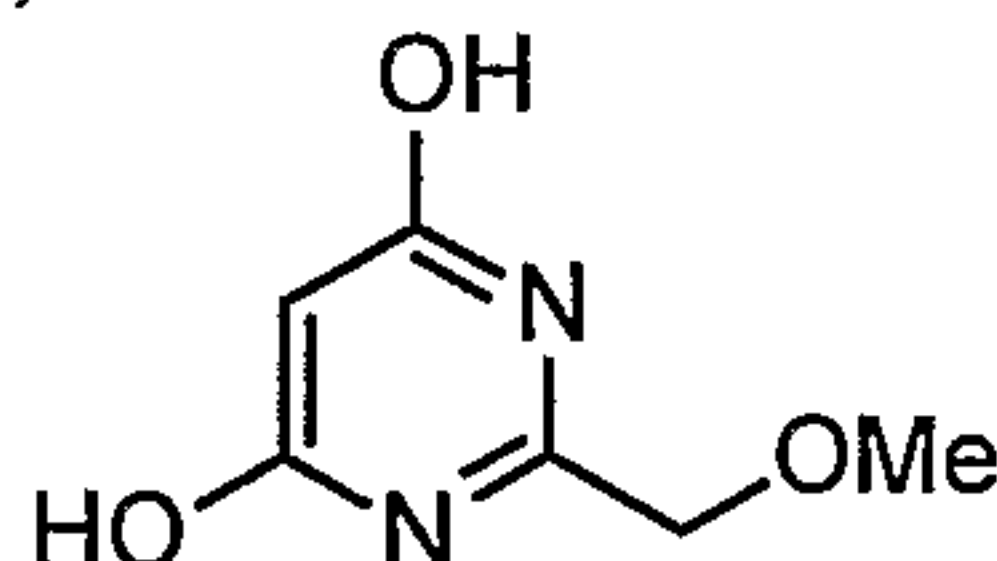
- 5 A. 6-[4-(3-CHLORO-PYRIDIN-2-YL)-PIPERAZIN-1-YL]-N,N-DIETHYL-N'-(4-FLUORO-PHENYL)-[1,3,5]TRIAZINE-2,4-DIAMINE



- To a rubber-septum-capped vial containing (4,6-dichloro-[1,3,5]triazin-2-yl)-diethylamine (0.2 M in toluene, 0.10 mL) and 4-(6-chloro-2-pyridyl)piperazine (0.2 M in toluene, 10 0.11 mL), add N,N-diisopropylethylamine (1 M in toluene, 0.05 mL). Heat the mixture at 60°C for 0.5 hours. After cooling, remove the volatiles by evaporation *in vacuo* (40°C at 2 torr) and add 4-fluoroaniline (0.2 M in toluene, 0.11 mL). Charge the reaction vessel with argon. Add 0.05 mL of 0.01M palladium solution prepared *in situ* as follows: mix equal volumes of 0.02 M Pd(OAc)₂ in toluene and 0.05 M 2-(dicyclohexylphosphino)biphenyl in 15 toluene. Add potassium *tert*-butoxide (1M in THF, 0.05 mL) to the reaction mixture and heat at 80°C for 2 hours. Quench by adding 3N HCl (0.025 mL), dilute with ethyl acetate (0.5 mL), and load the whole mixture onto a 6-mL cartridge containing 1 g of SCX (a benzenesulfonic acid-impregnated silica gel strong cation exchanger). Wash the SCX cartridge with ethyl acetate (4 mL) and then elute the product with 10% Et₃N in EtOAc (5 20 mL). Concentrate the eluent to give the pure product: LCMS M+1 = 457.3

- B. (3,4-DIFLUORO-PHENYL)-{2-MORPHOLIN-4-YLMETHYL-6-[4-(3-TRIFLUOROMETHYL-PYRIDIN-2-YL)-PIPERAZIN-1-YL]-PYRIMIDIN-4-YL}-AMINE

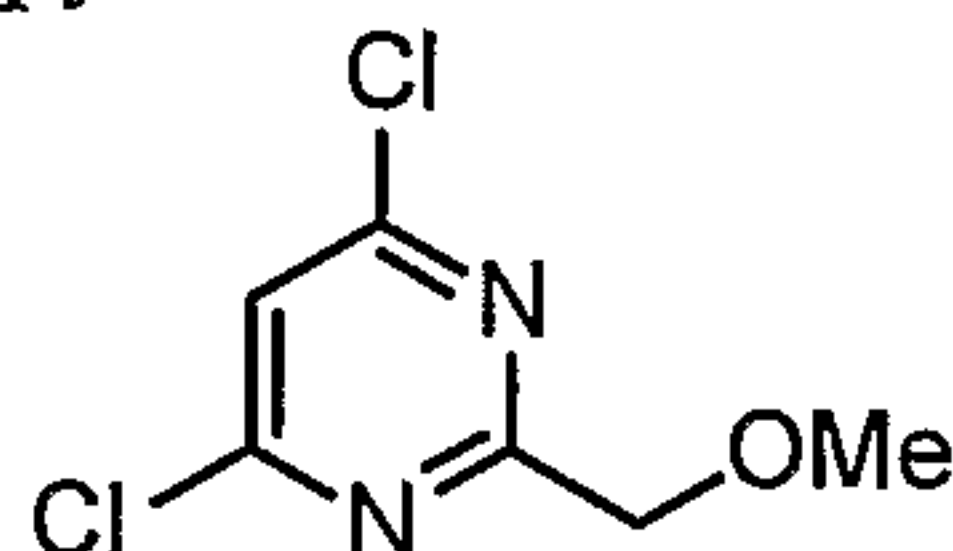
1. 2-methoxymethyl-pyrimidine-4,6-diol



- 25 Reflux the mixture of malonic acid diethyl ester (7.96 g, 50 mmol), 2-methoxyacetamidine hydrochloride (6.2 g, 50 mmol), and NaOMe methanol solution (4.37 M, 22.7

mL, 100 mmol) in MeOH (30 mL) for 24 hours. Concentrate, dilute with H₂O (50 mL), wash with EtOAc, and concentrate the aqueous layer. Extract the solid with MeOH and concentrate to afford 2-methoxymethyl-pyrimidine-4,6-diol.

2. *4,6-dichloro-2-methoxymethyl-pyrimidine*

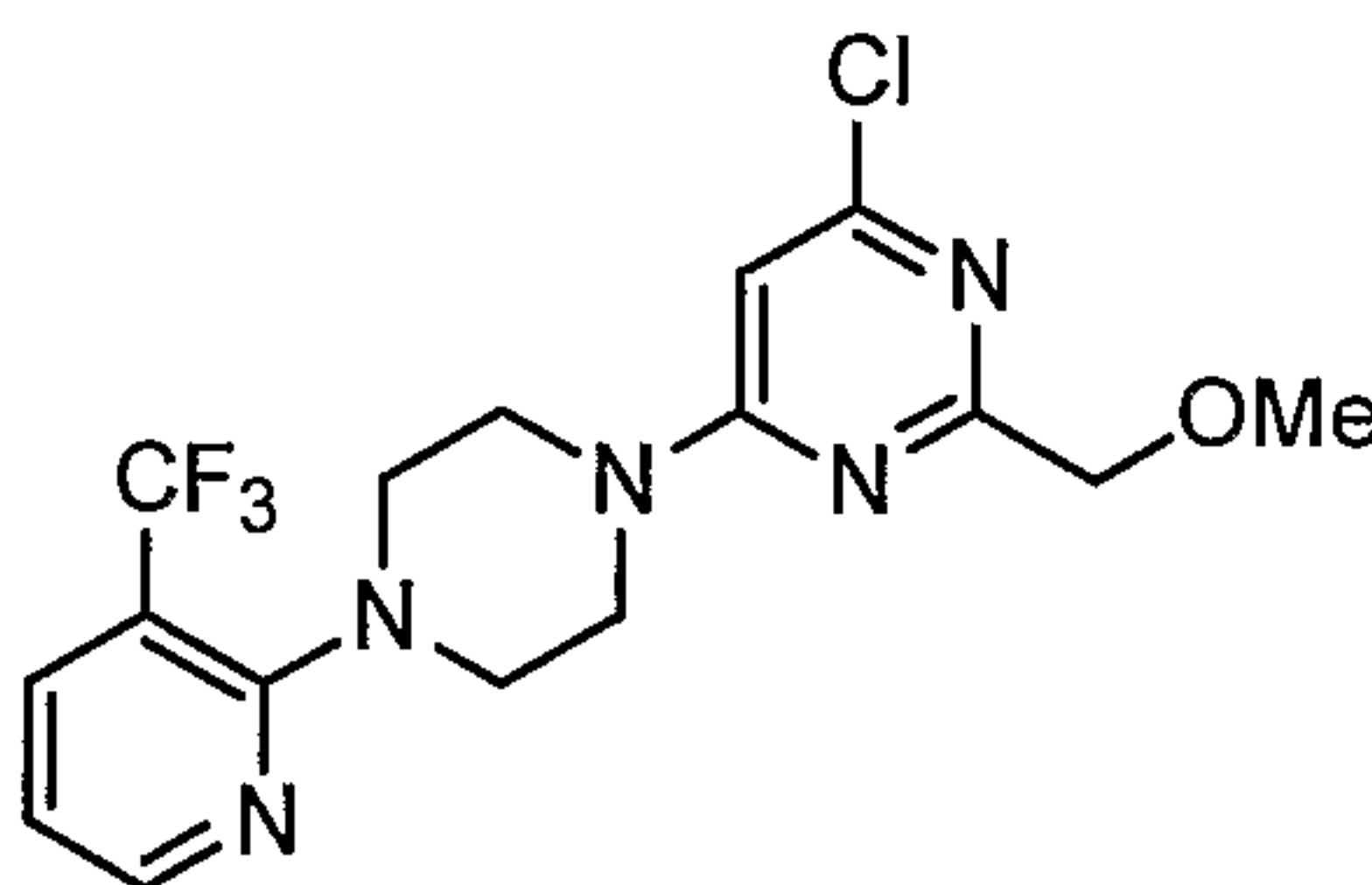


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Reflux the mixture of 2-methoxymethyl-pyrimidine-4,6-diol (4.1 g) and POCl₃ (30 mL) for 2 hours. Cool to room temperature, concentrate, partition between saturated aqueous NaHCO₃ and EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and purify by flash column chromatography (2:1 hexanes/EtOAc) to give 4,6-dichloro-2-methoxymethyl-pyrimidine.

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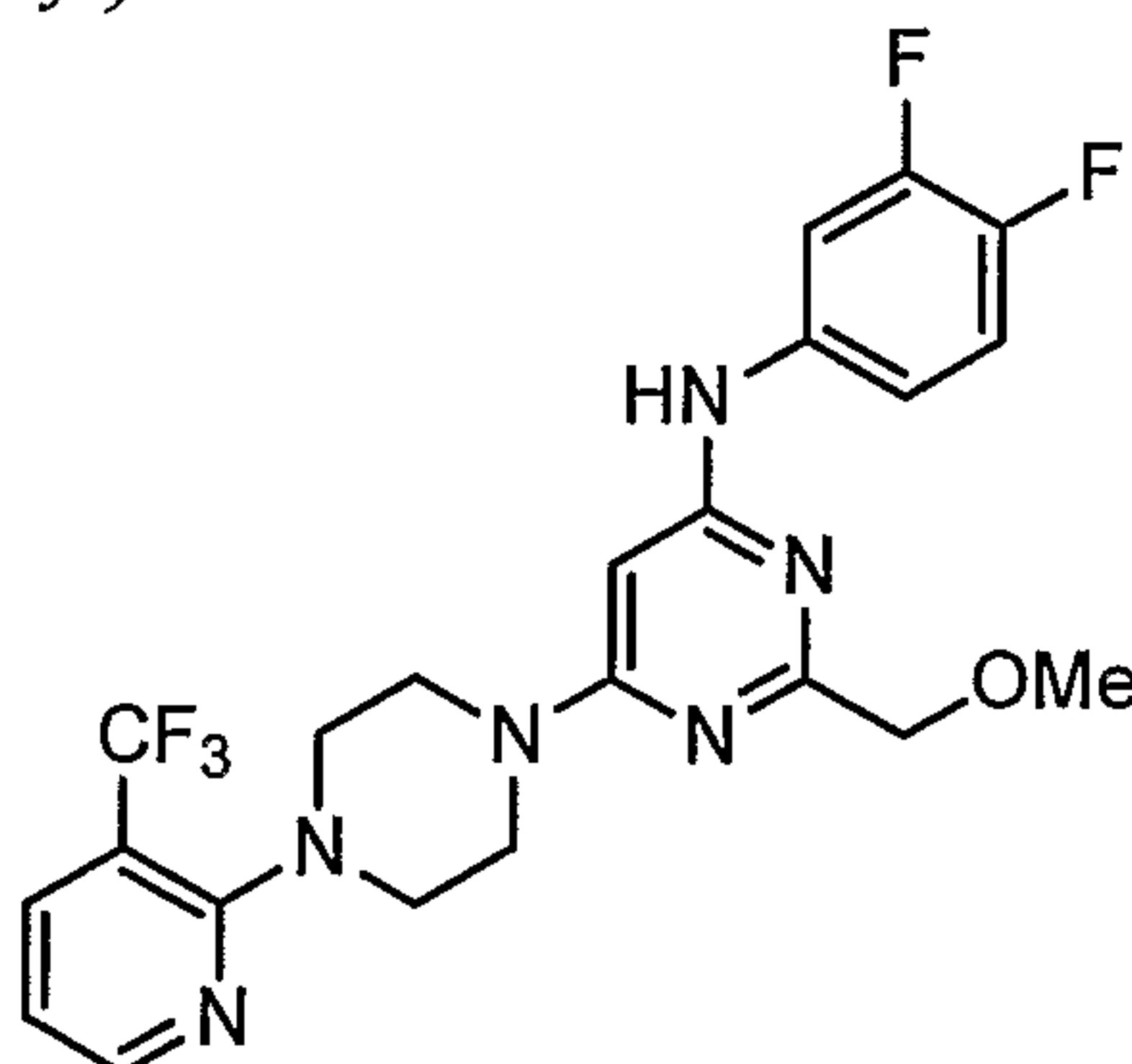
3. *4-chloro-2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidine*



Combine 4,6-dichloro-2-methoxymethyl-pyrimidine (800 mg, 4.14 mmol), 1-(3-trifluoromethyl-pyridin-2-yl)-piperazine (960 mg, 4.14 mmol), sodium bicarbonate (500 mg), and ethanol (50 mL). Reflux for 4 hours, let cool to room temperature, vacuum filter, and evaporate the mother liquor. Purify the residue by column chromatography eluting with 20:1 dichloromethane/methanol to obtain 4-chloro-2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidine as a white solid.

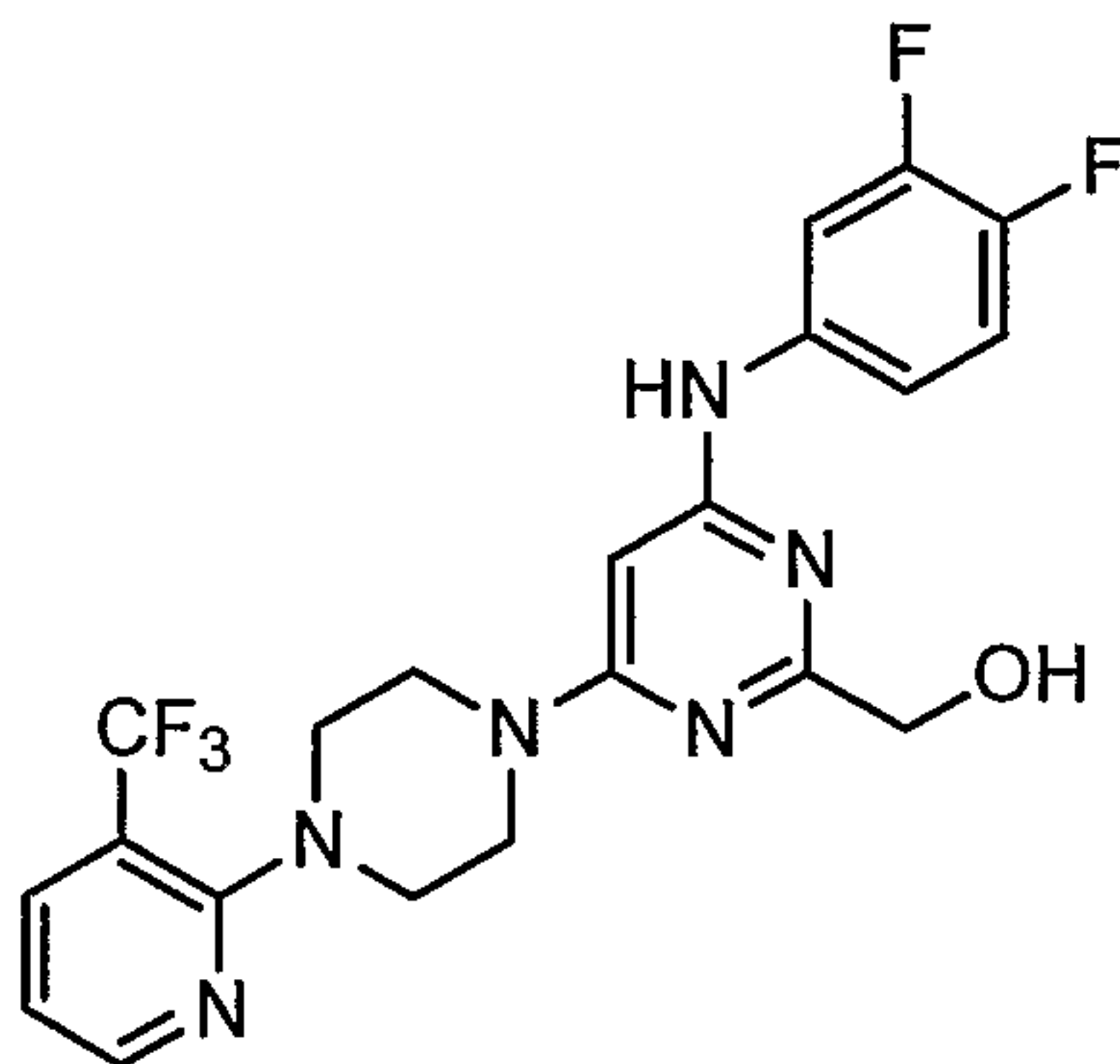
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4. *(3,4-difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine*



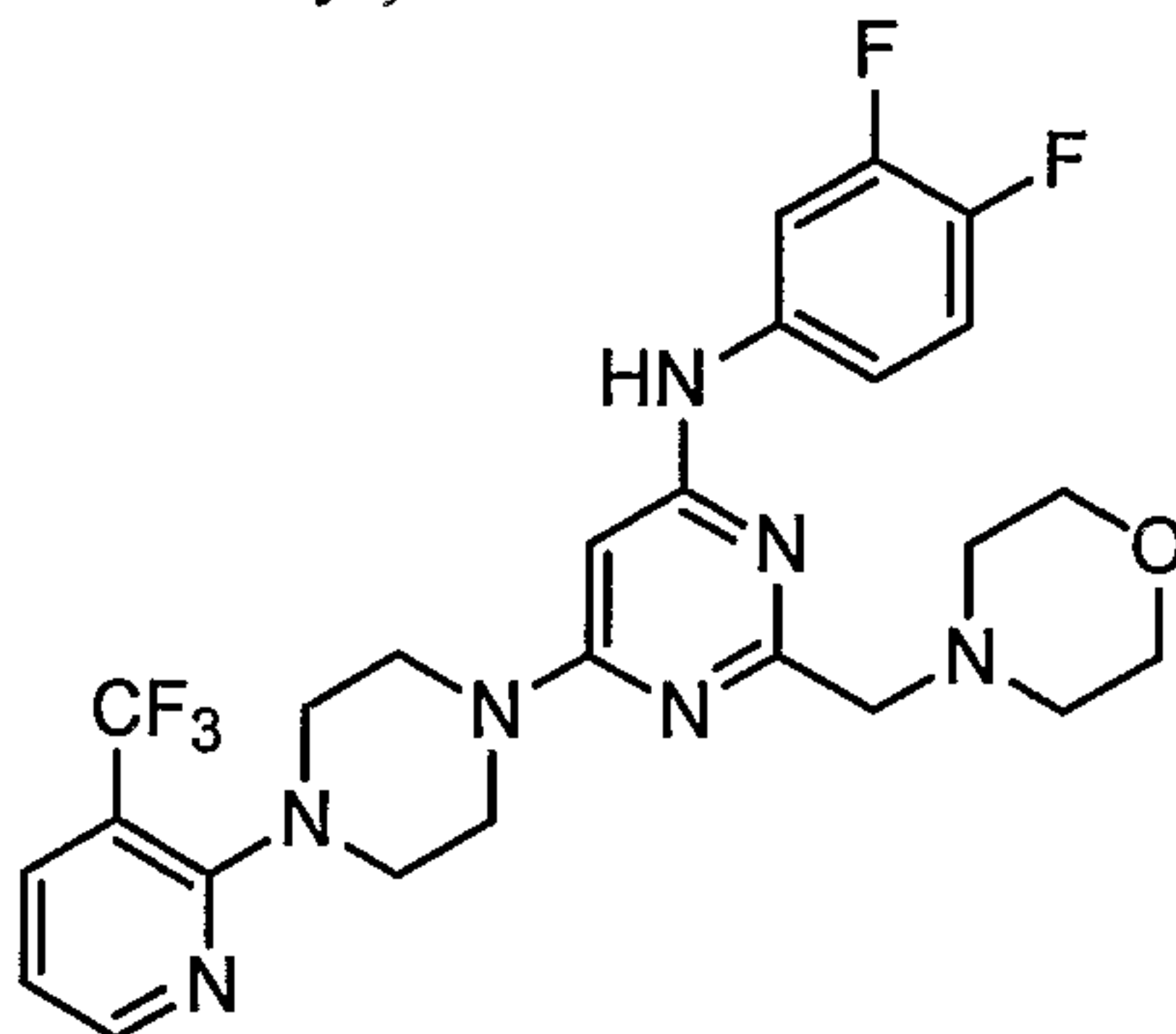
To a de-gassed mixture of 4-chloro-2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidine (100 mg, 0.258 mmol), 3,4-difluoroaniline (37 mg, 0.284 mmol), and 1M (THF) potassium *tert*-butoxide (0.0516 mmol), in dioxane (4mL) under nitrogen add Pd(OAc)₂ (0.01 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.013 mmol). Stir the mixture at 80°C for 16 hours, concentrate, extract with EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and purify by preparative TLC (1:3 hexanes/EtOAc) to give (3,4-difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine. ¹H NMR (CDCl₃, 400 MHz) δ 3.29-3.36 (m, 5H, piperidine-H); 3.53 (s, 3H, OCH₃); 3.66-3.72 (m, 3H, piperidine-H); 4.40 (s, 2H, CH₂O); 5.74(s, 1H, pyrimidine-H); 6.26 (s, 1H, NH); 6.90-7.26(m, 4H, aromatic-H); 7.88 (d, 1H, aromatic-H); 8.43 (d, 1H, aromatic-H).

5. {4-(3,4-difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-methanol



To a solution of (3,4-difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine (40 mg) in dichloromethane (10 mL), add 2 drops of BBr₃. Stir the mixture 1 hour at room temperature and concentrate. Purify by preparative TLC (5:95 MeOH/CH₂Cl₂ eluent) to afford {4-(3,4-difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-methanol.

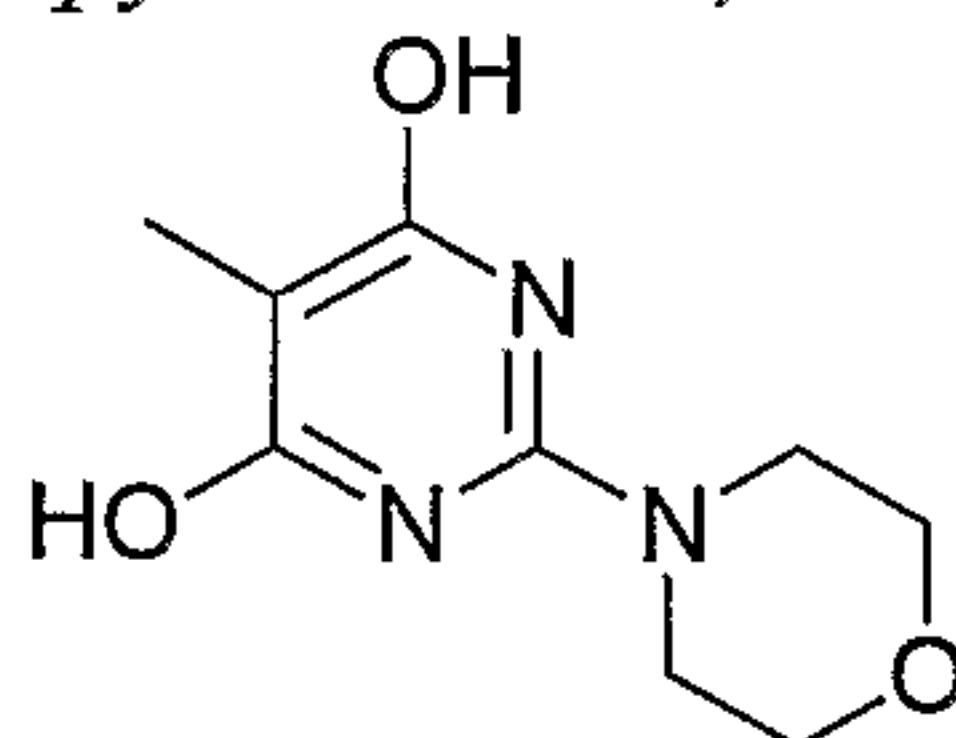
6. (3,4-difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine



To a cooled solution (0°C) of {4-(3,4-difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-methanol (50 mg, 0.103 mmol), add triethylamine (60 µL, 0.429 mmol) followed by methanesulfonyl chloride (18 µL, 0.236 mmol). Stir the mixture for 1 hour at room temperature, and then concentrate. Mix the residue with morpholine (100 µL) and N,N-dimethylacetamide (1 mL). Heat the solution at 70°C for 4 hours, and then partition the reaction mixture between saturated aqueous NaCl and EtOAc. Wash the organic layer with water, dry over Na₂SO₄, and concentrate. Purify by preparative TLC (7:93:1 MeOH/CH₂Cl₂/NH₄OH eluent) to yield (3,4-difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine. ¹H NMR (CDCl₃, 400 MHz) δ 2.60-2.70 (m, 4H, piperidine-H); 3.30-3.42 (m, 4H, piperidine-H); 3.55 (s, 2H, CH₂N); 3.61-3.72 (m, 4H, morpholine-H); 3.75-3.83 (m, 4H, morpholine-H); 5.72(s, 1H, pyrimidine-H); 6.75 (s, 1H, NH); 6.93-7.33 (m, 4H, aromatic-H); 7.89 (d, 1H, aromatic-H); 8.44 (d, 1H, aromatic-H).

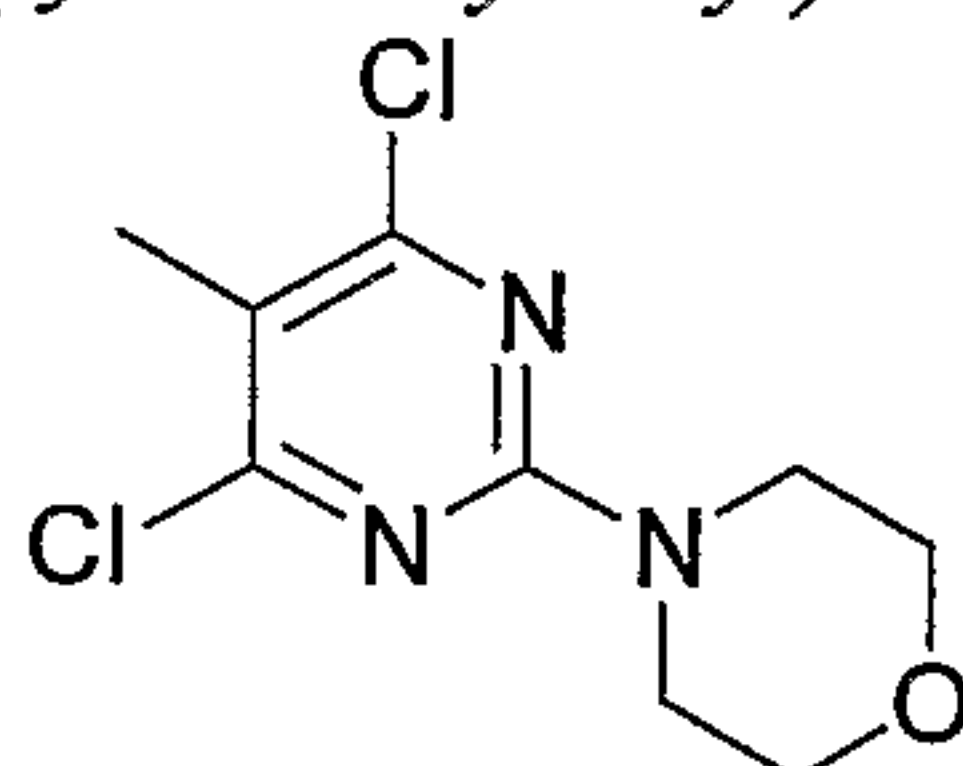
C. (3,4-DIFLUOROPHENYL)(5-METHYL-2-MORPHOLIN-4-YL-6-{4-[3-(TRIFLUOROMETHYL)(2-PYRIDYL)]PIPERAZINYL}PYRIMIDIN-4-YL)AMINE

1. *5-Methyl-2-morpholin-4-ylpyrimidine-4,6-diol*



Heat a mixture of sodium methoxide in methanol (15 ml, 45 mmol), morpholinoformamidinium hydrobromide (6.3 g, 30 mmol) and diethyl methylmalonate (5.22 g, 30 mmol) at 50°C for 2 hours. Cool the mixture and concentrate under reduced pressure. Dissolve the white gum in water and acidify the solution with concentrated sulfuric acid. Collect the resulting white solid by filtration, washed with water and air dry to give the title compound.

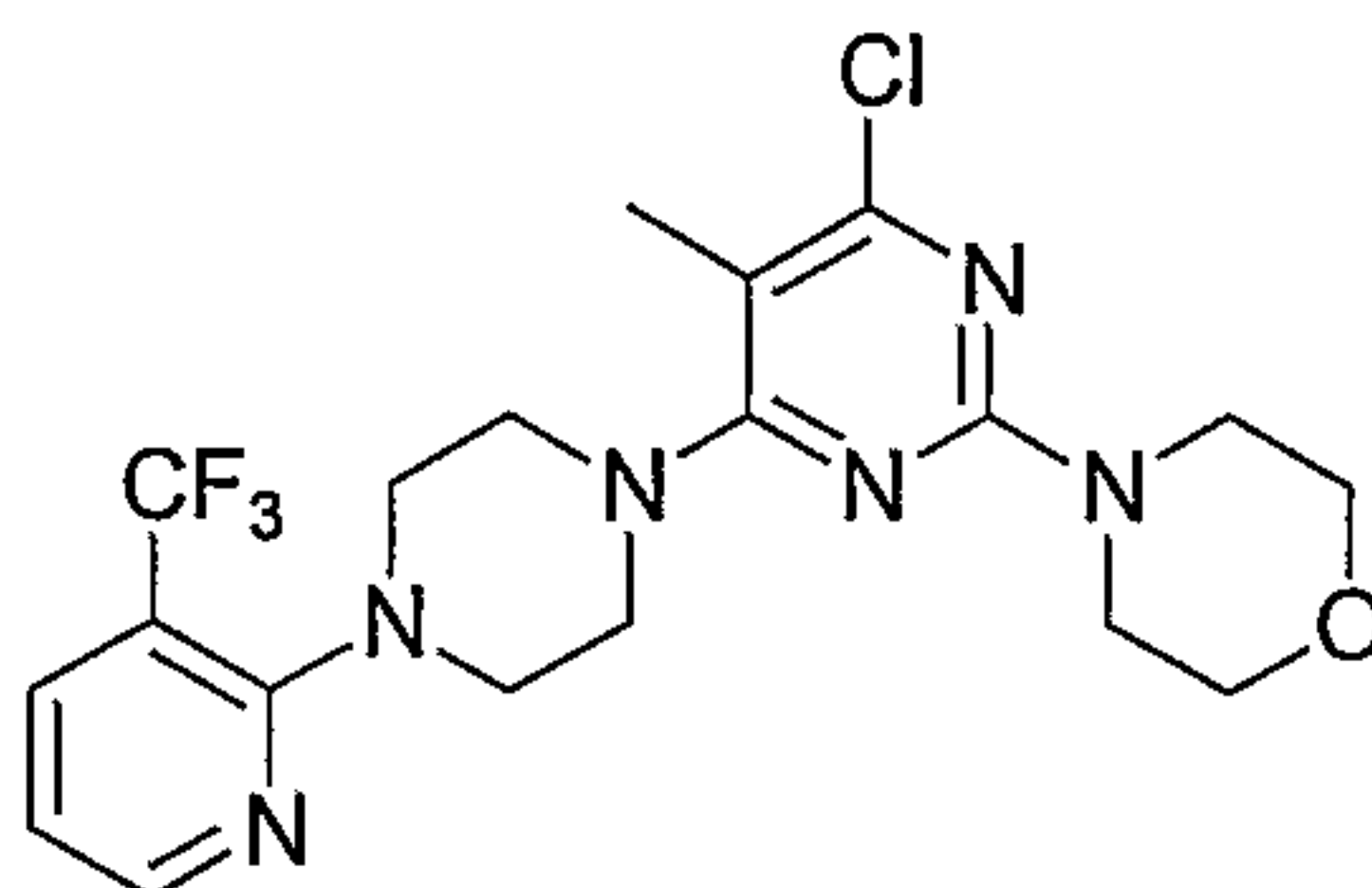
2. *4-(4,6-Dichloro-5-methylpyrimidin-2-yl)morpholine*



Heat a mixture of 5-methyl-2-morpholin-4-ylpyrimidine-4,6-diol (3.57 g, 17 mmol), N,N-diethylaniline (4.37 g, 35 mmol) and phosphorus oxychloride (25 mL) at 90°C for 2

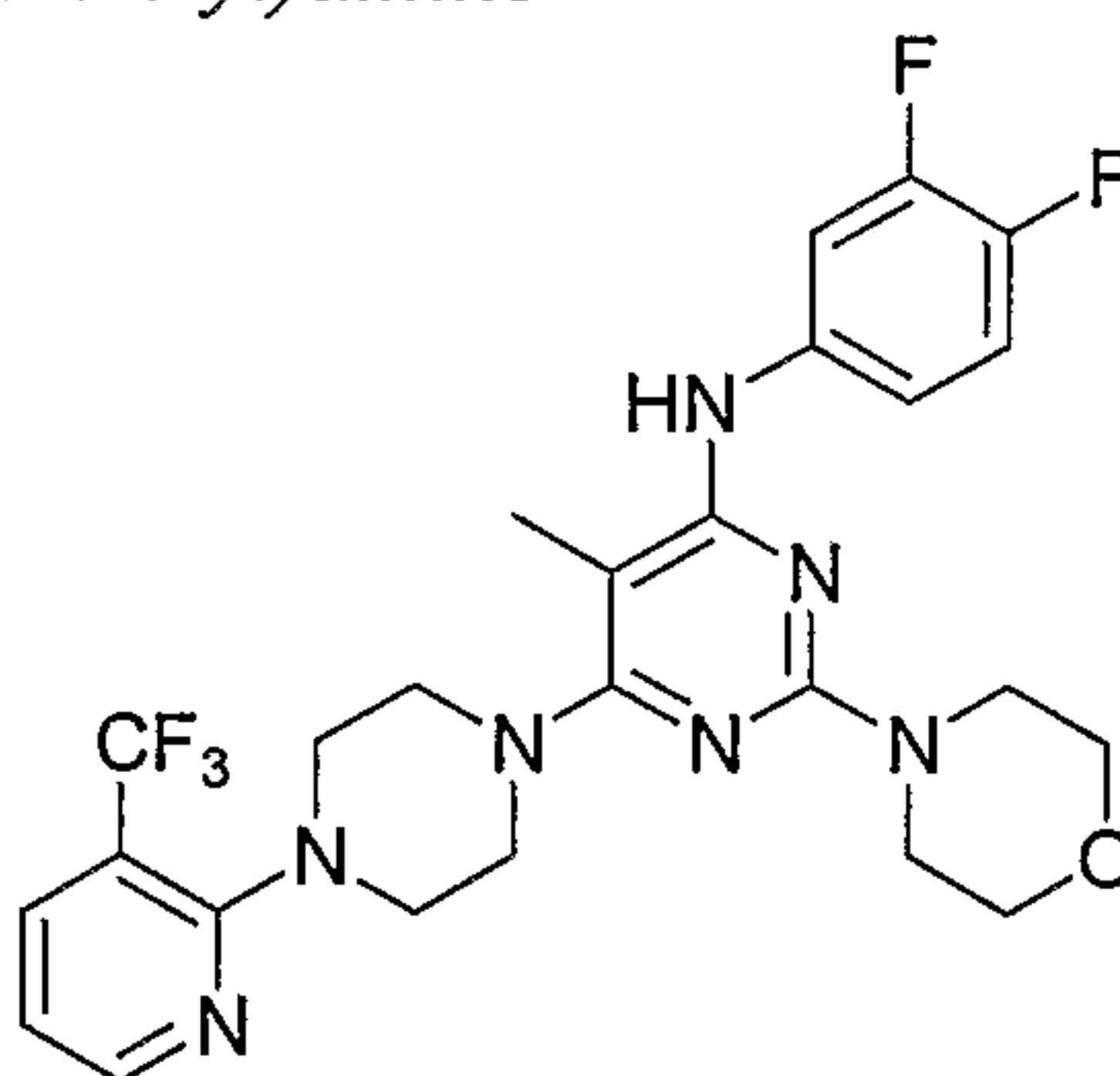
hours. Remove the excess phosphorus oxychloride by evaporation, add water (100 mL) and extract the solution with ethyl acetate (3 x 100 mL). Wash the combined organics with 1M hydrochloric acid (100 mL), water (100 mL), brine (100 mL), dry (MgSO₄) and concentrate under reduced pressure to give the title compound, which was used in the next step without further purification.

3. *4-(4-Chloro-5-methyl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-2-yl)morpholine*



Heat a mixture of 4-(4,6-dichloro-5-methylpyrimidinyl-2-yl)morpholine (496 mg, 2.0 mmol), 4-(6-trifluoromethyl-2-pyridyl)piperazine (462 mg, 2.0 mmol), potassium carbonate (345 mg, 2.5 mmol) and ethanol (10 mL) at 78°C for 8 hours. Cool the mixture, dilute with water (20 mL) and extract with ethyl acetate (3 x 25 mL). Wash the combined organics with brine (25 mL), dry (MgSO₄) and concentrate under reduced pressure. Purify the residue using flash chromatography on silica gel (80% hexane/ 20% ether) to give the title compound.

4. *(3,4-Difluorophenyl)(5-methyl-2-morpholin-4-yl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-4-yl)amine*



Add 3,4-difluoroaniline (26 mg, 0.2 mmol) to a solution of 4-(4-chloro-5-methyl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-2-yl)morpholine (88 mg, 0.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.02 mmol), and (*rac*)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (17 mg, 0.02 mmol) in toluene (2 mL) under nitrogen followed by potassium *tert*-butoxide (45 mg, 0.4 mmol). Stir the mixture at 90°C for 8 hours, dilute with aqueous ammonium chloride, and extract with ethyl acetate (3 x 10 mL). Dry (MgSO₄) the combined extracts and concentrate under reduced pressure. Purify

the residue by flash chromatography on silica gel (60% hexane/ 40% ether) to give the title compound. ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (s, 3H), 3.39 (brs, 8H), 3.70-3.76 (m, 8H), 6.15 (s, 1H), 6.99-7.08 (m, 3H), 7.61-7.68 (m, 1H), 7.89 (d, 1H), 8.45 (d, 1H). LCMS M+1 = 536.

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EXAMPLE 3

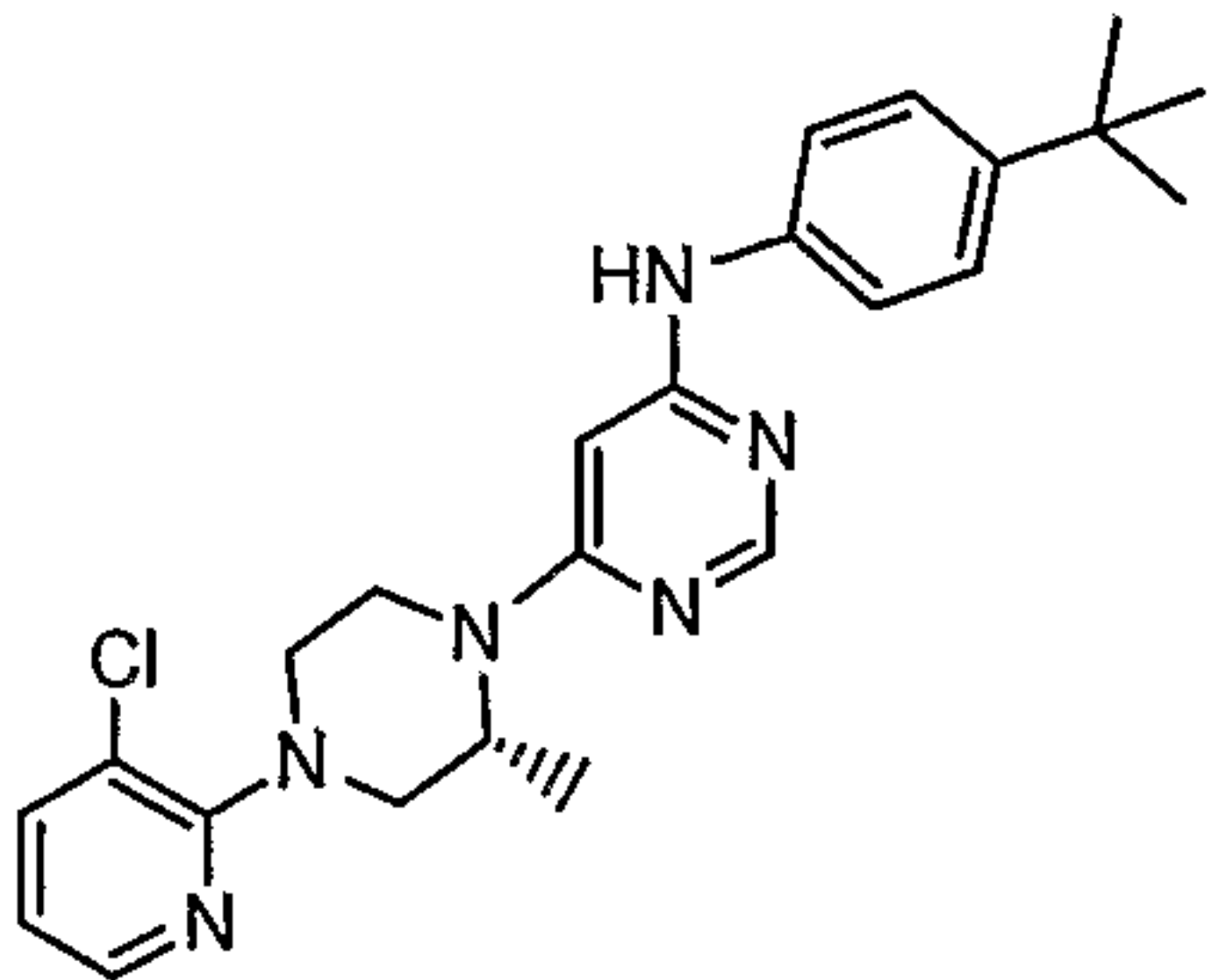
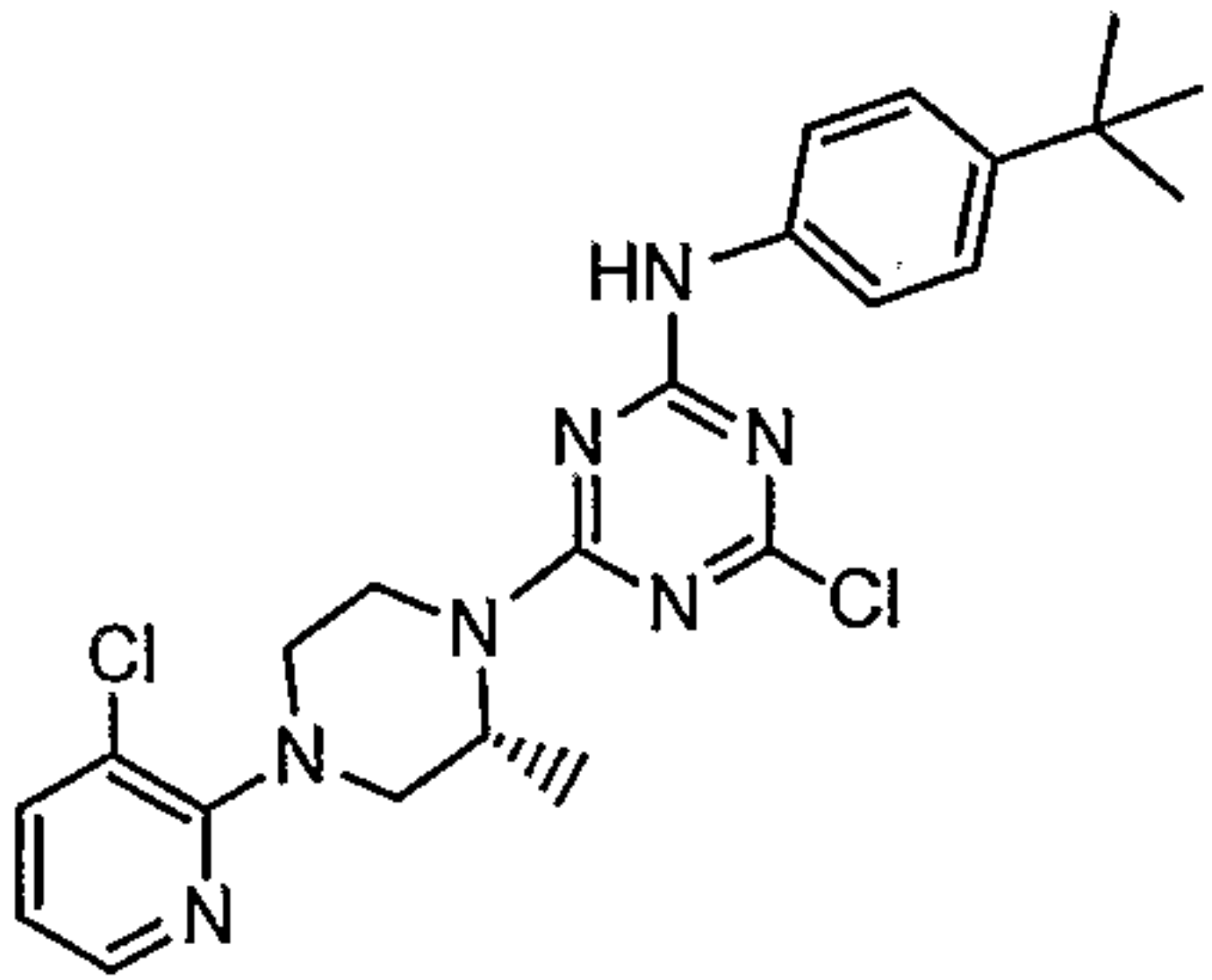
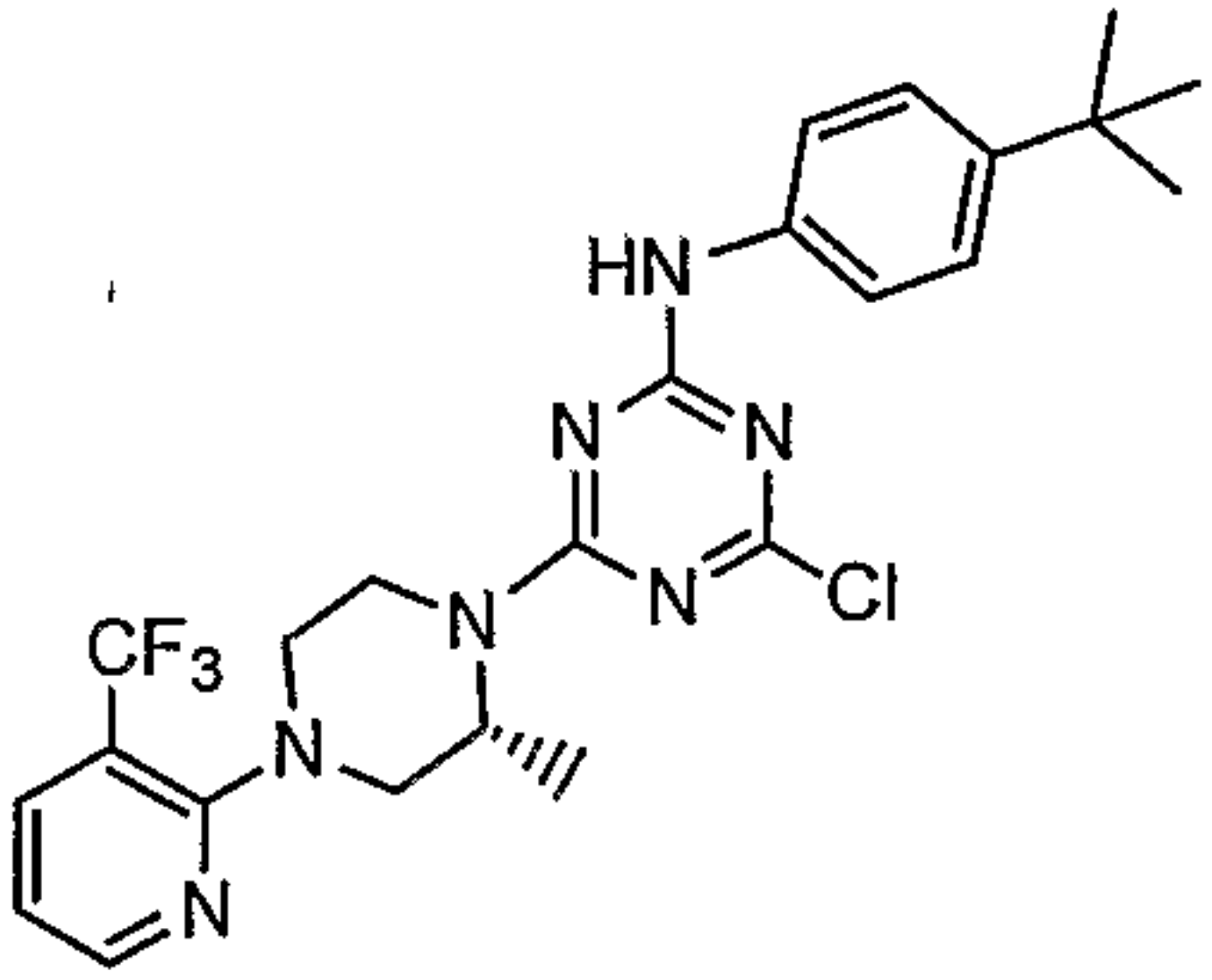
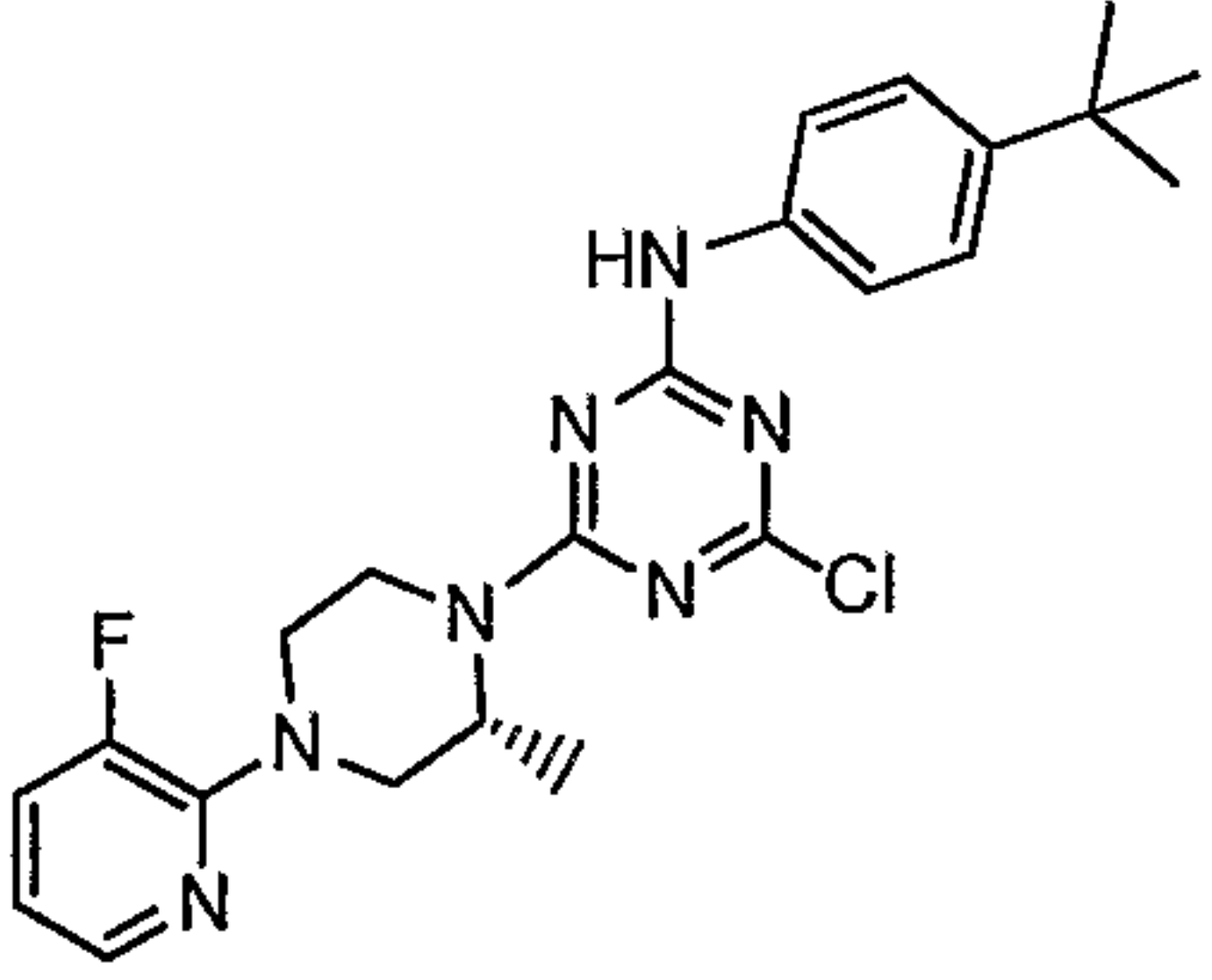
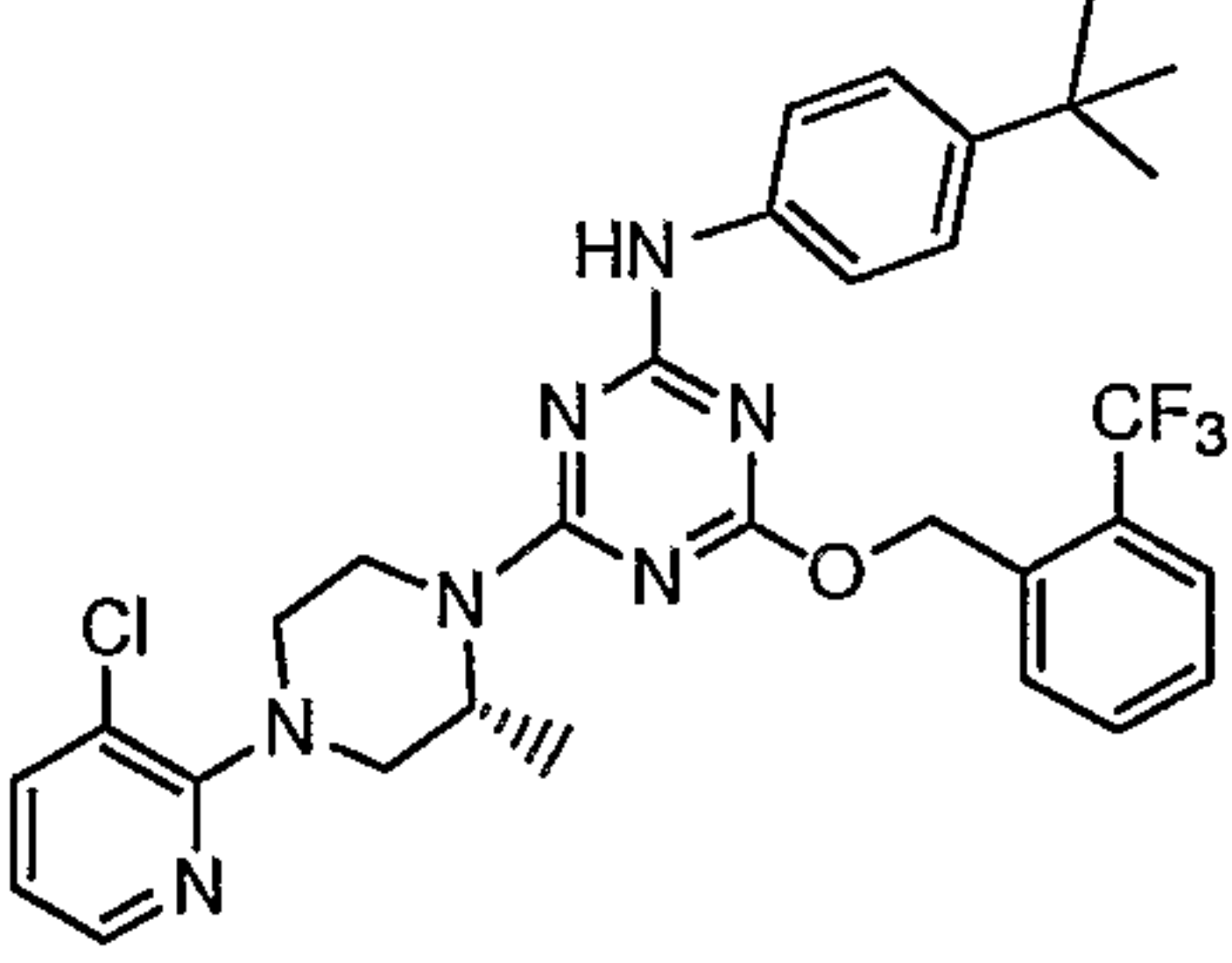
Representative Substituted Heterocyclic Diarylamine Analogues

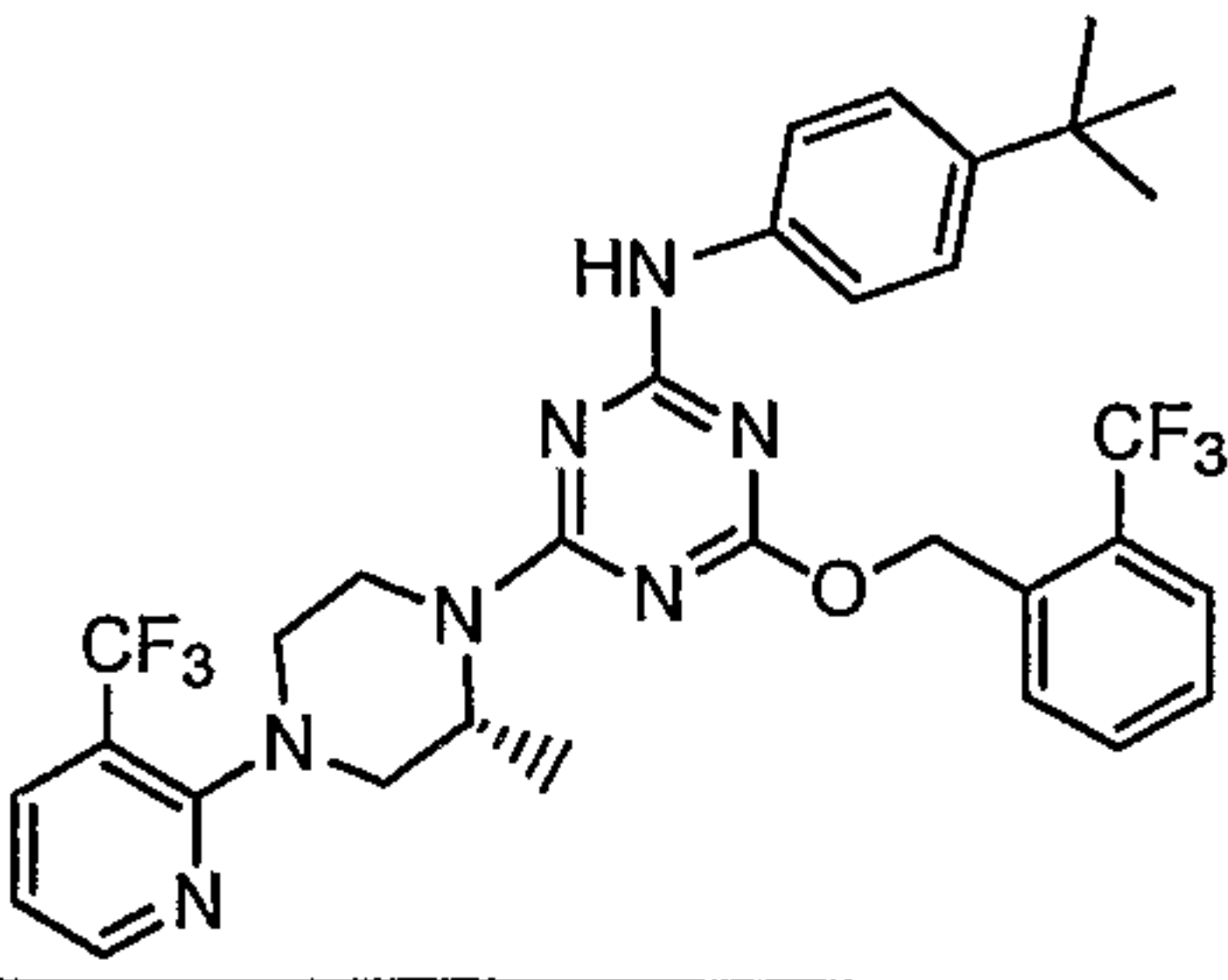
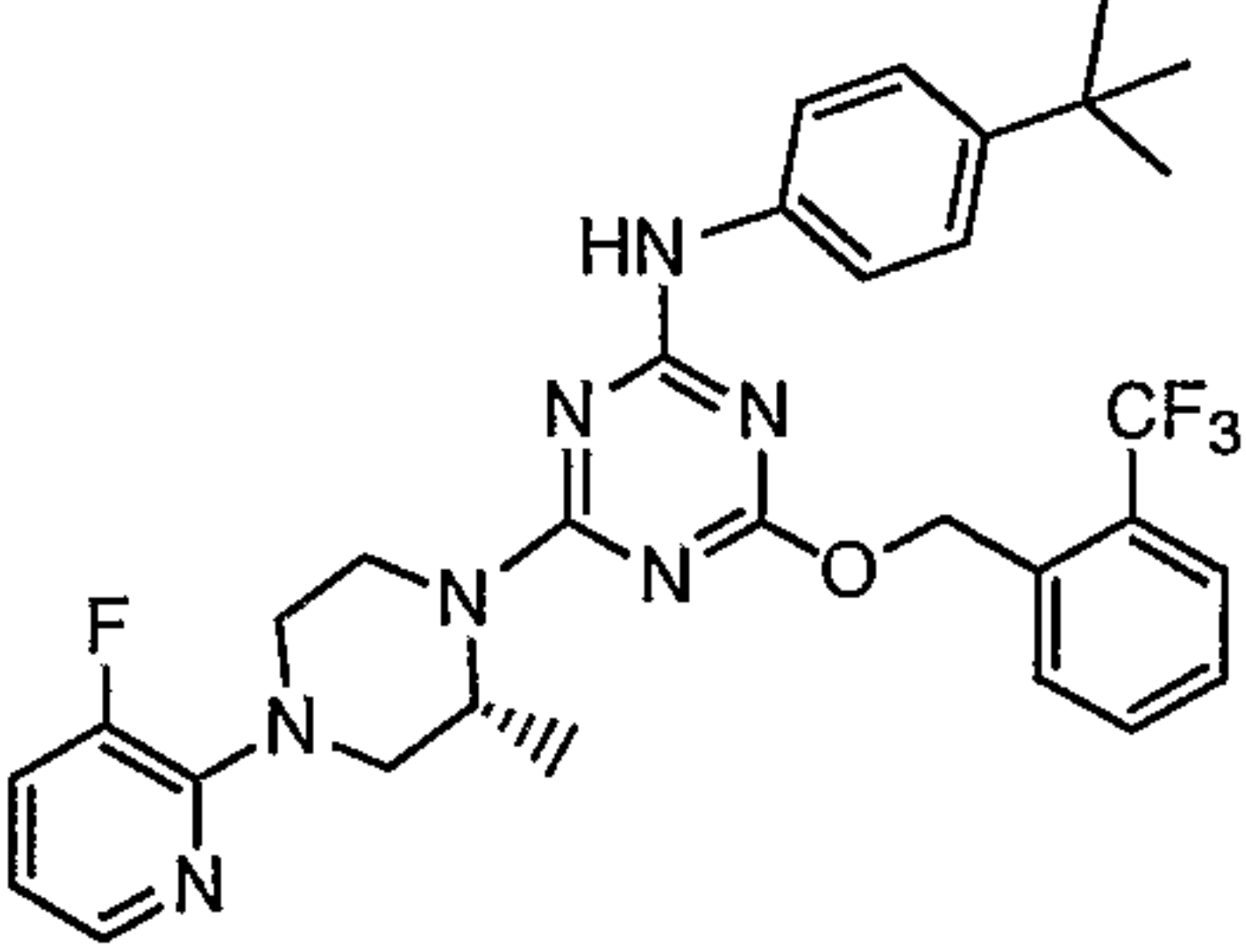
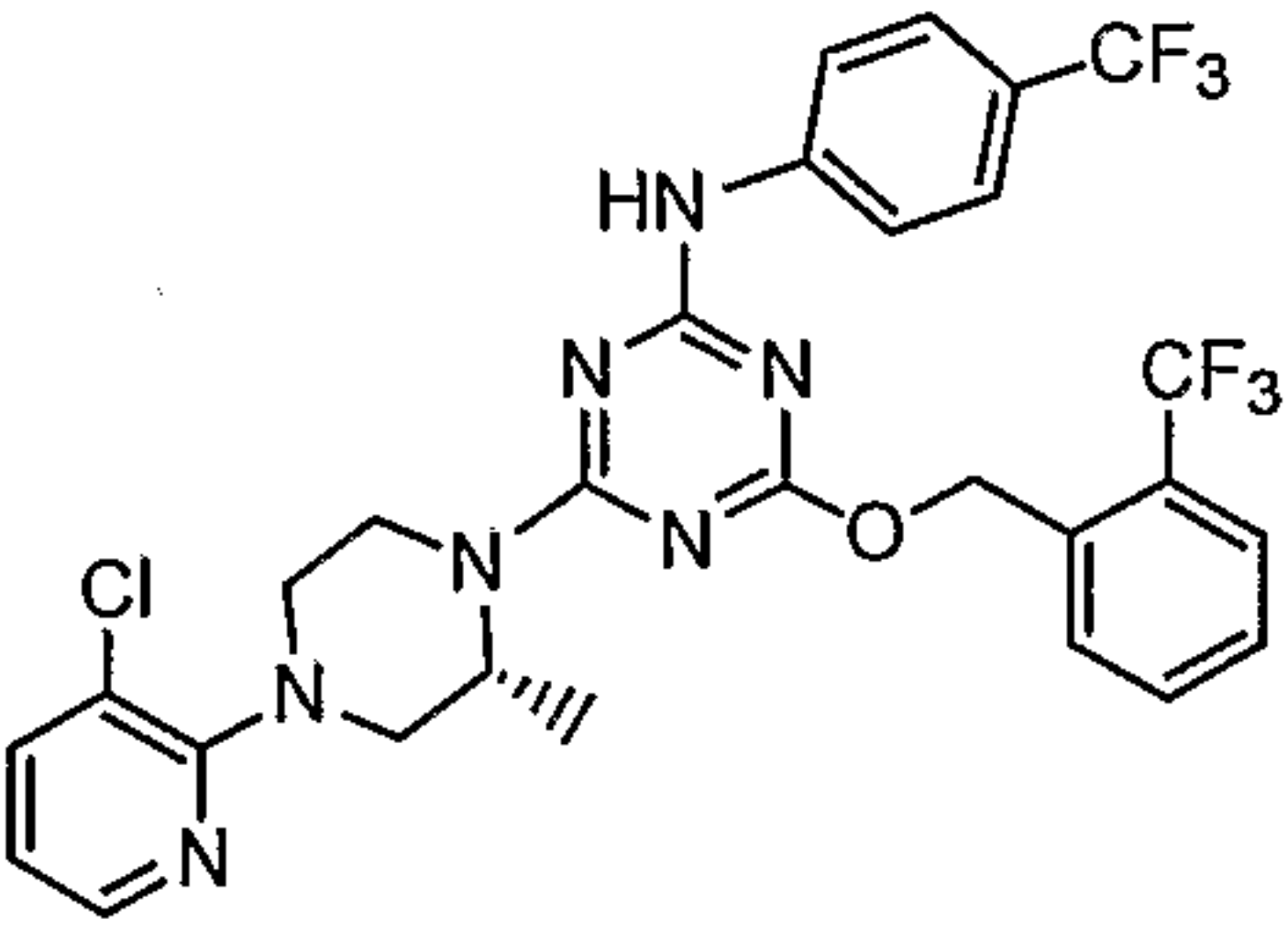
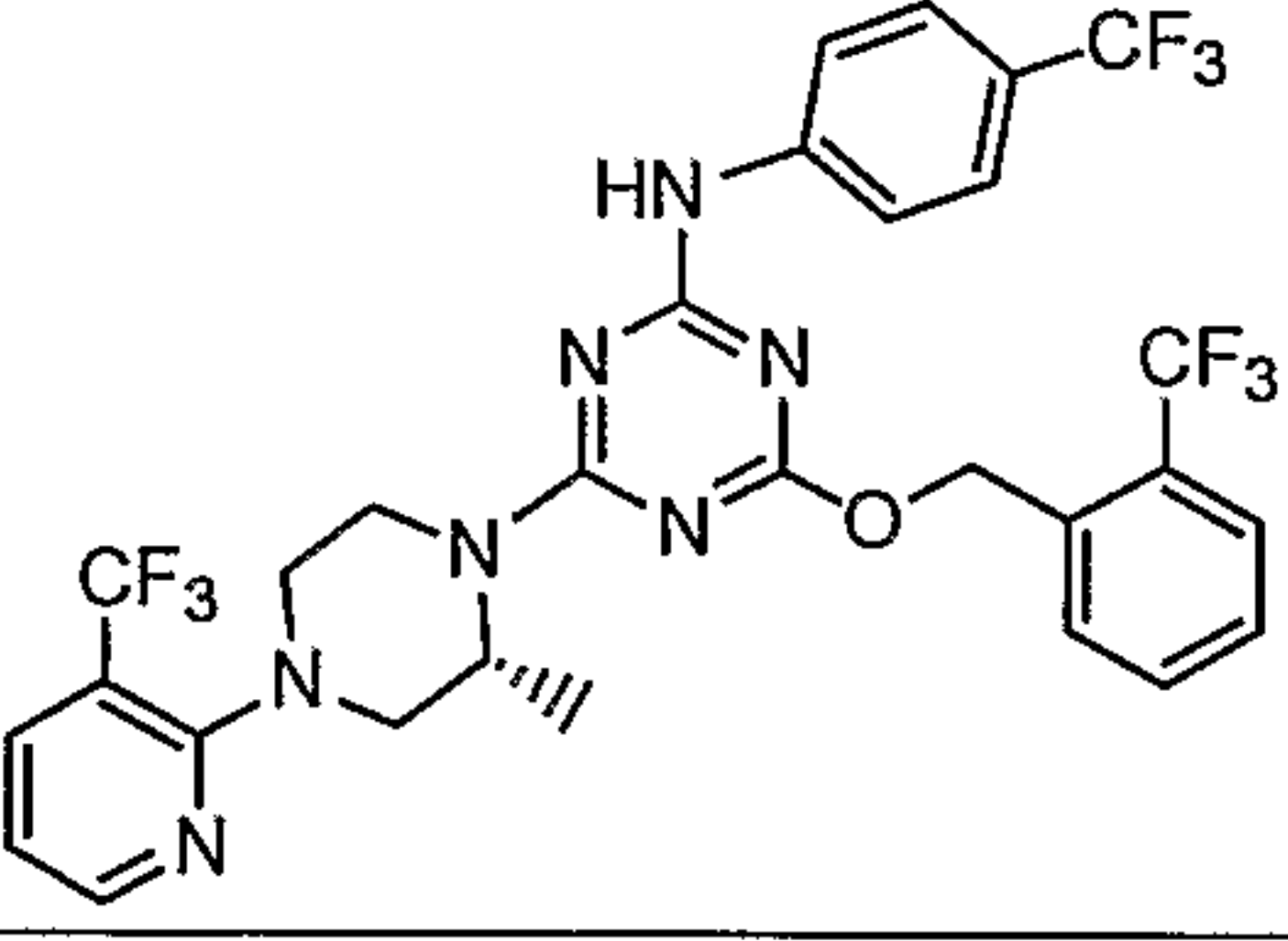
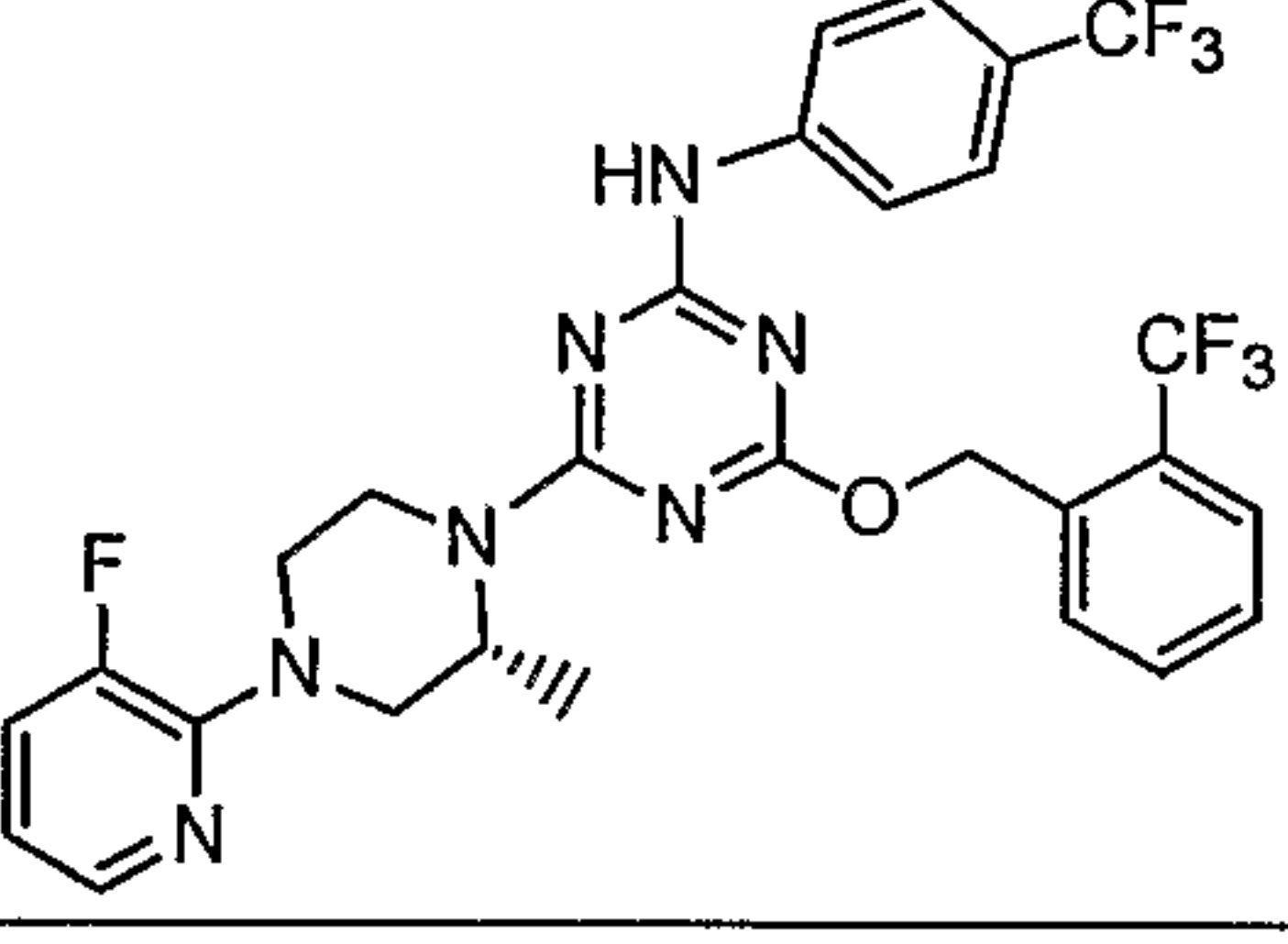
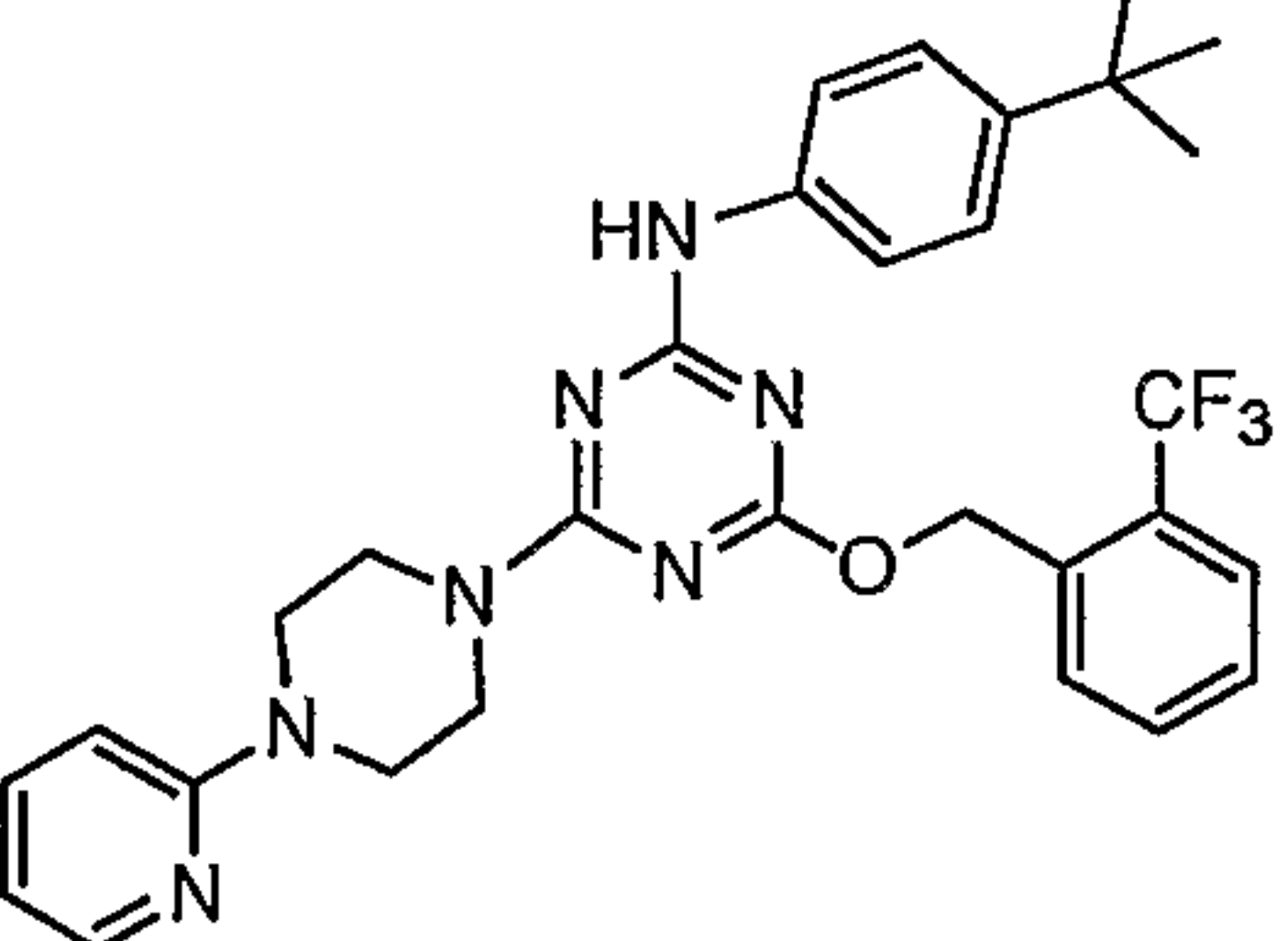
Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table I were prepared using such methods. In the column labeled "IC₅₀" a * indicates that the IC₅₀ determined as described in Example 6 is 1 micromolar or less (*i.e.*, the concentration of such compounds that is required to provide a 50% decrease in the fluorescence response of cells exposed to one IC₅₀ of capsaicin is 1 micromolar or less). Mass Spectroscopy data in the column labeled "MS" is Electrospray MS, obtained in positive ion mode with a 15V or 30V cone voltage, using a Micromass Time-of-Flight LCT, equipped with a Waters 600 pump, Waters 996 photodiode array detector, Gilson 215 autosampler, and a Gilson 841 microinjector. MassLynx (Advanced Chemistry Development, Inc; Toronto, Canada) version 4.0 software was used for data collection and analysis. Sample volume of 1 microliter was injected onto a 50x4.6mm Chromolith SpeedROD C18 column, and eluted using a 2-phase linear gradient at 6ml/min flow rate. Sample was detected using total absorbance count over the 220-340nm UV range. The elution conditions were: Mobile Phase A- 95/5/0.05 Water/Methanol/TFA; Mobile Phase B-5/95/0.025 Water/Methanol/TFA.

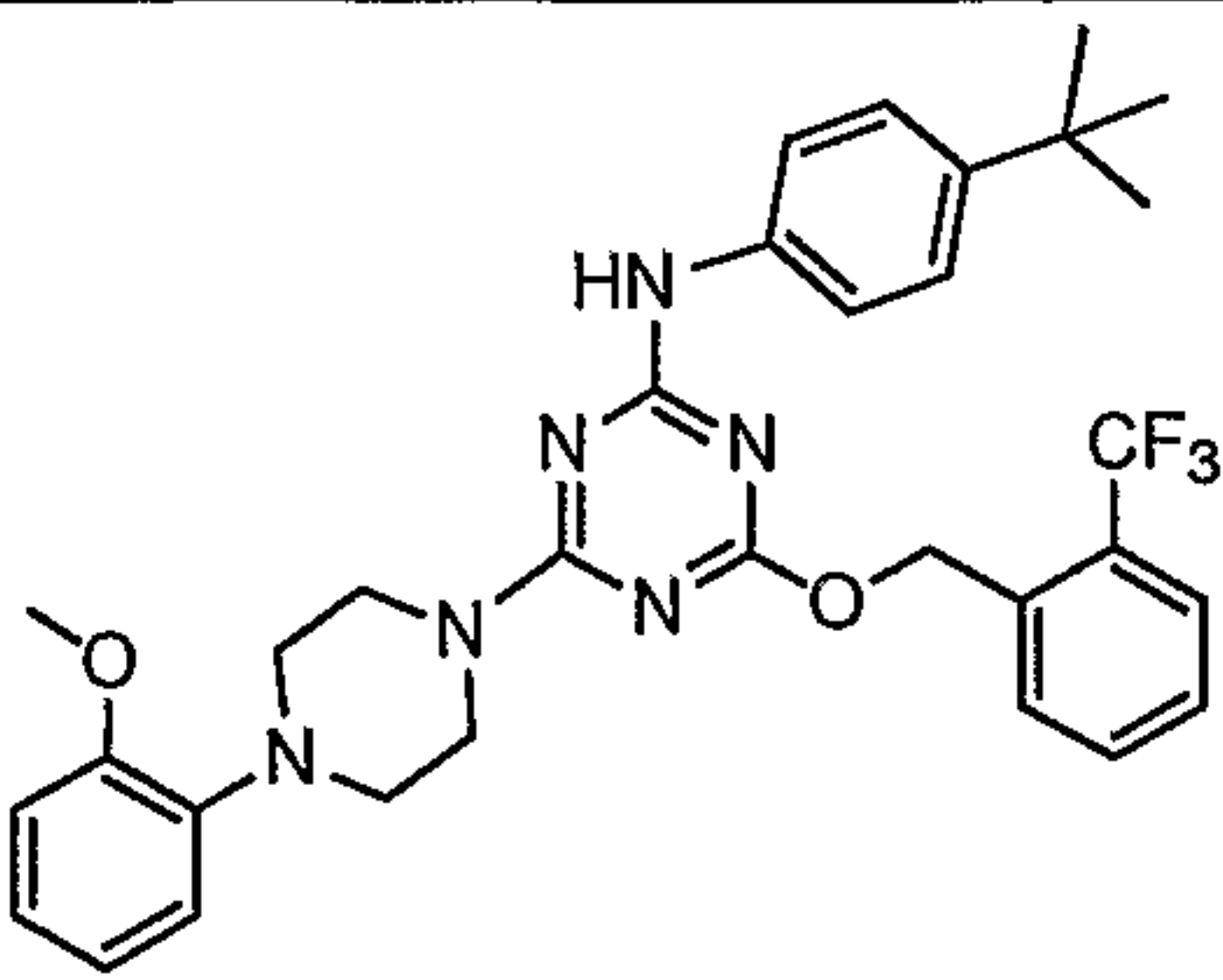
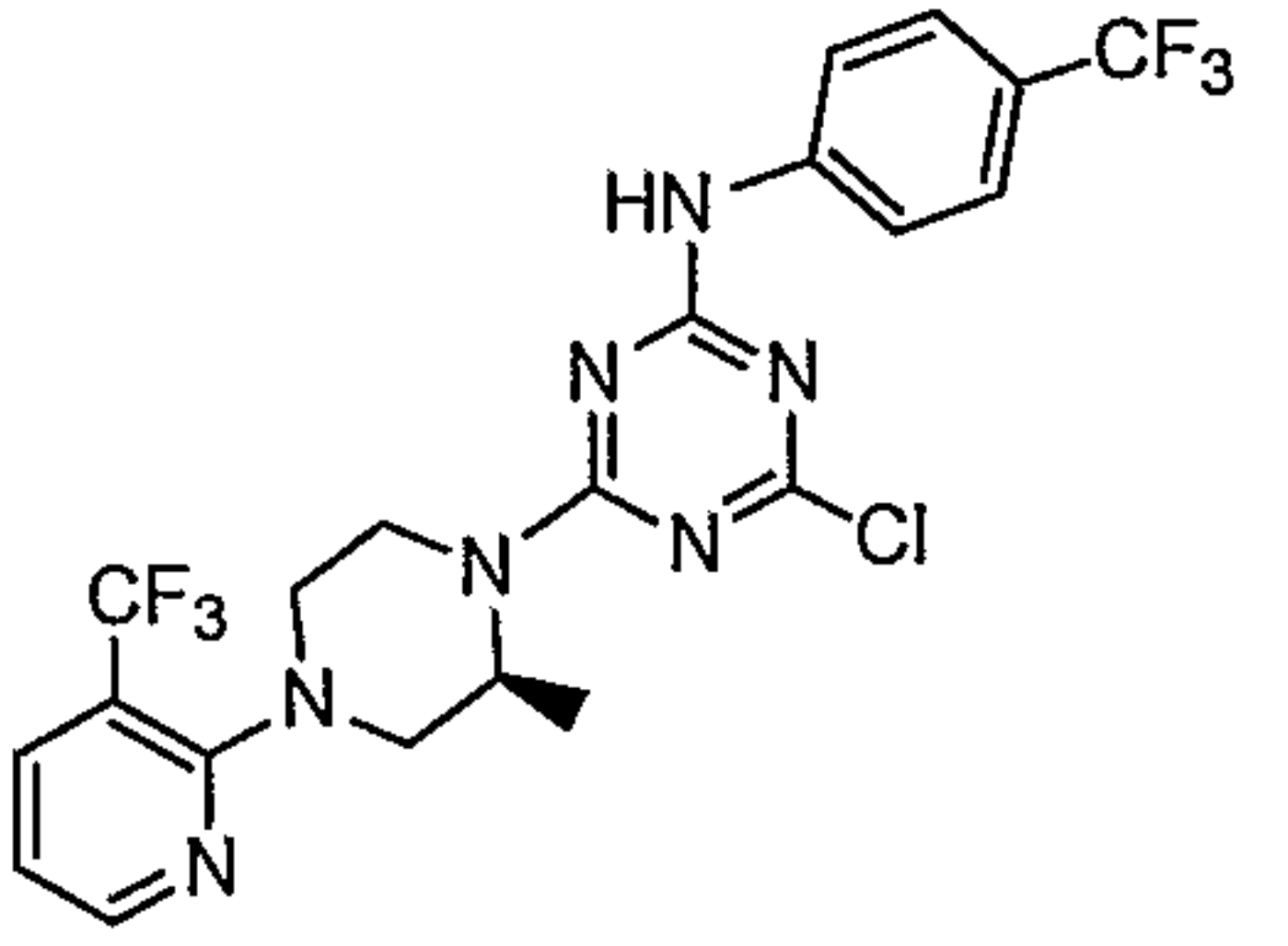
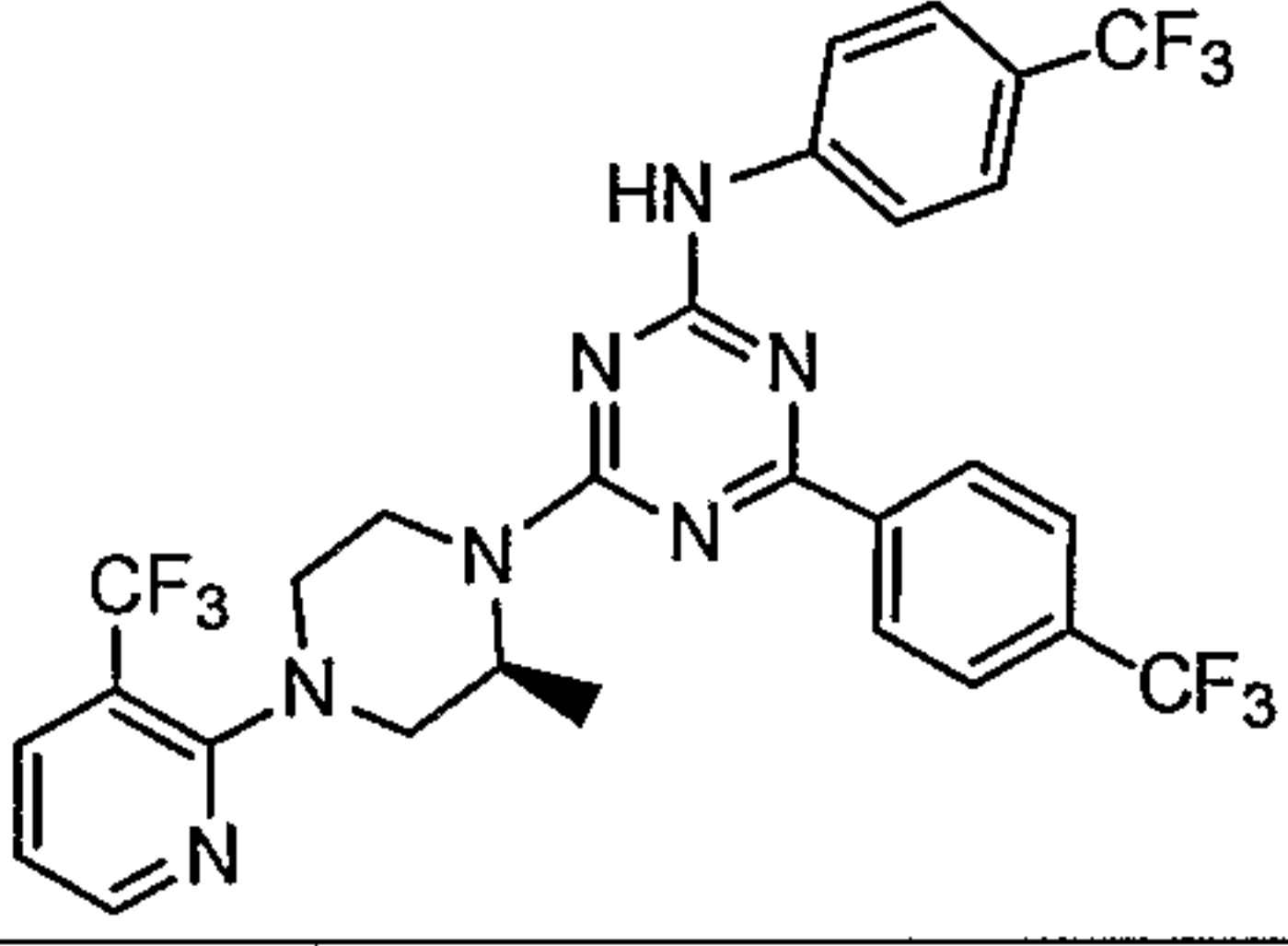
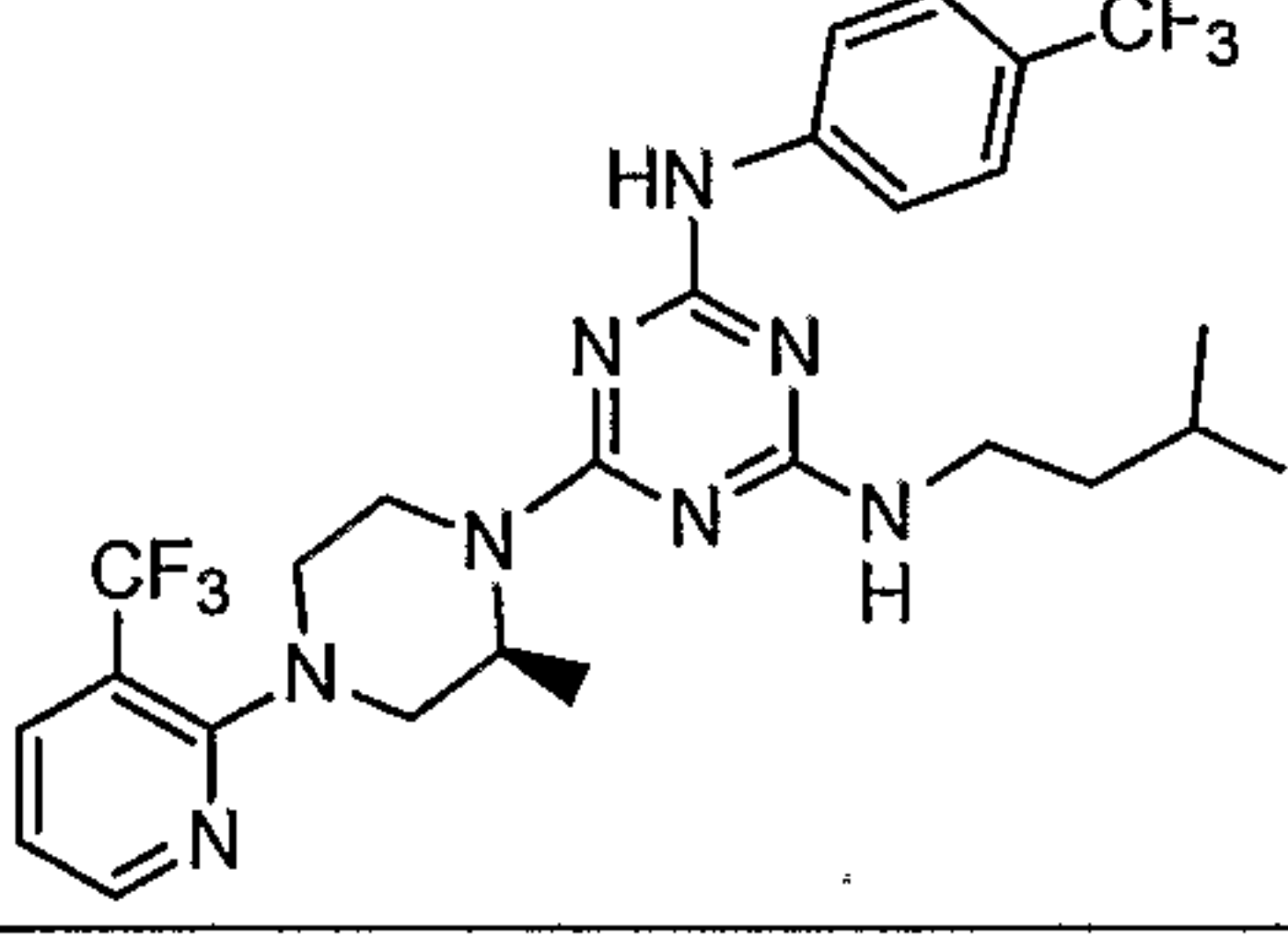
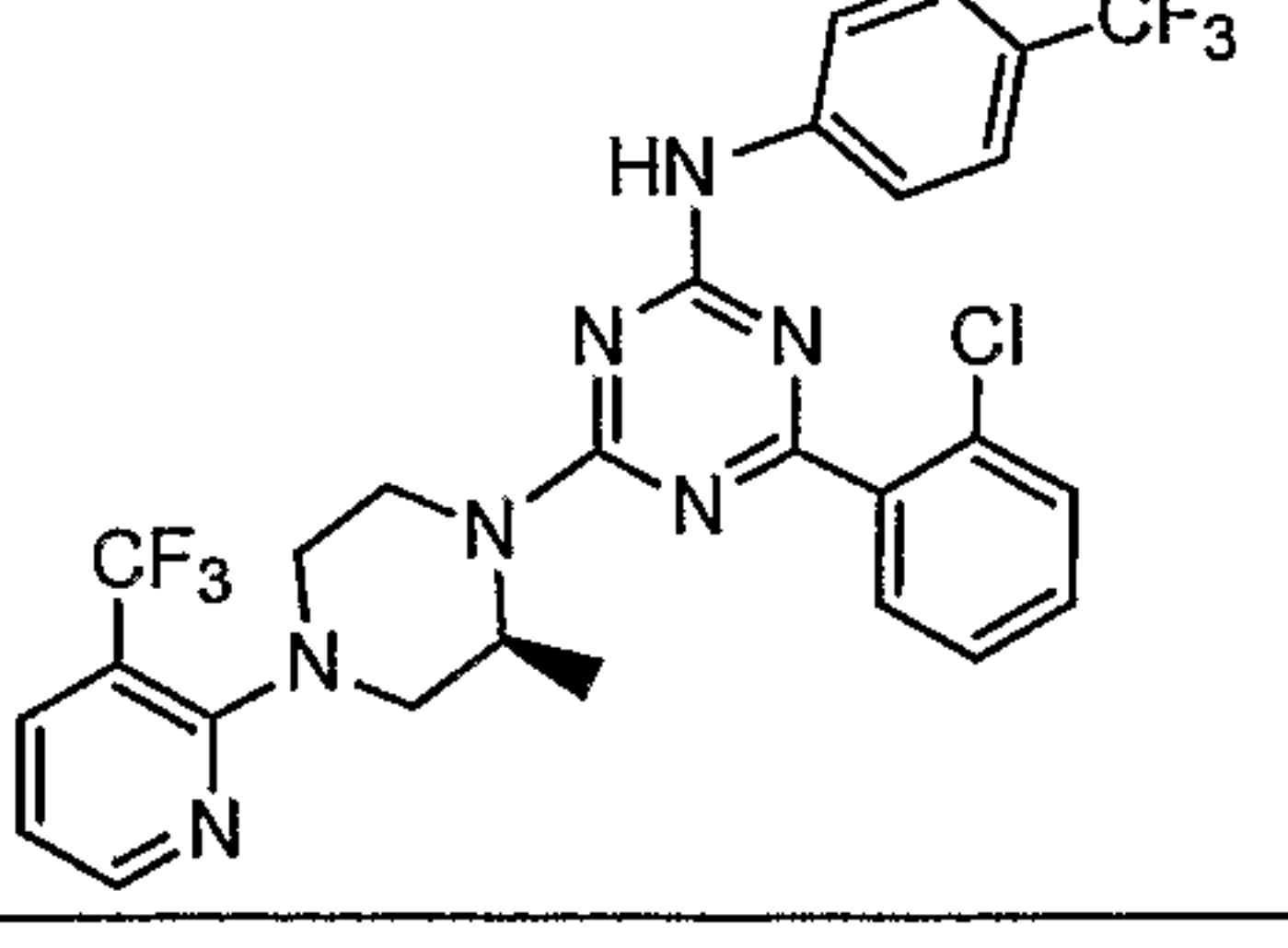
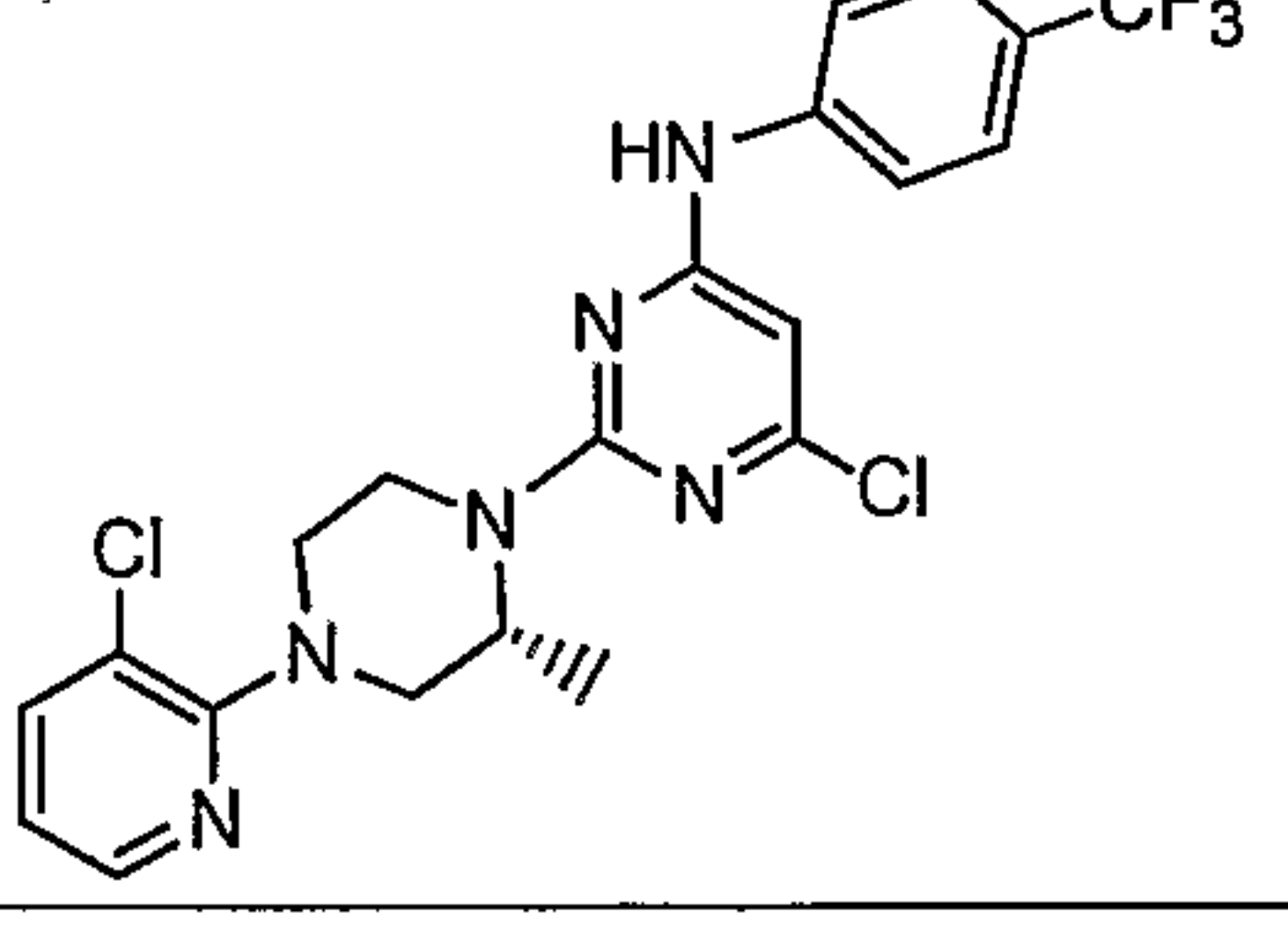
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		0	10
		0.5	100
		1.2	100
		1.21	10

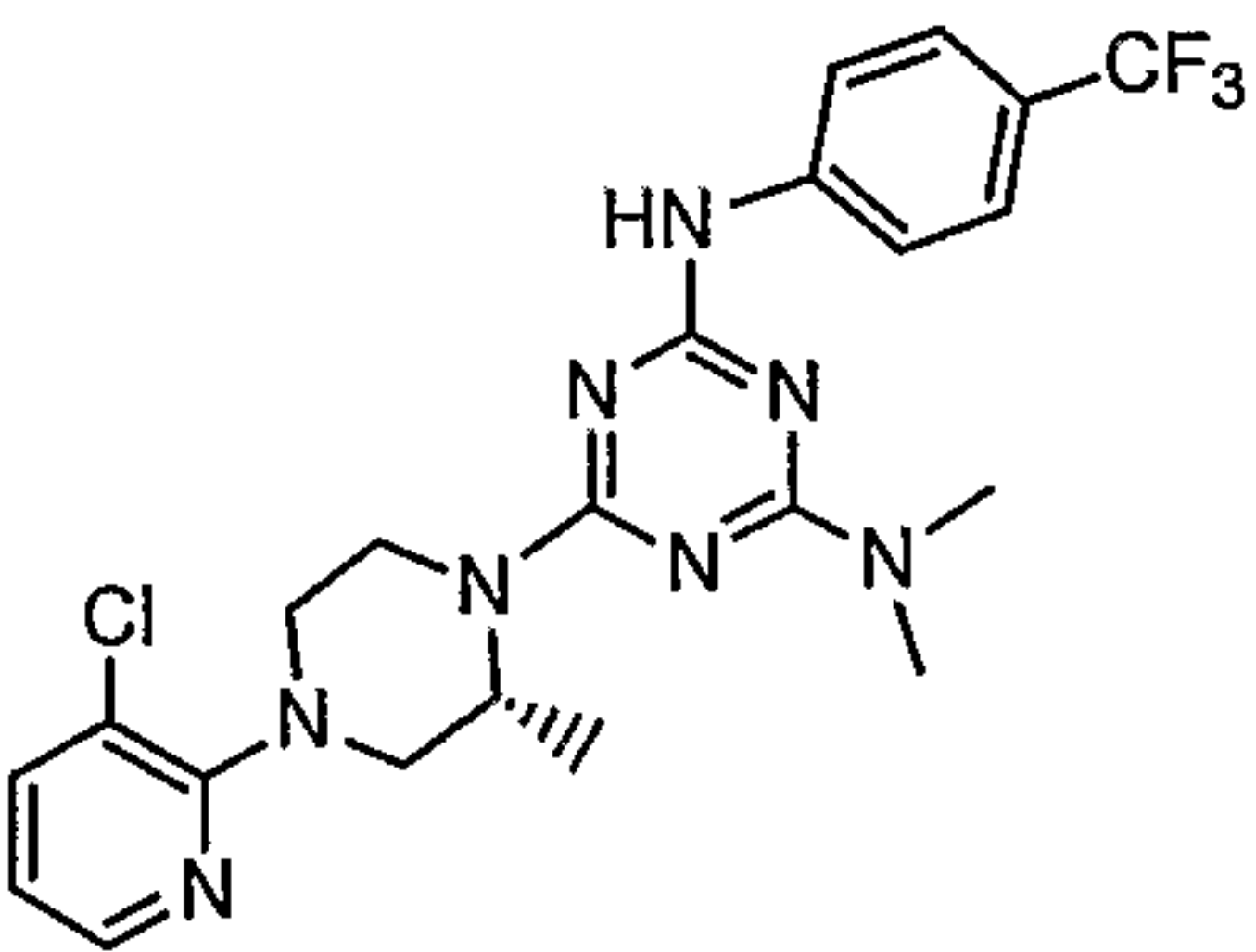
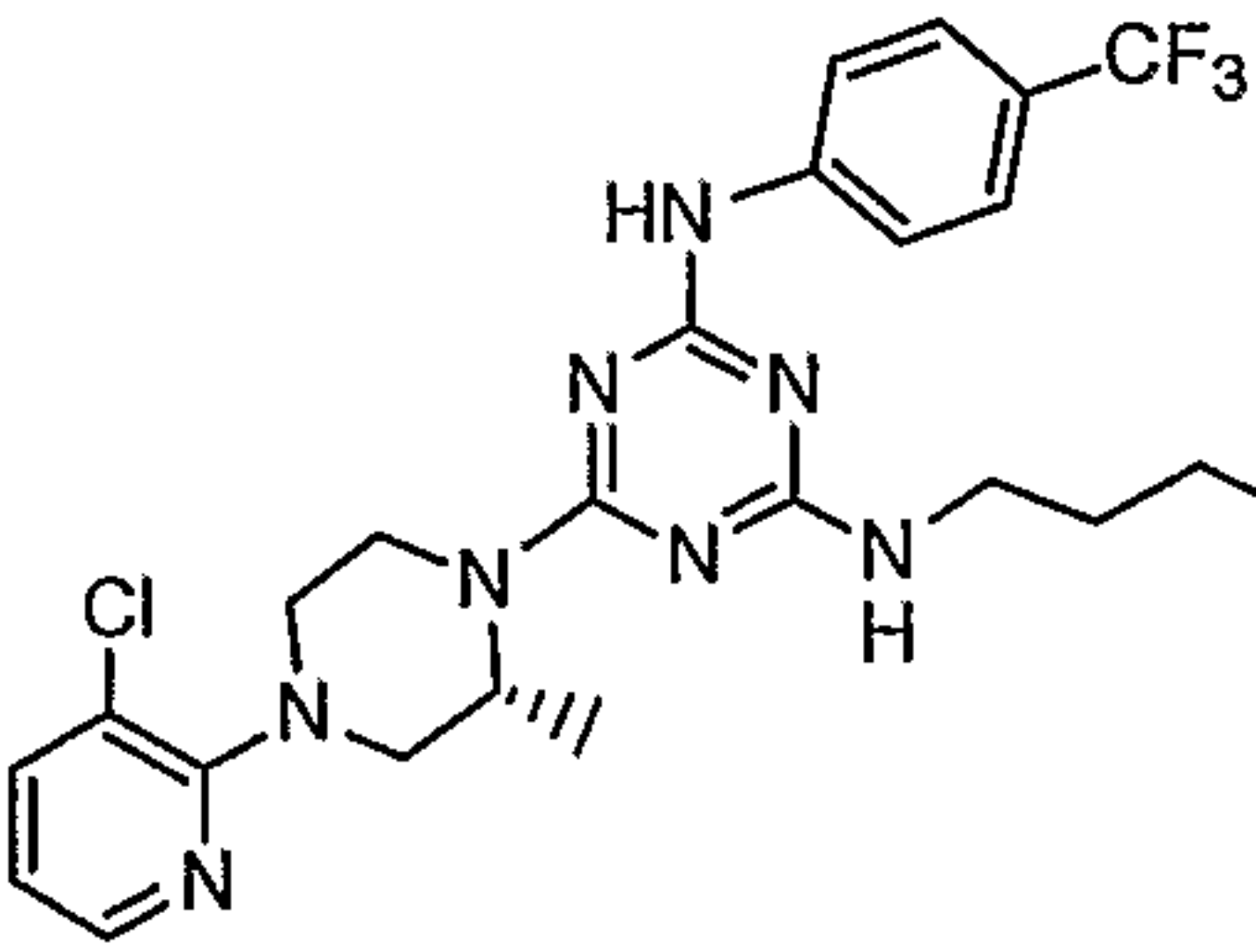
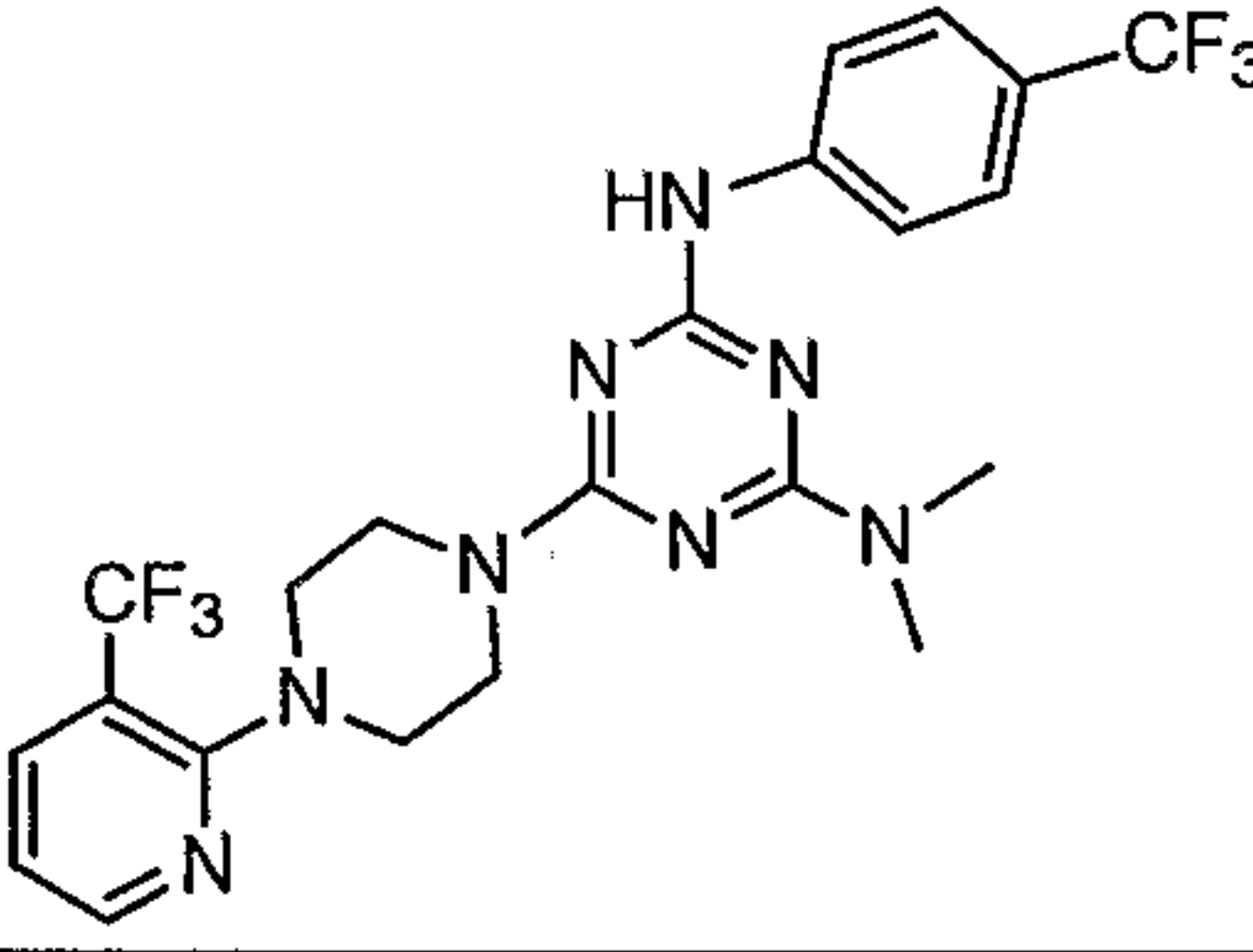
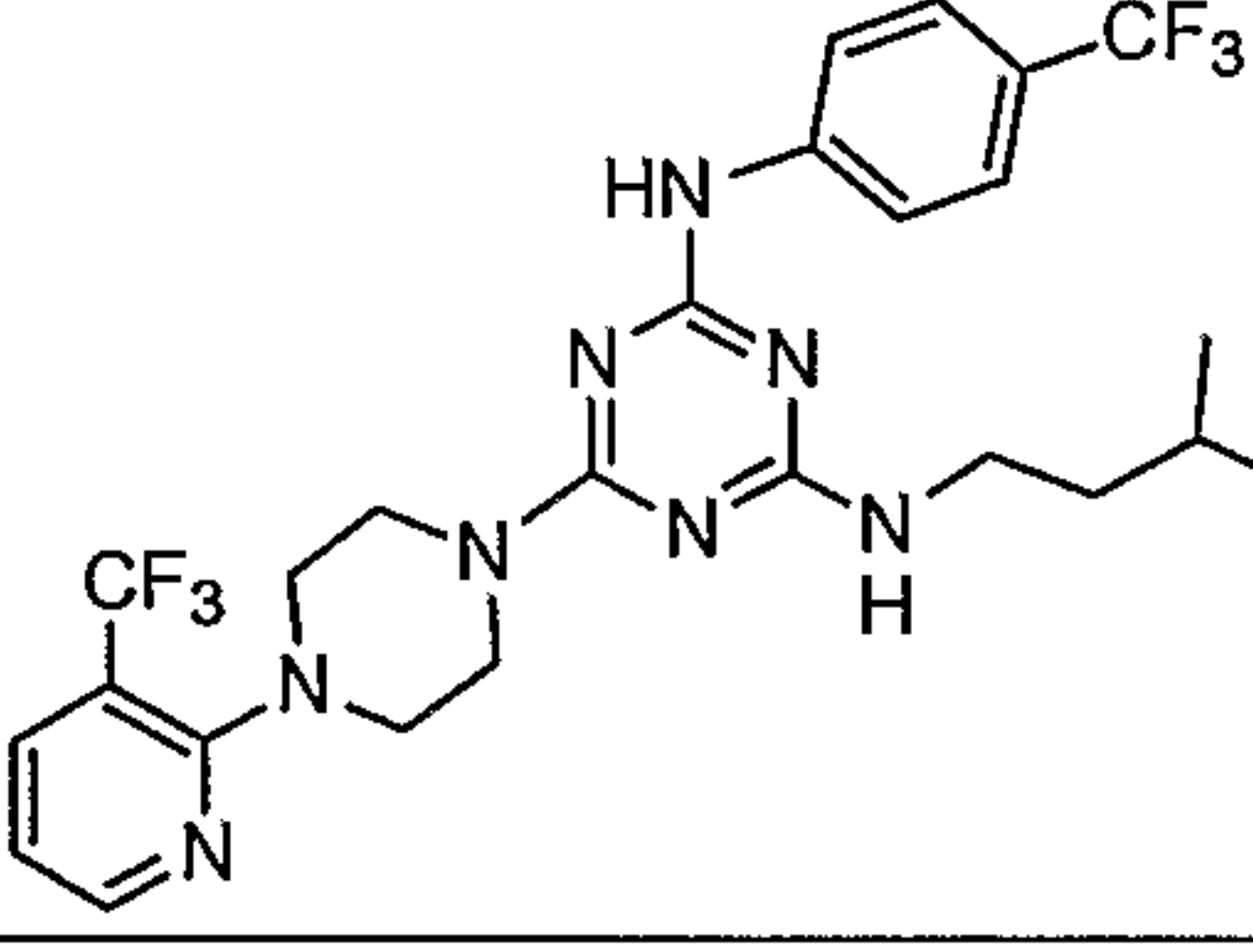
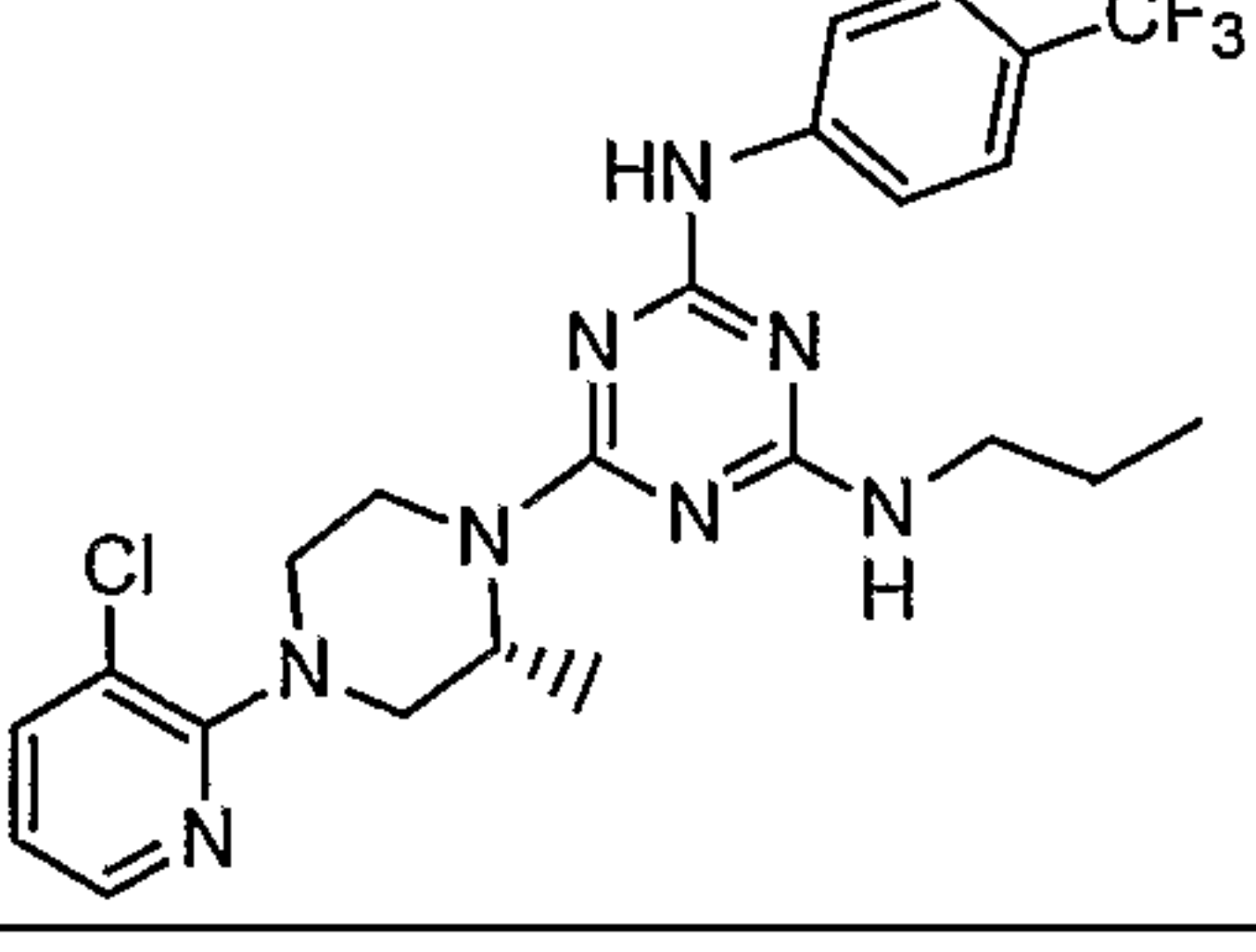
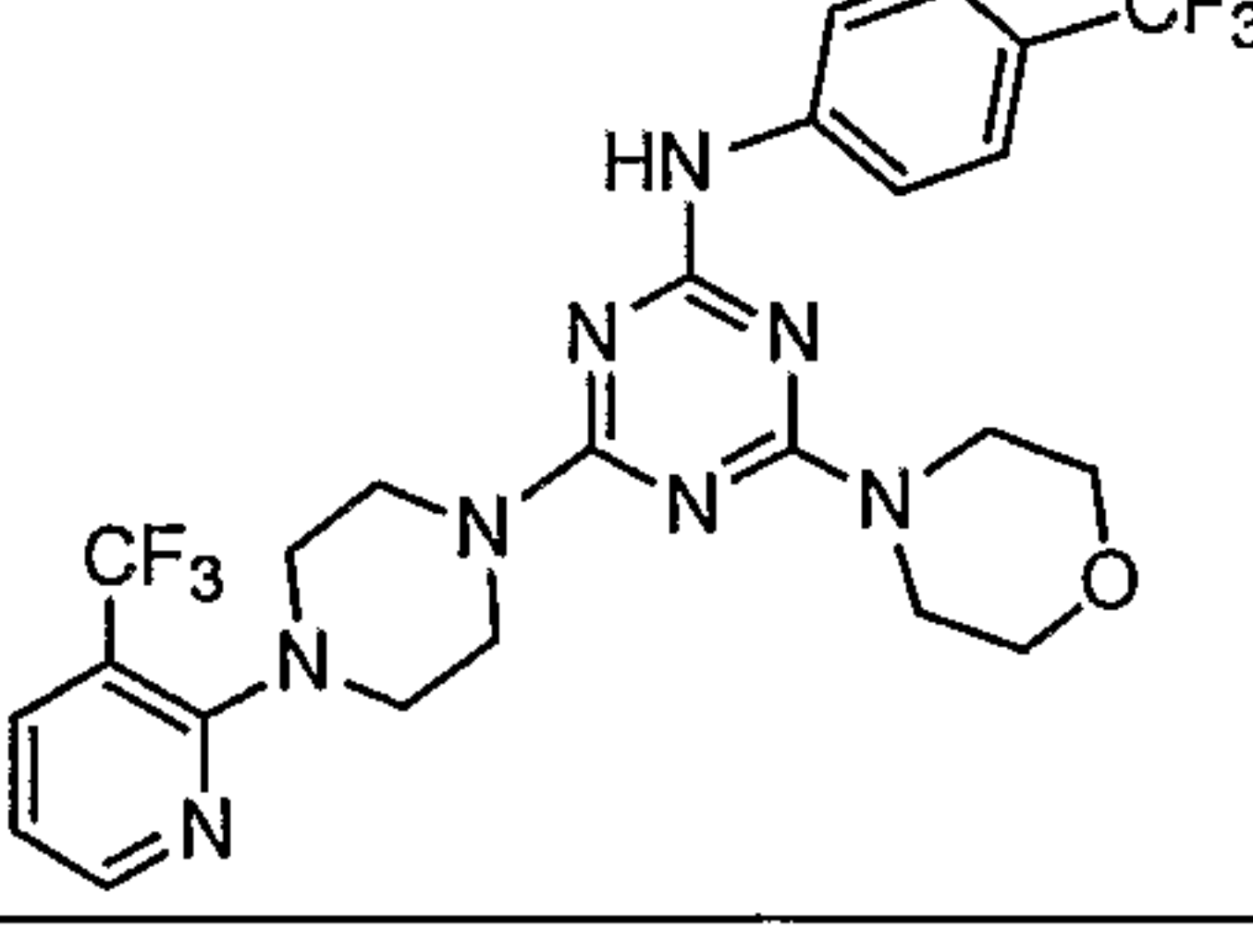
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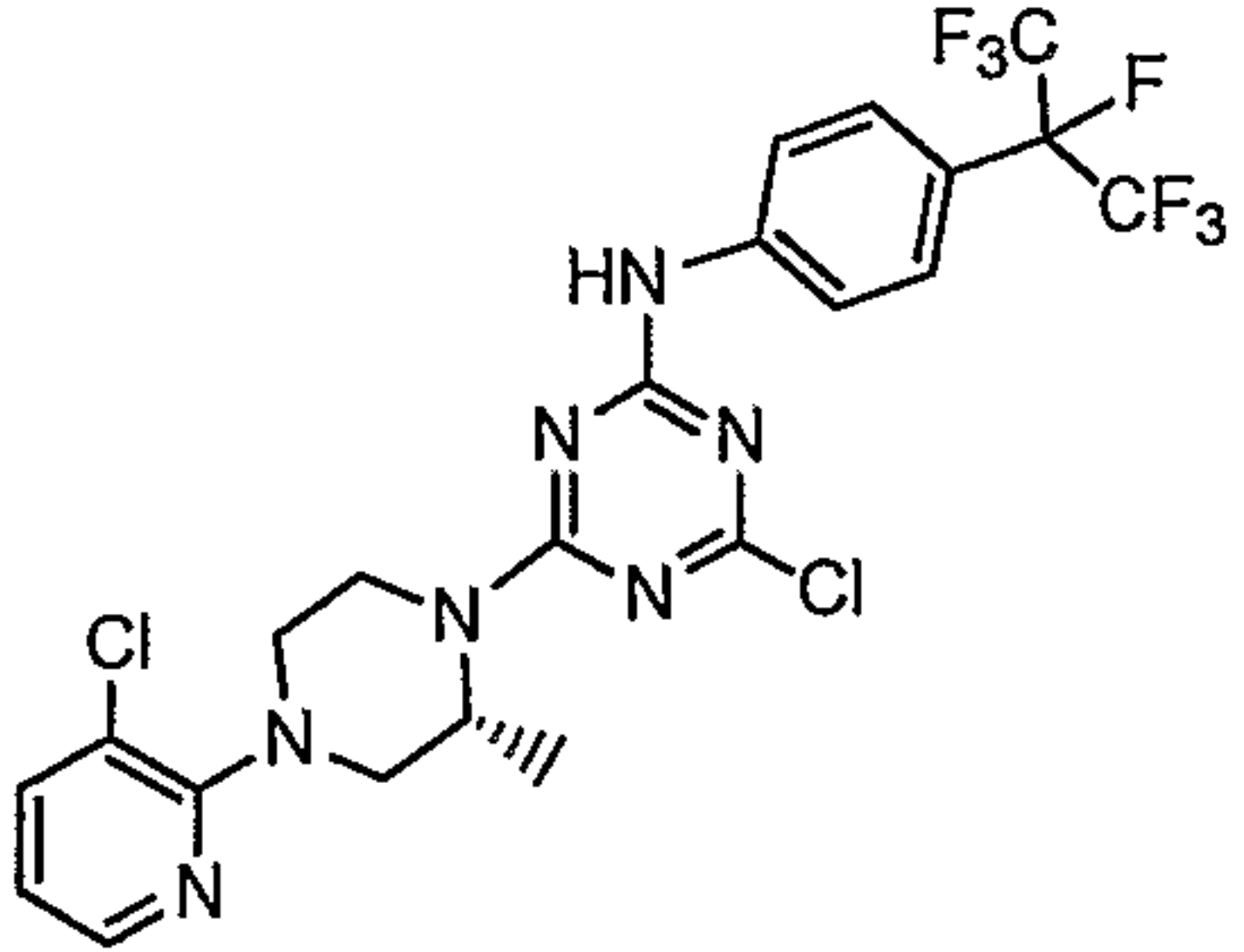
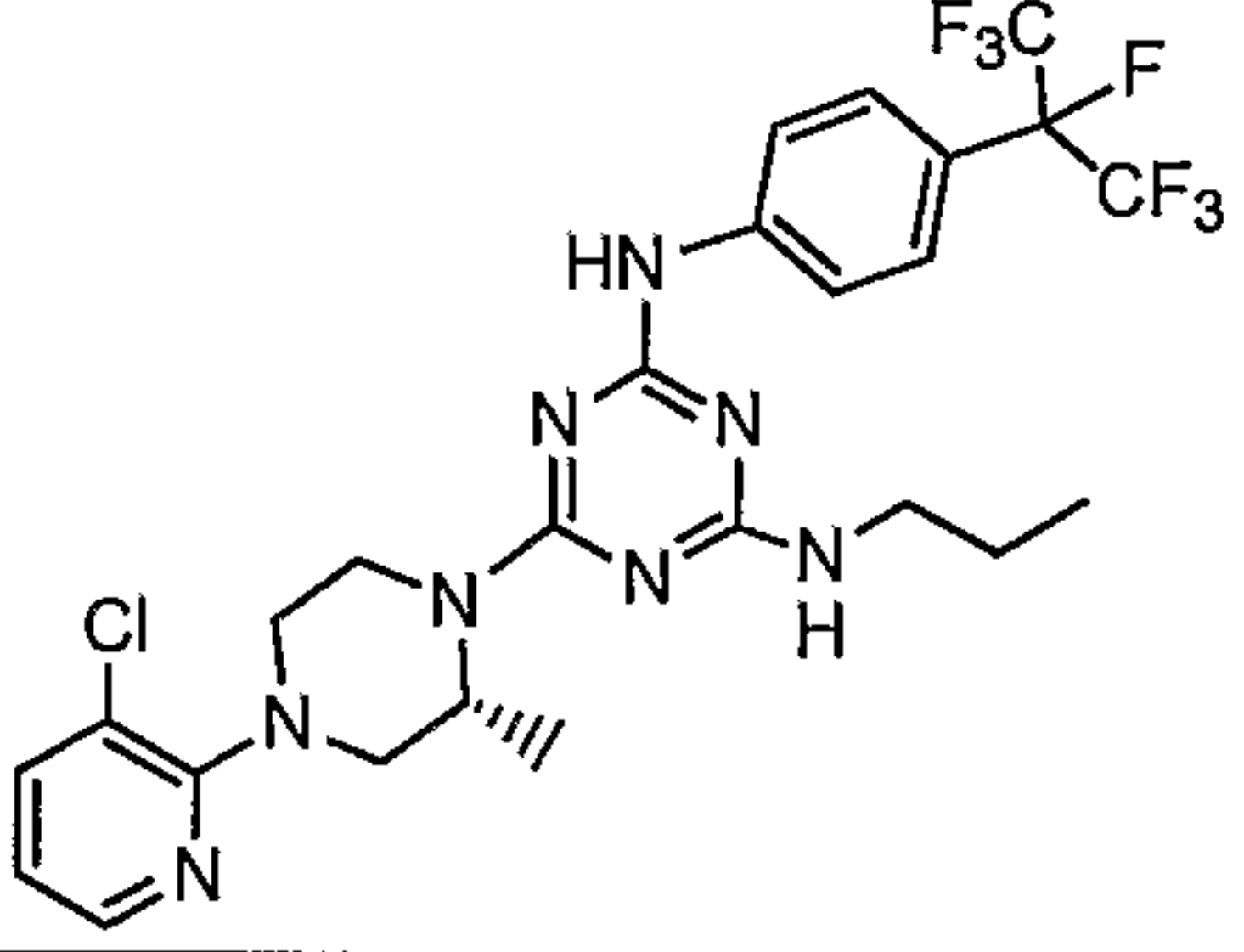
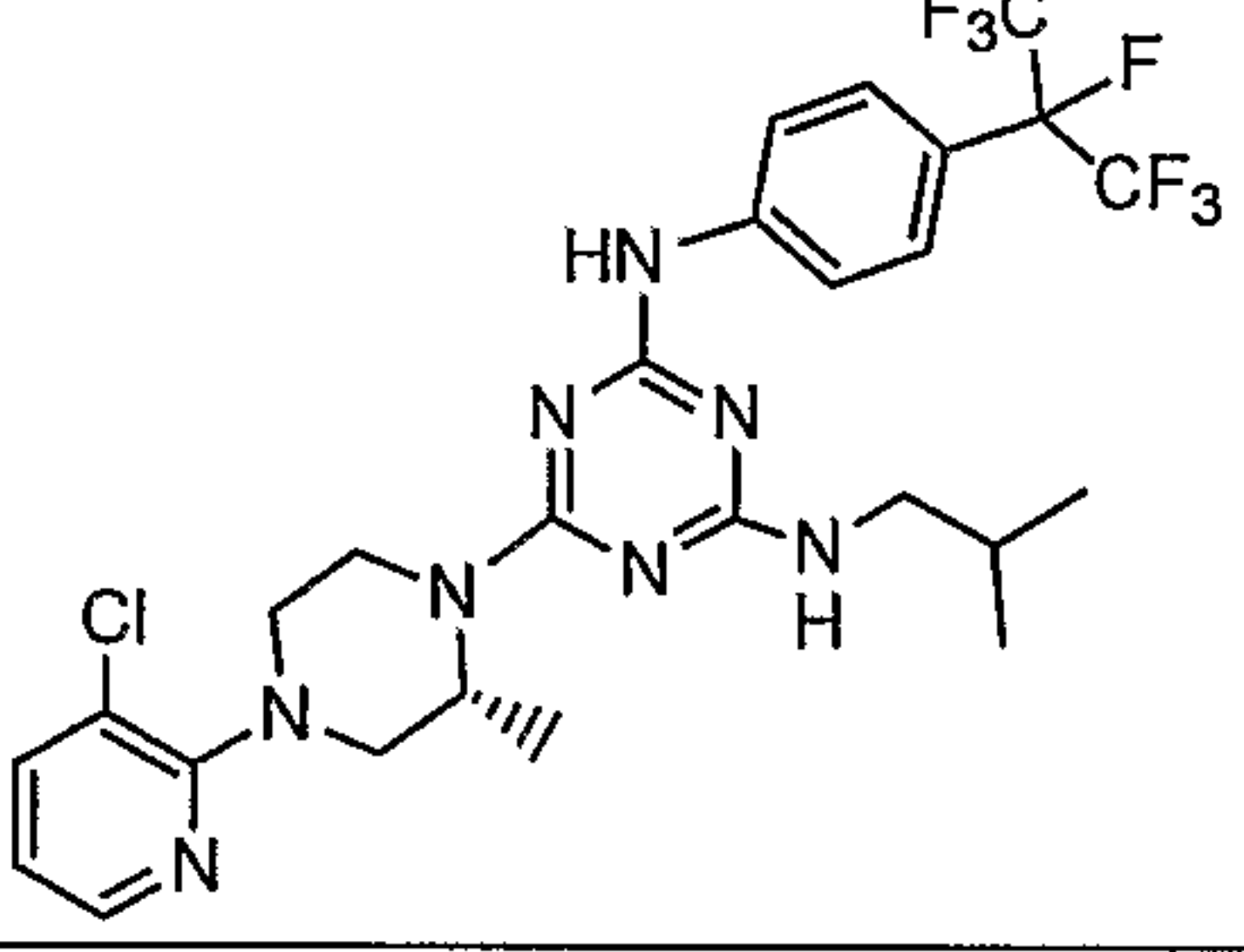
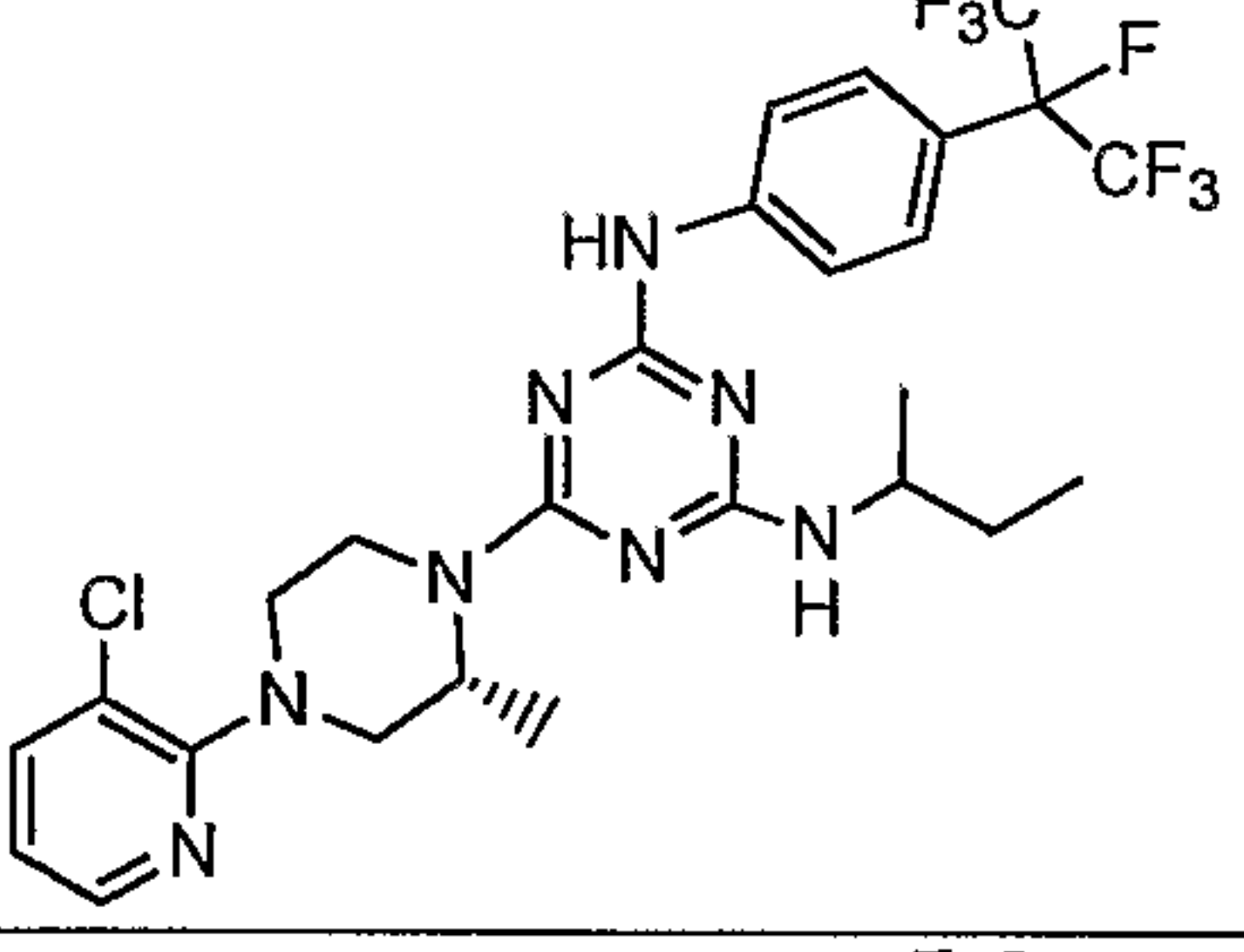
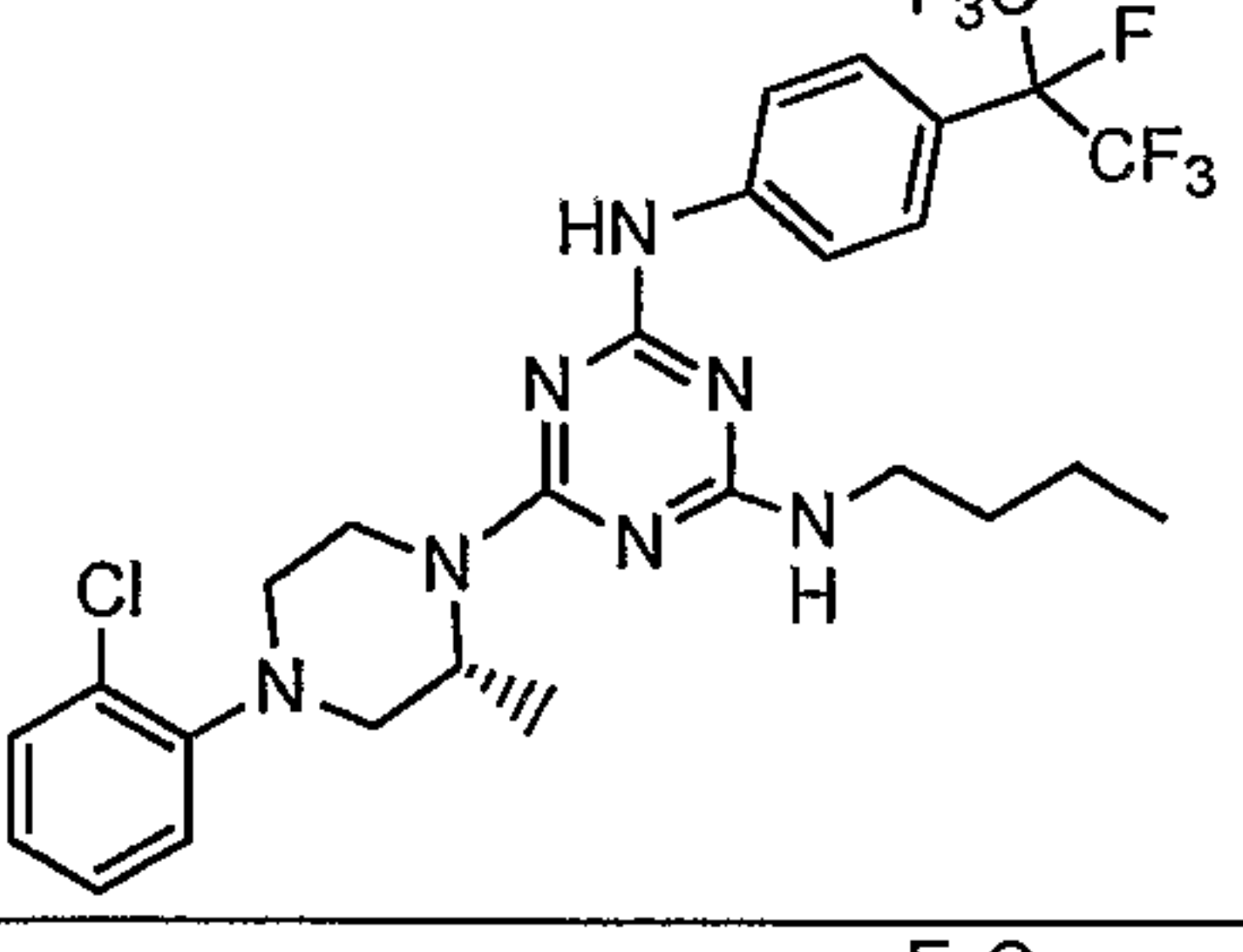
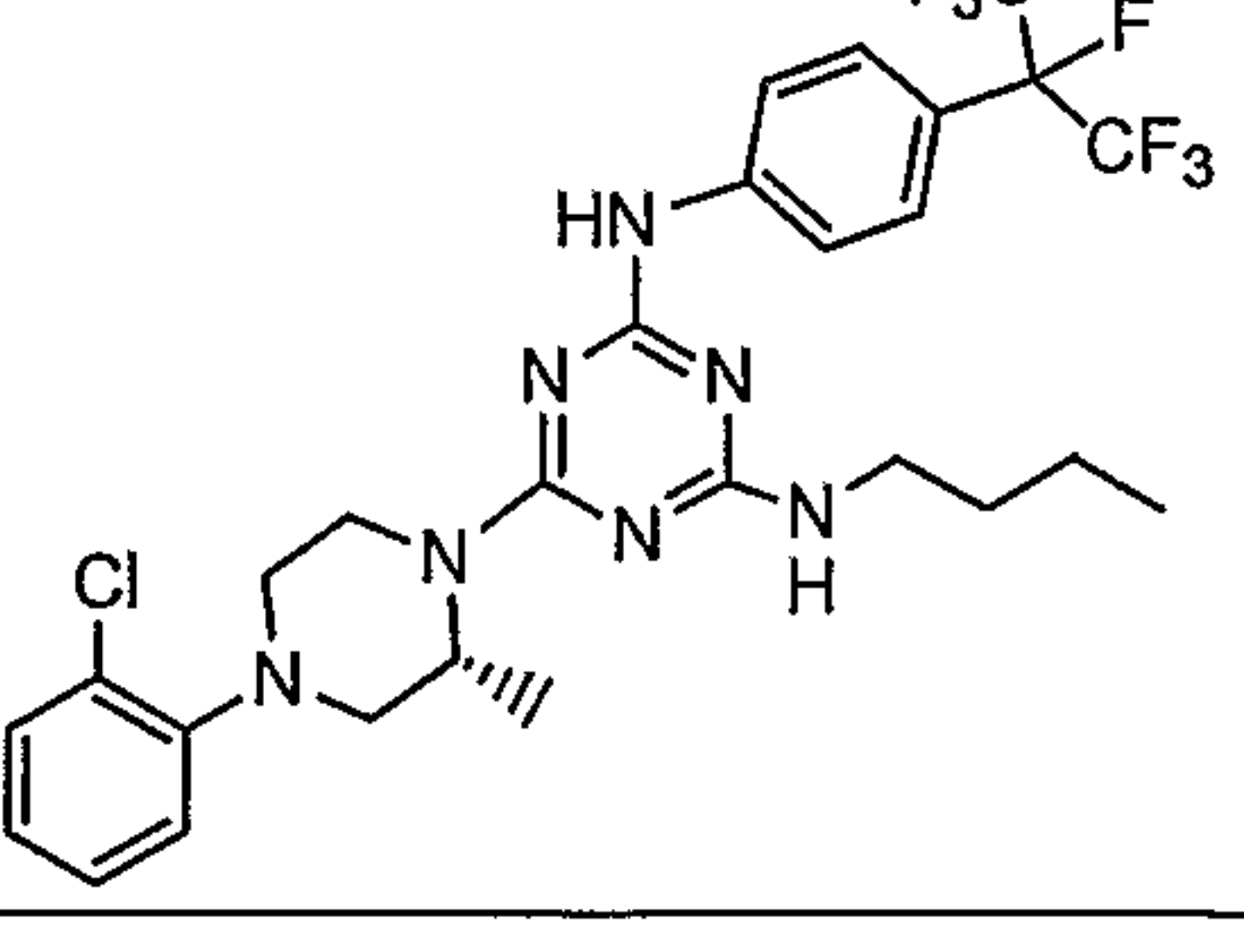
Table I
Representative Substituted Biaryl Piperazinyl-Pyridin-2-ylamine Analogues

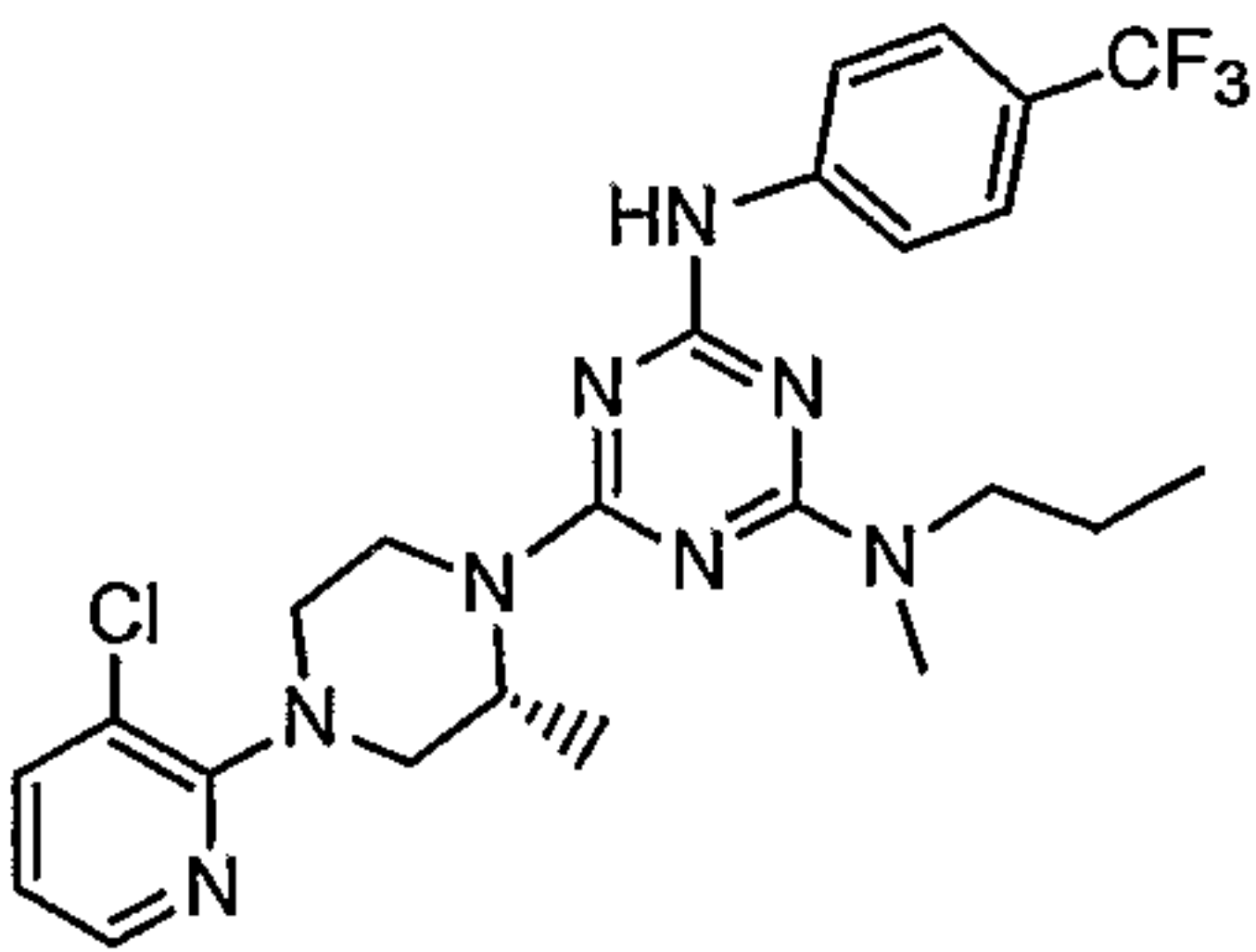
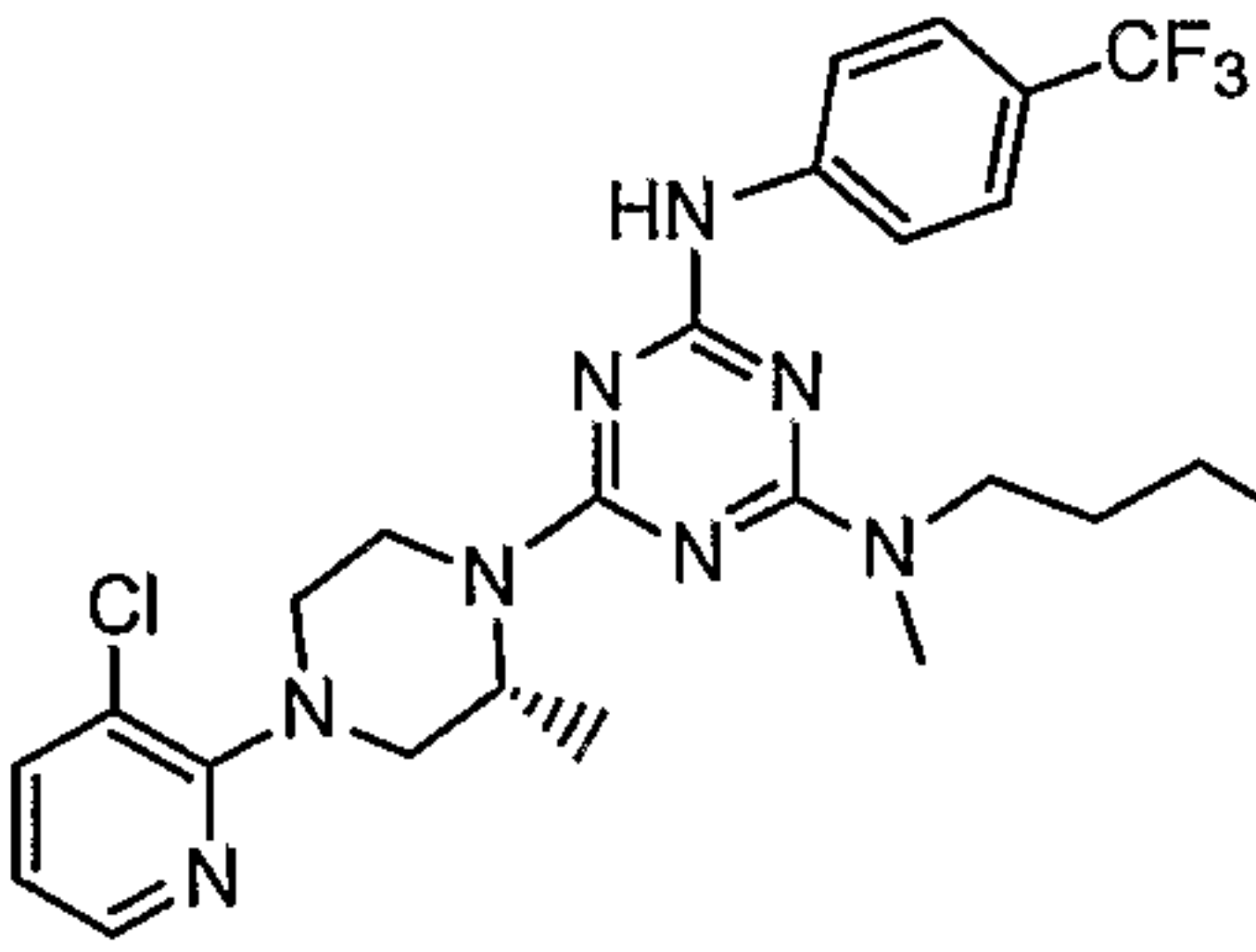
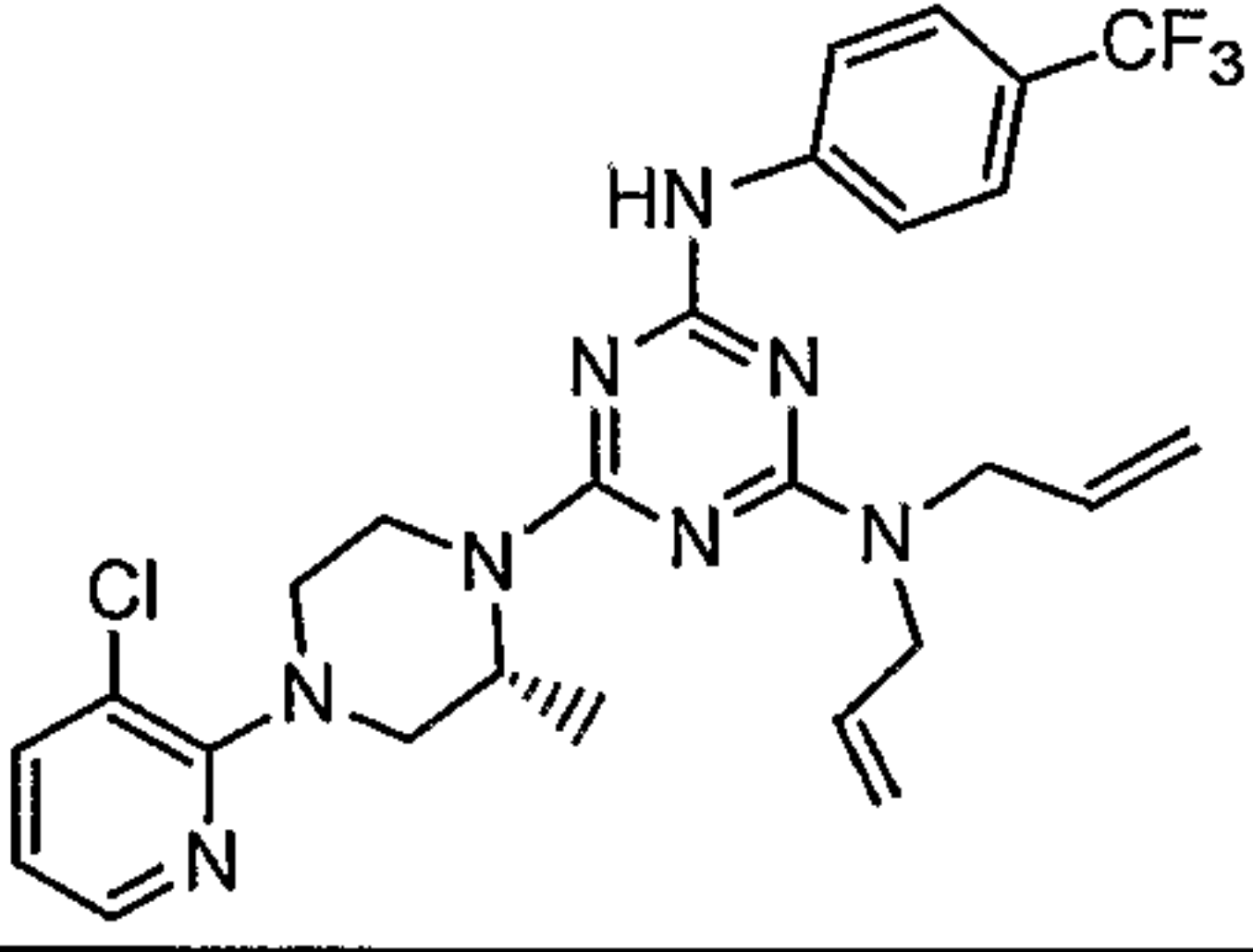
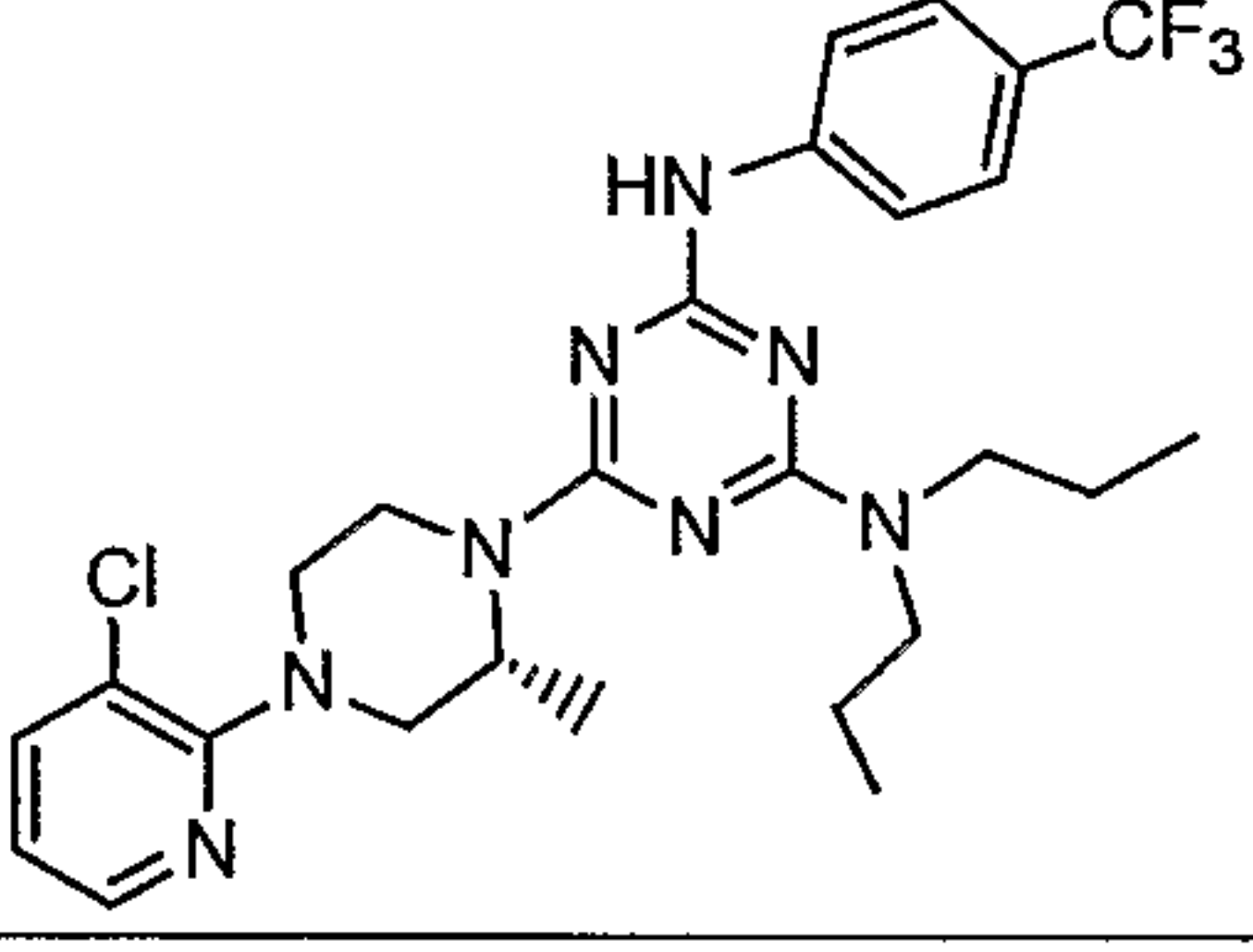
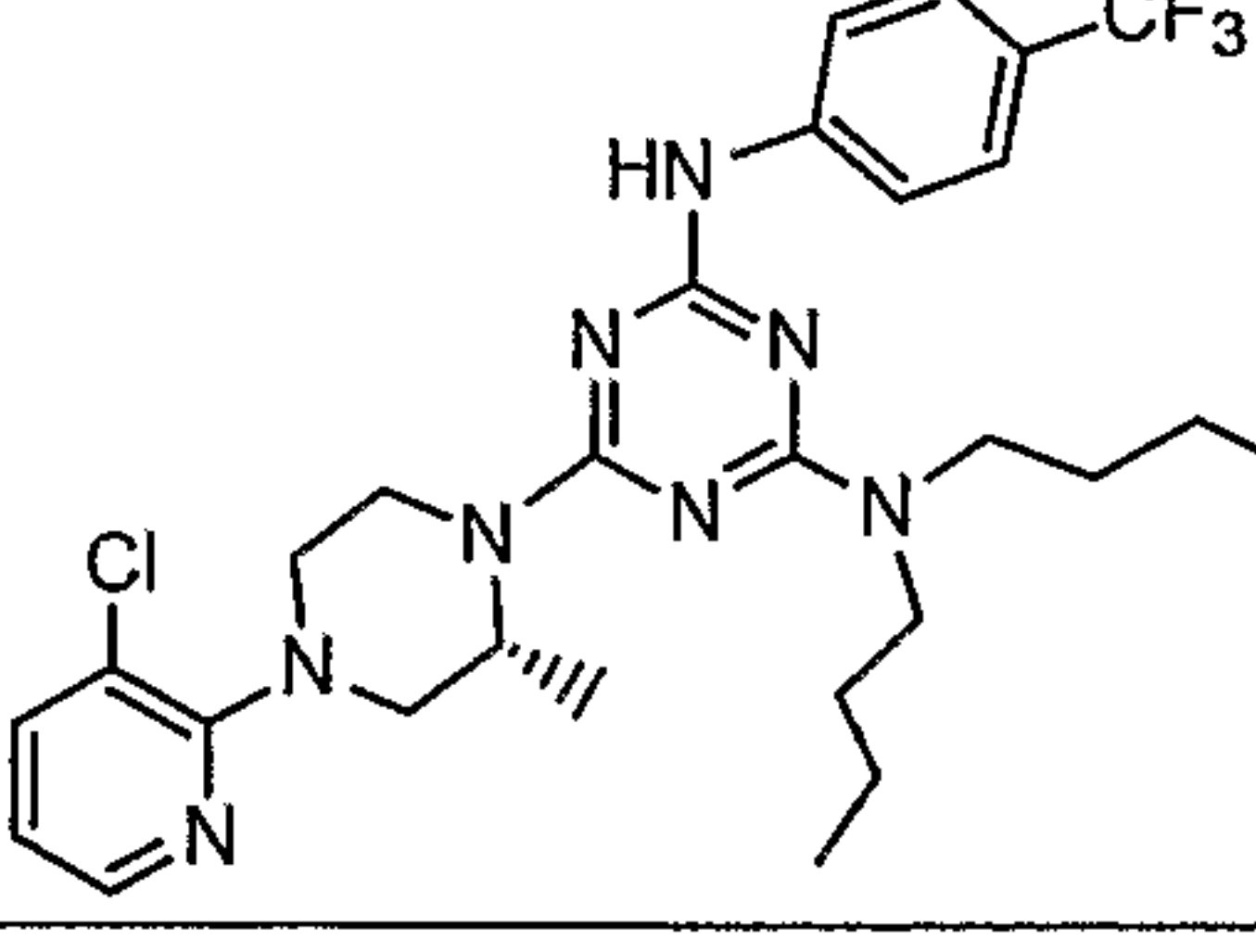
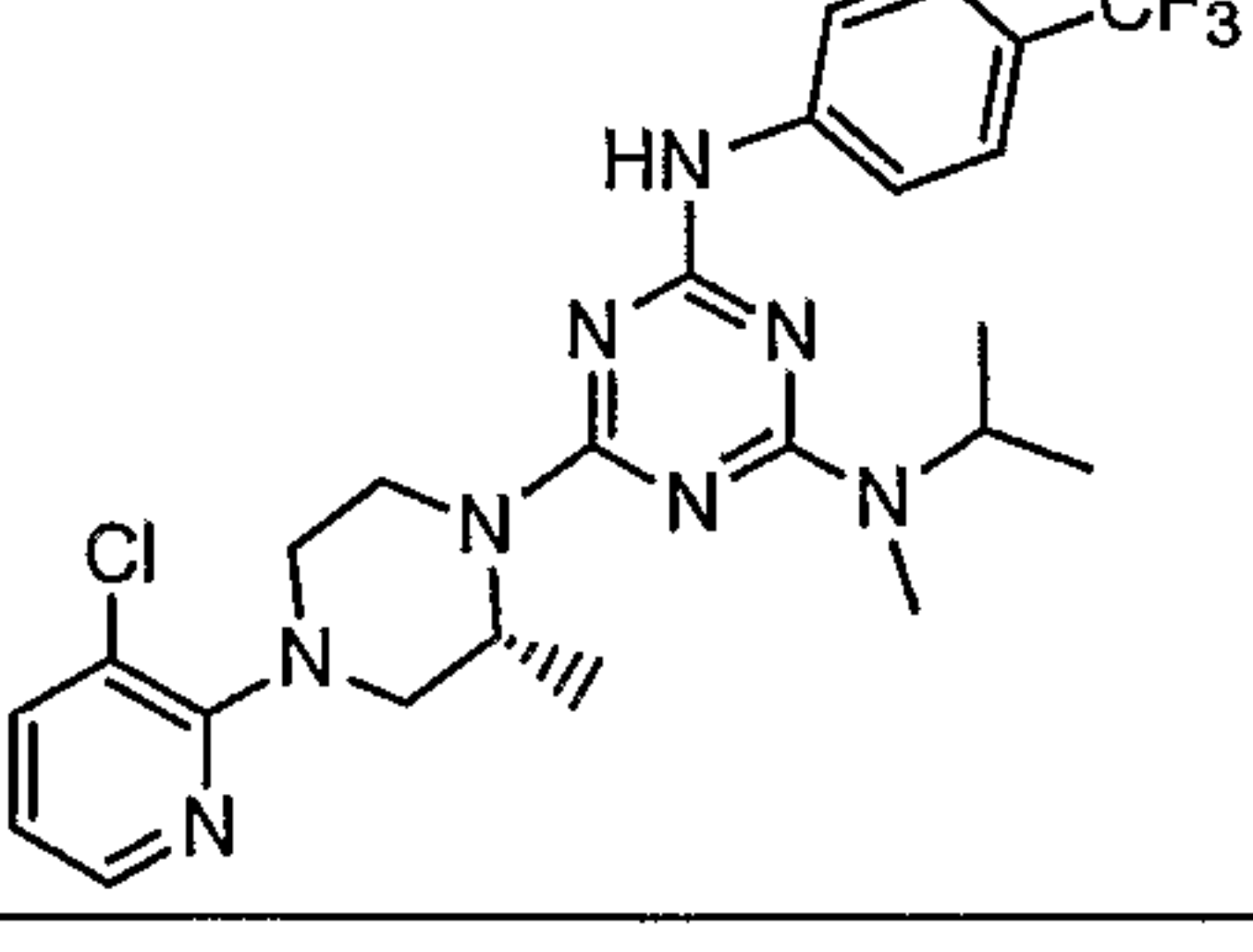
Compound	Name	IC ₅₀	MS
1. 	(4- <i>tert</i> -Butyl-phenyl)-{6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-amine (R)	*	437.26
2. 	(4- <i>tert</i> -Butyl-phenyl)-{4-chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R)	*	472.23
3. 	(4- <i>tert</i> -Butyl-phenyl)-{4-chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R)	*	506.25
4. 	(4- <i>tert</i> -Butyl-phenyl)-{4-chloro-6-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R)		456.25
5. 	(4- <i>tert</i> -Butyl-phenyl)-[4-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine (R)	*	612.33

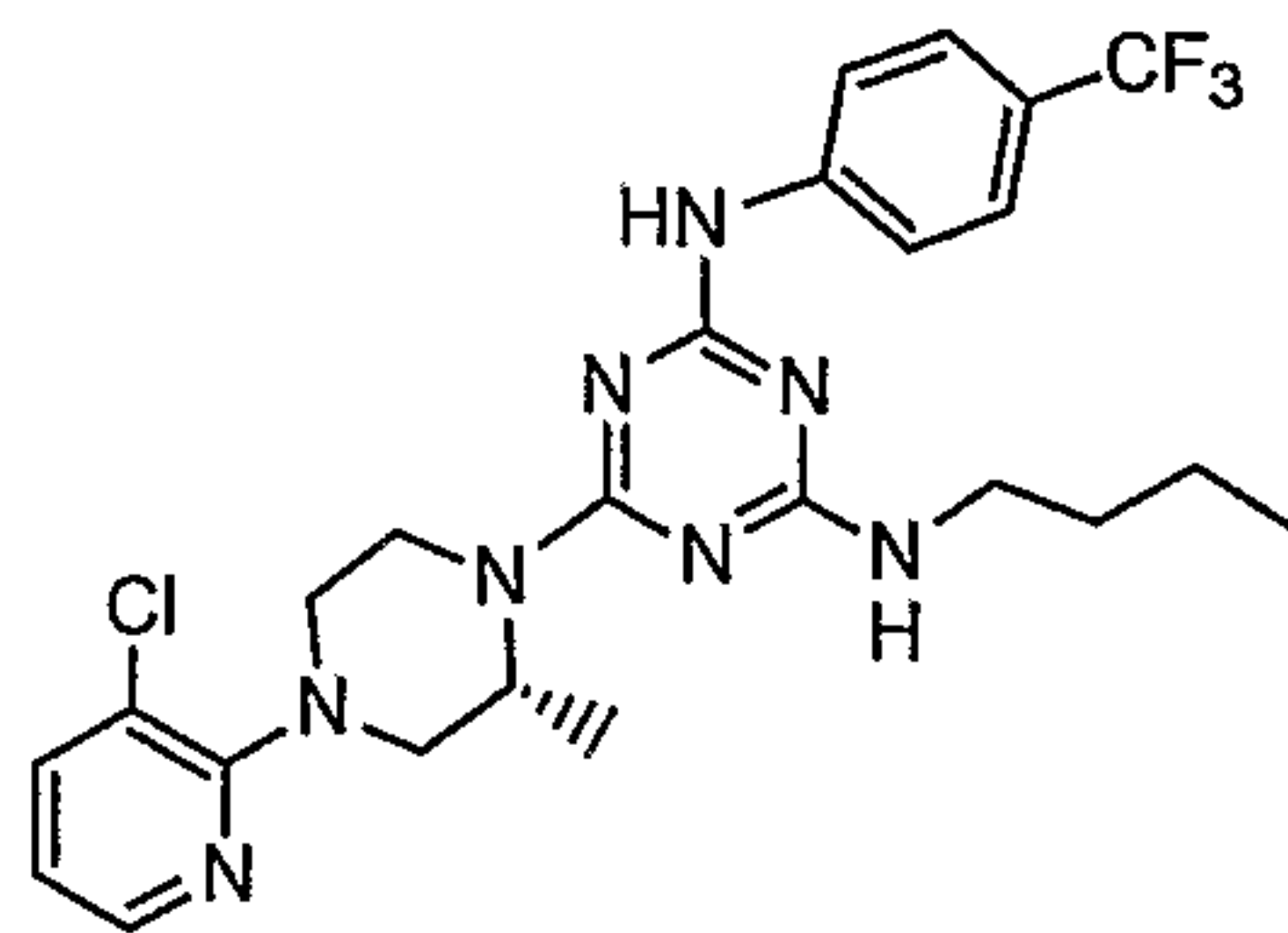
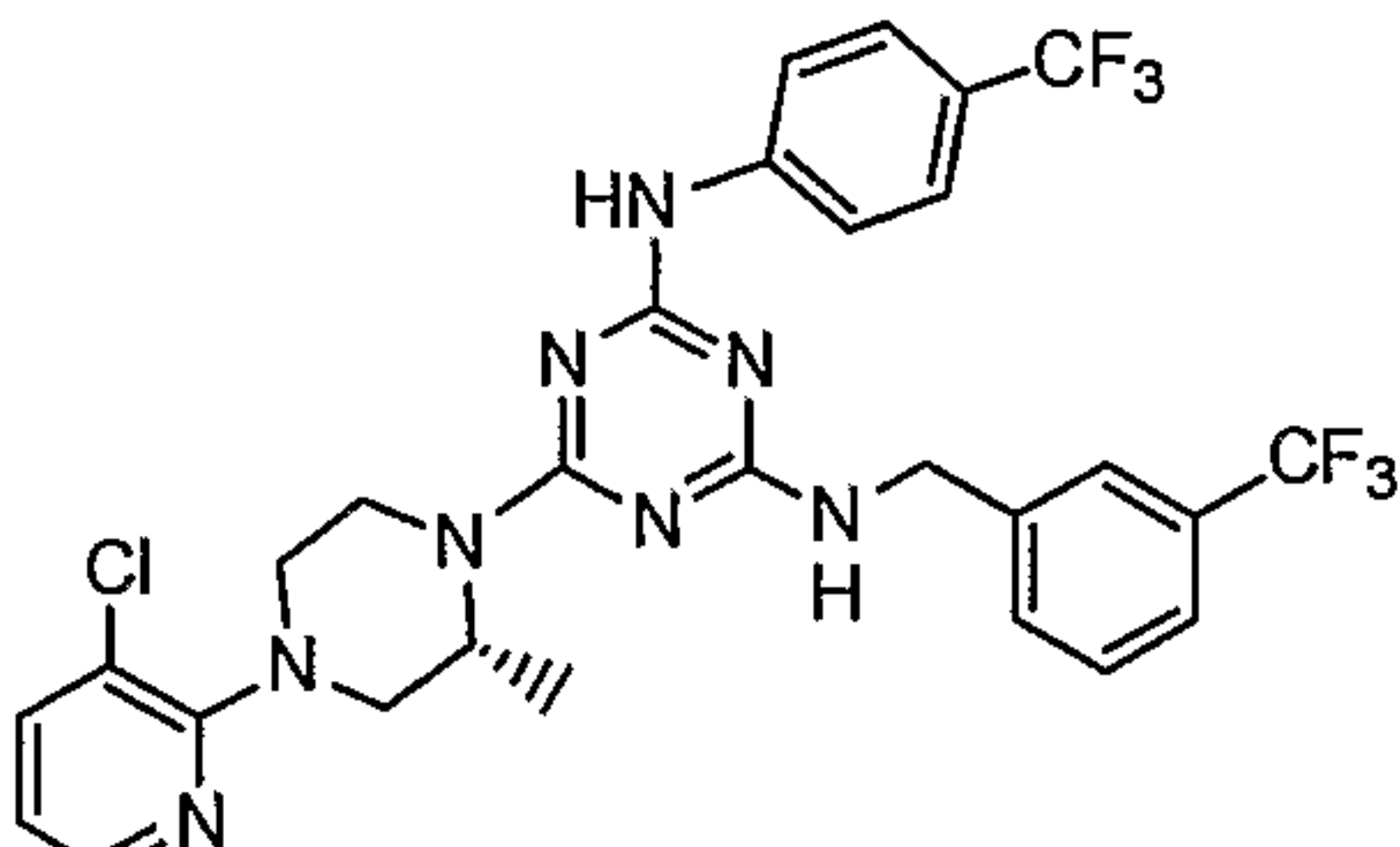
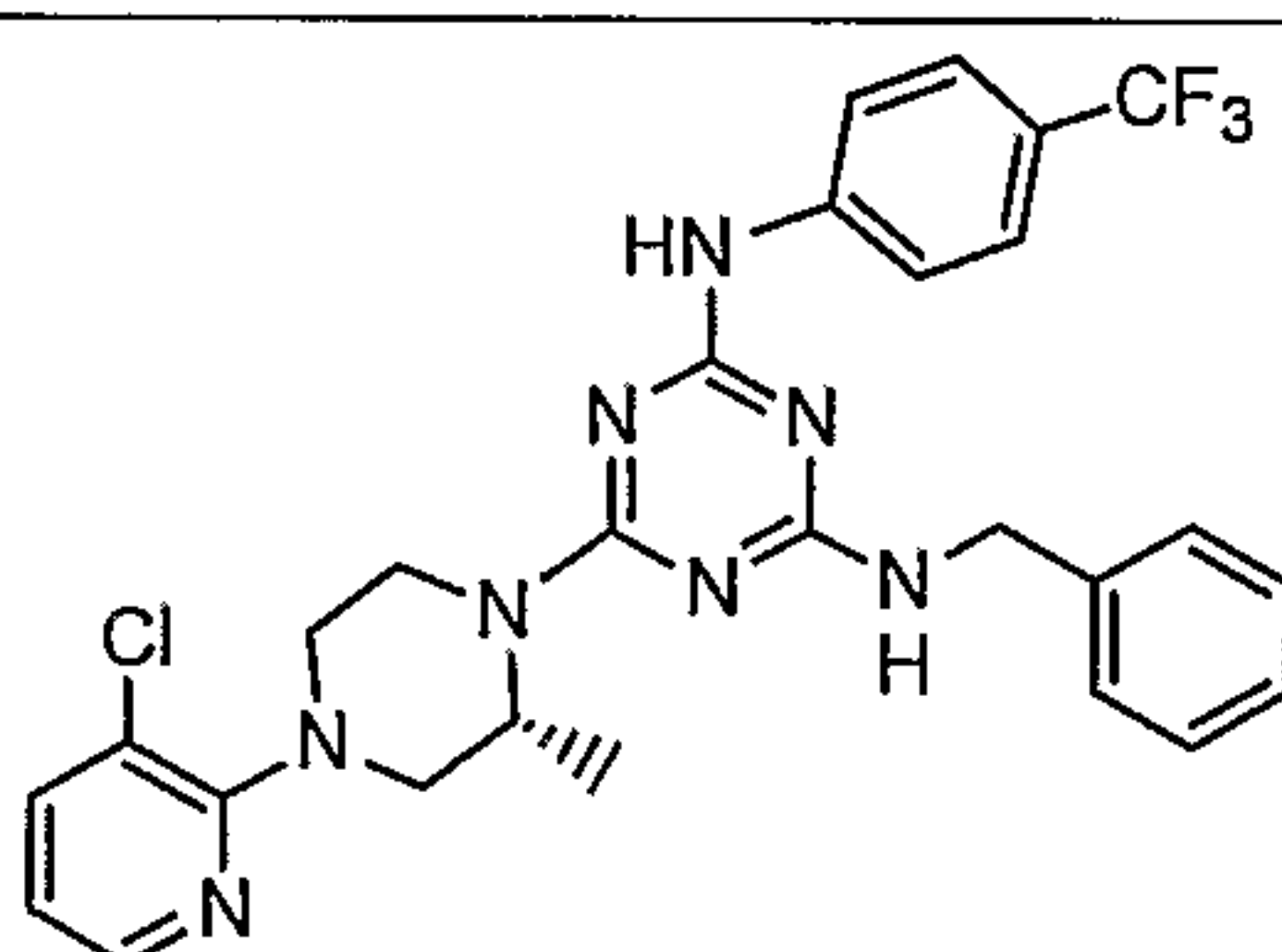
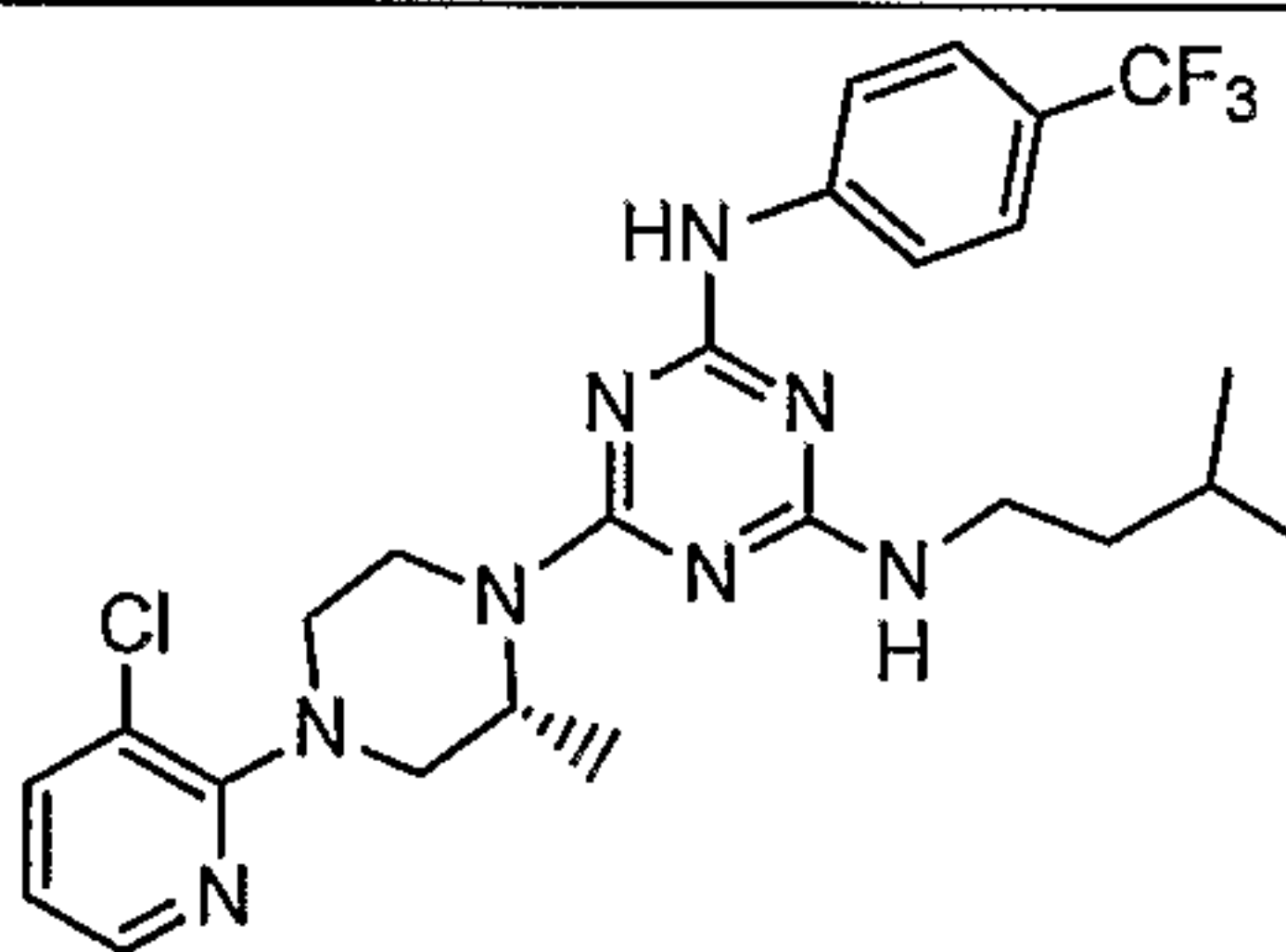
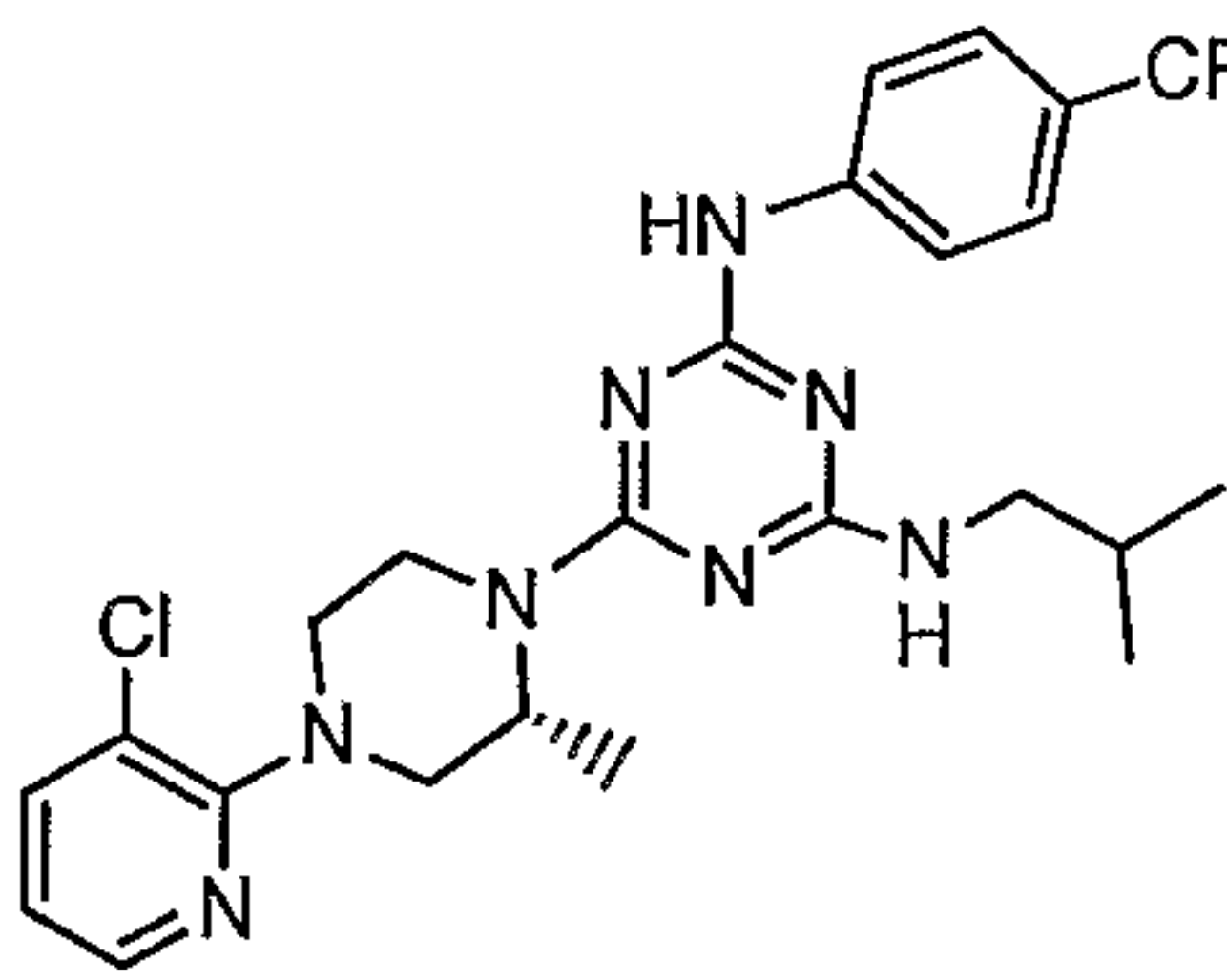
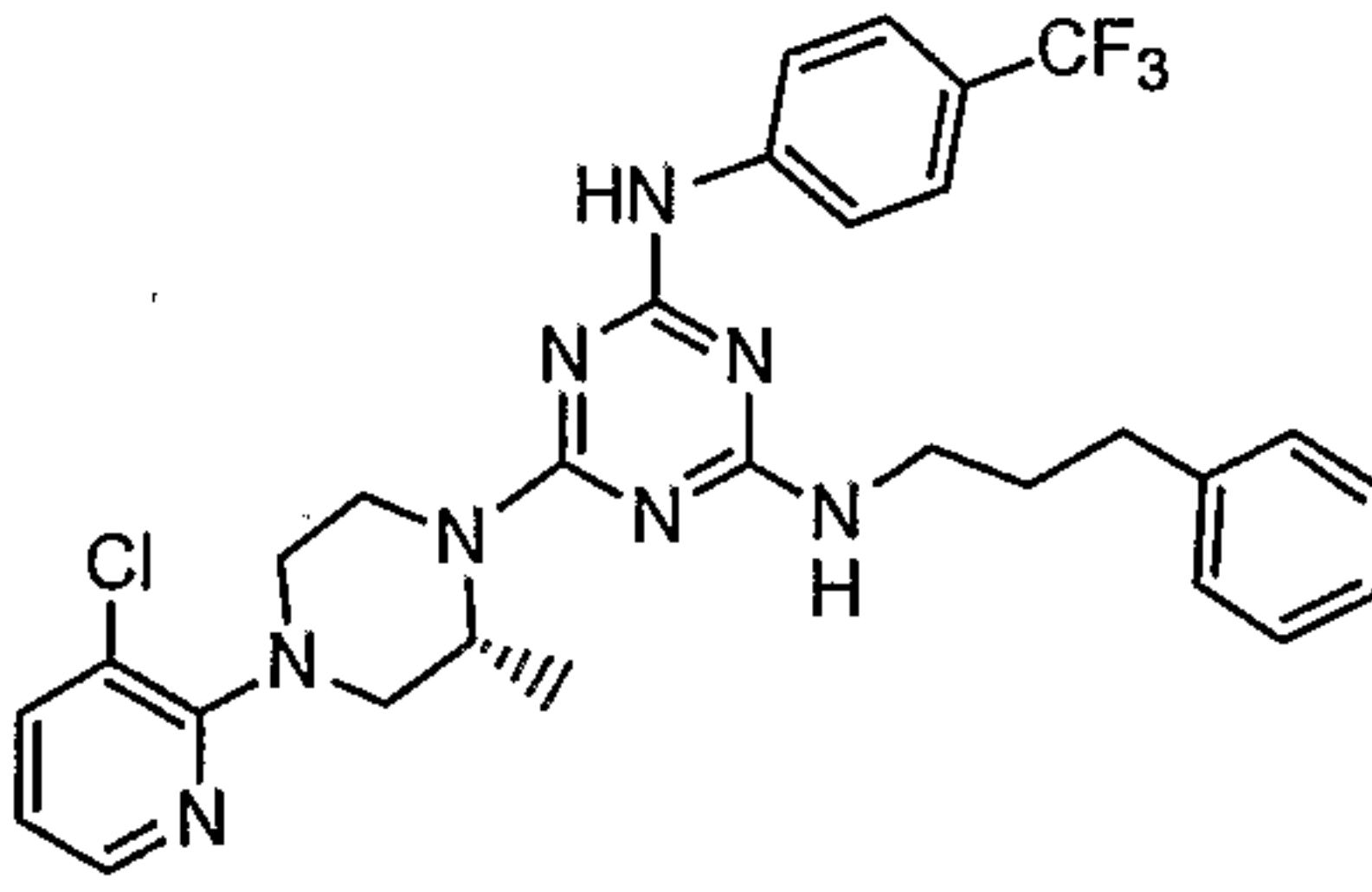
Compound	Name	IC ₅₀	MS
6.		*	646.33
7.		*	596.33
8.		*	624.24
9.		*	658.27
10.		*	608.26
11.		*	564.28

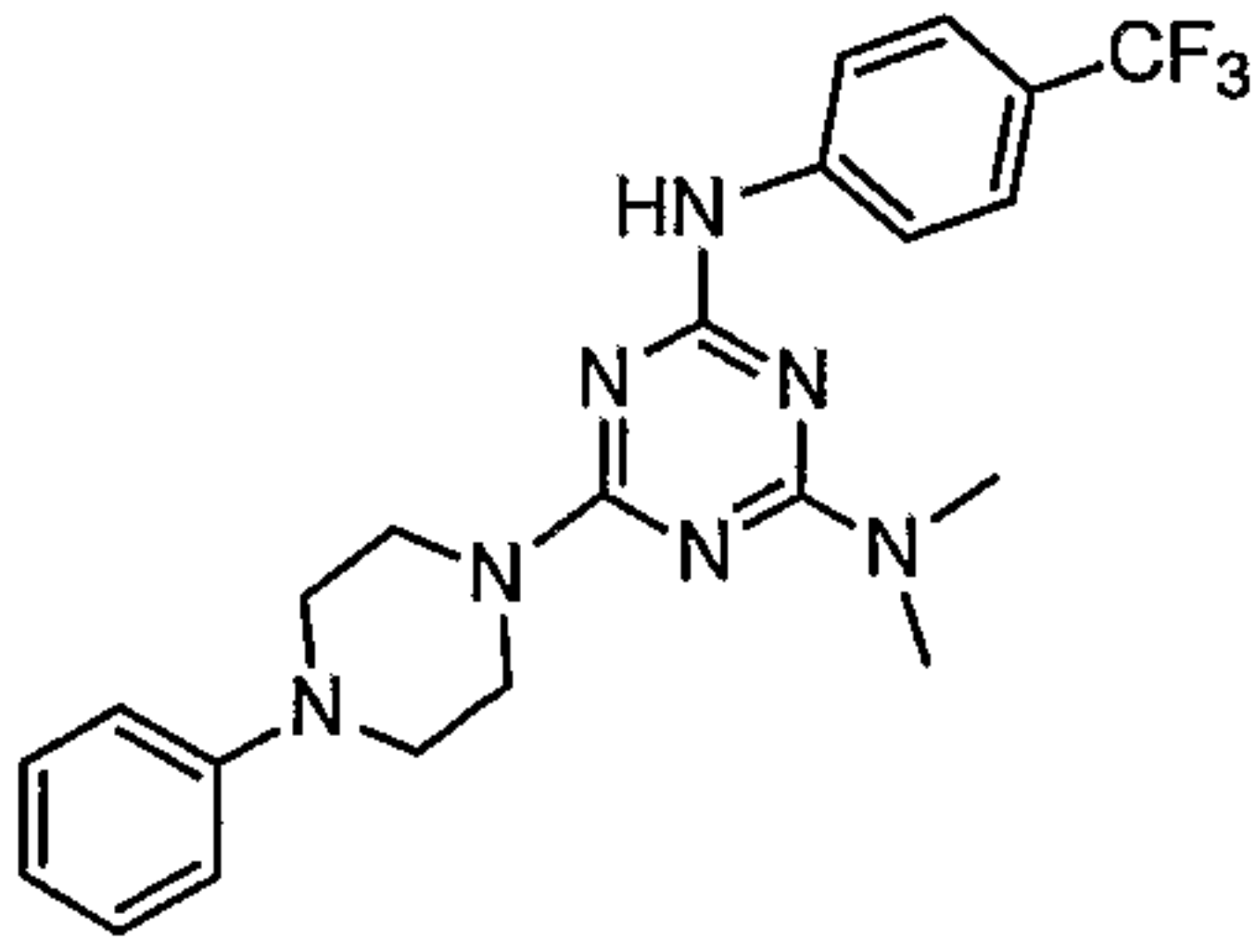
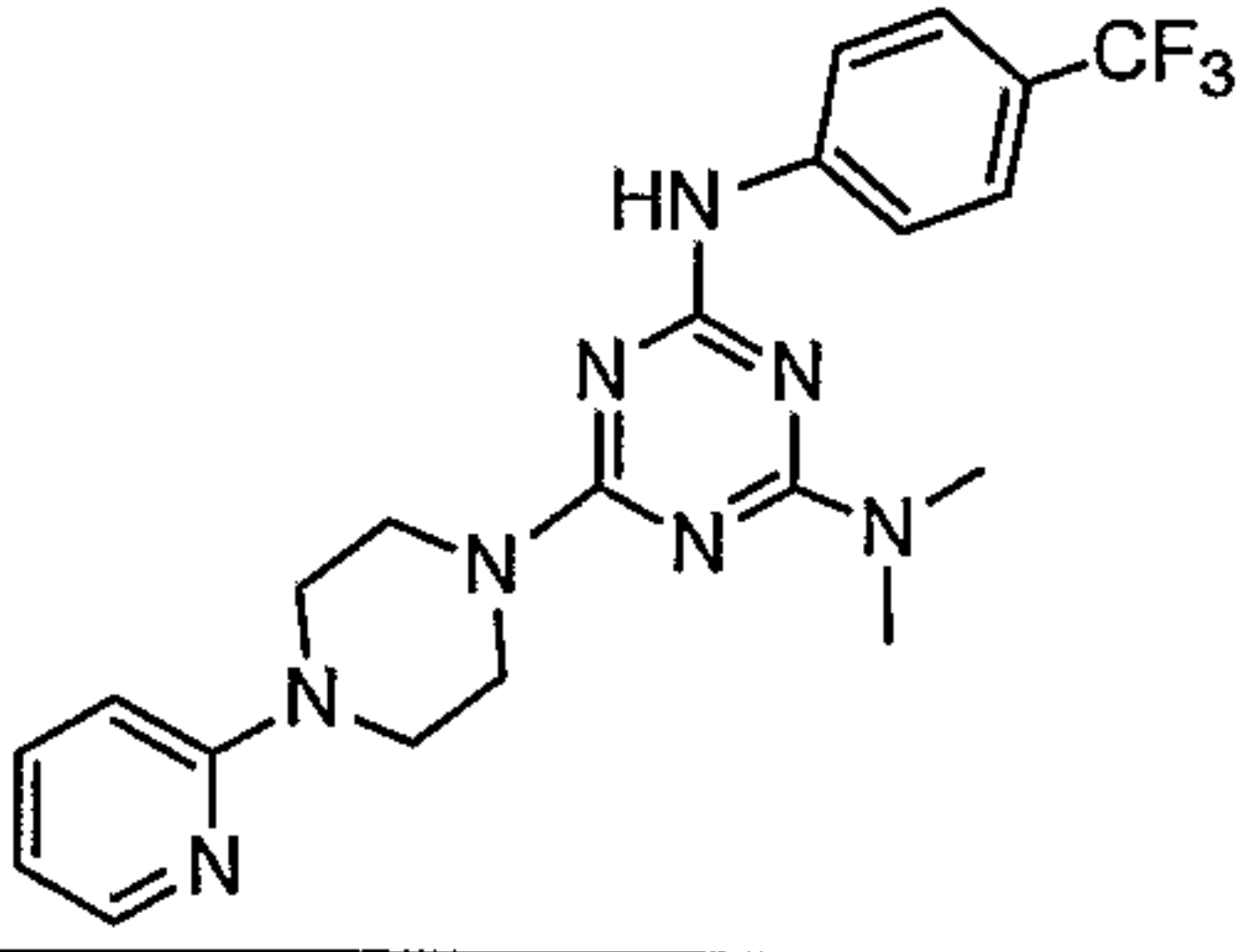
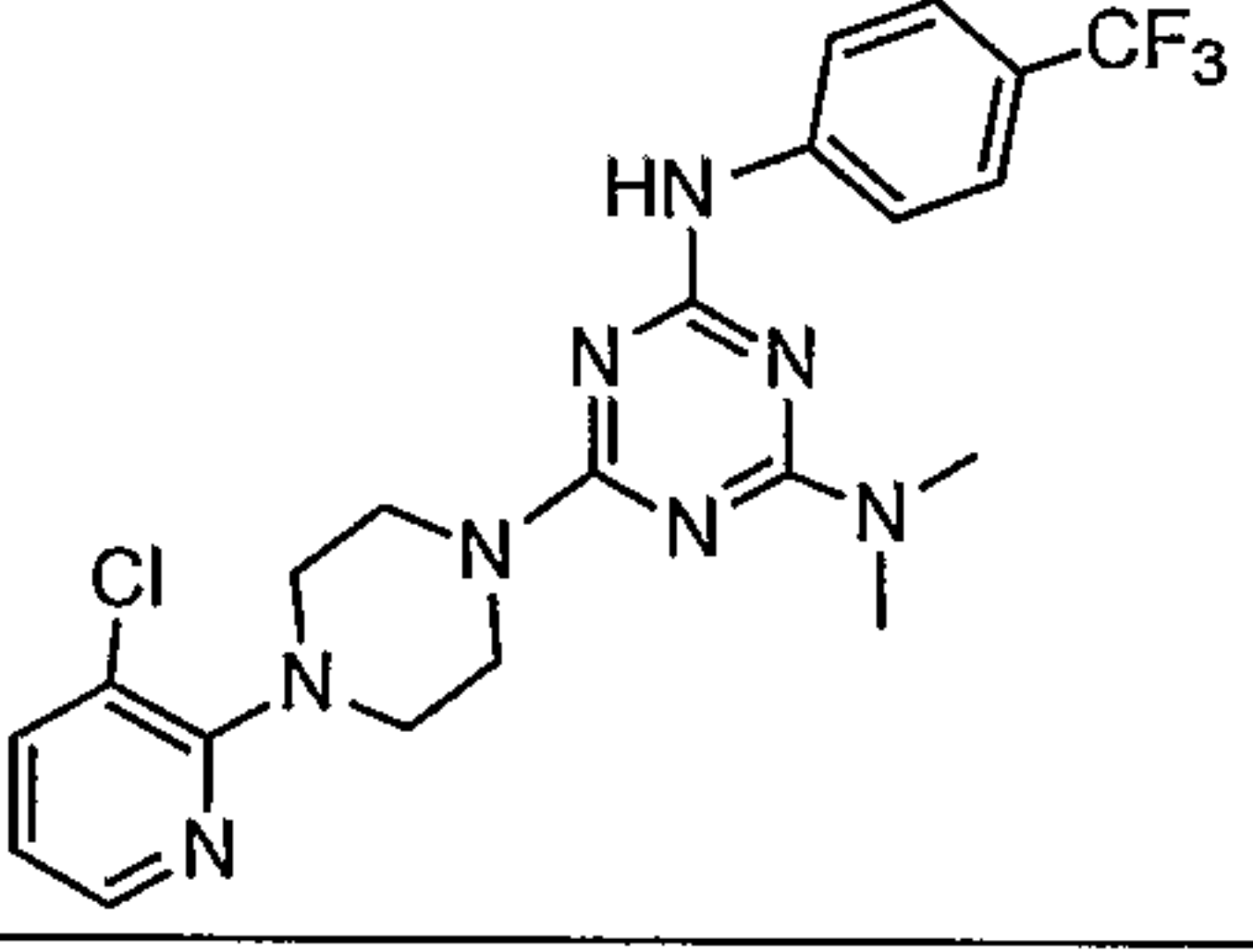
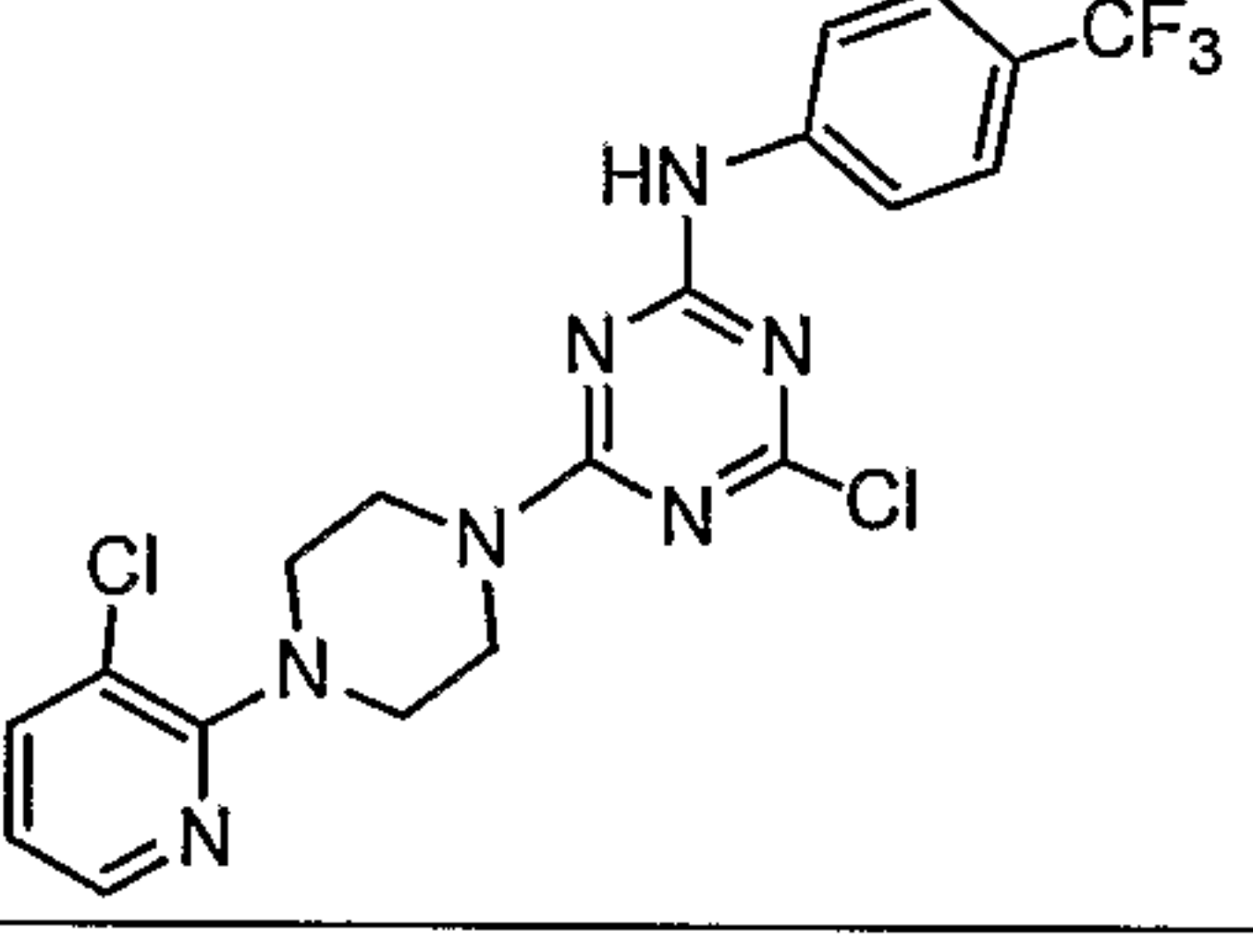
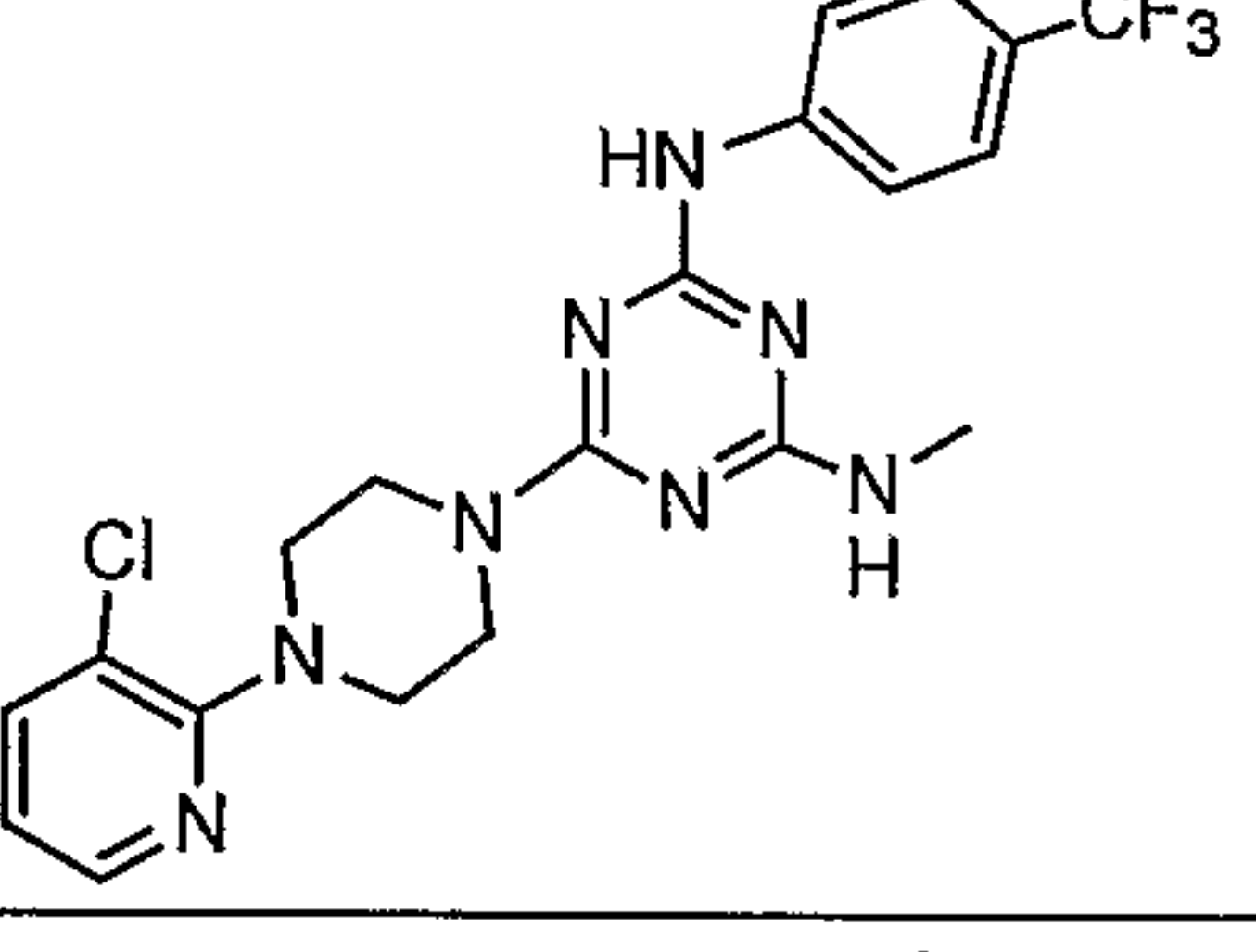
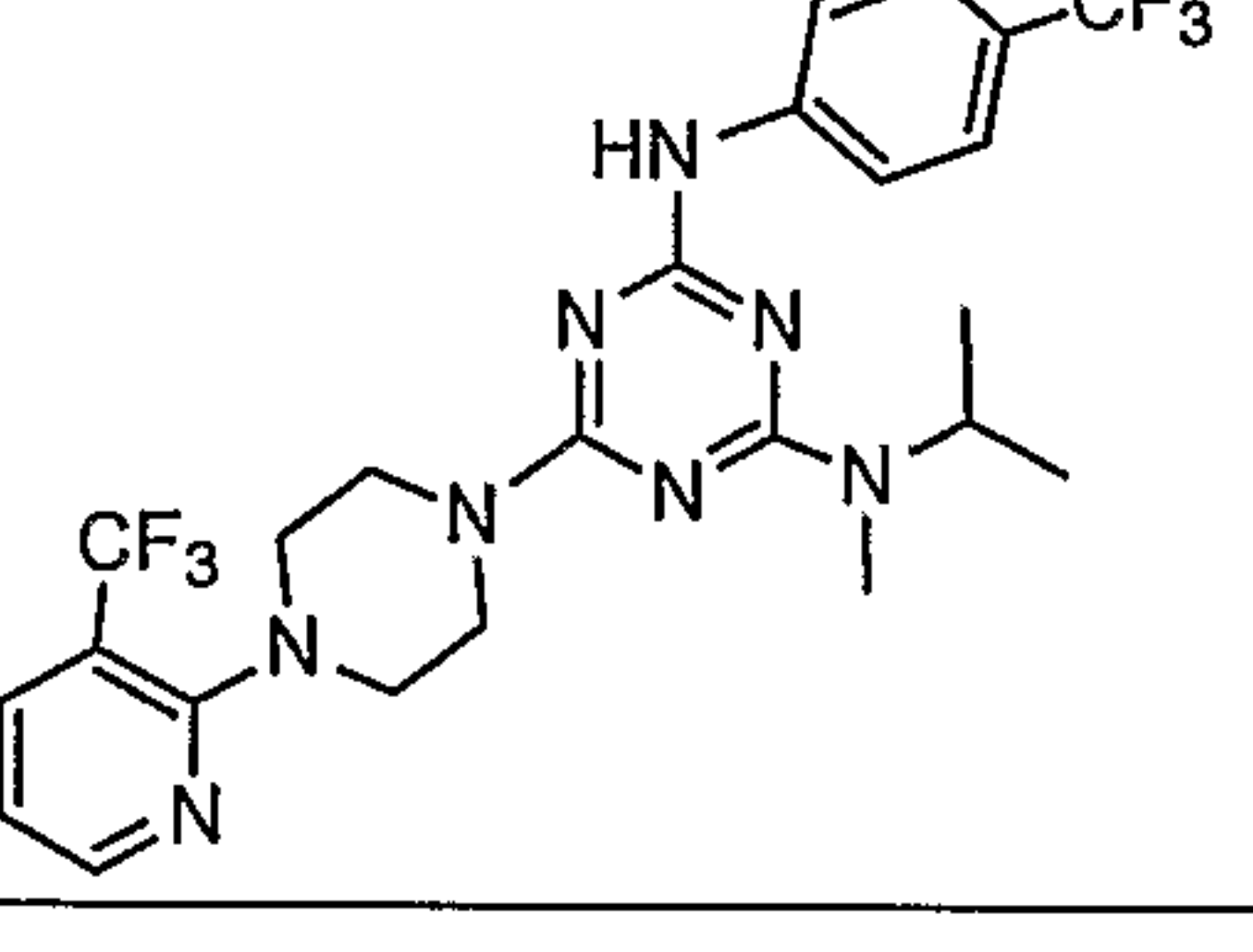
Compound	Name	IC ₅₀	MS
12. 	(4- <i>tert</i> -Butyl-phenyl)-[4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine	*	593.28
13. 	{4-Chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine (S)	*	518.06
14. 	[4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(4-trifluoromethyl-phenyl)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine (S)	*	628.15
15. 	N-(3-Methyl-butyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S)	*	569.26
16. 	{4-(2-Chloro-phenyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine (S)	*	594.21
17. 	{6-Chloro-2-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-(4-trifluoromethyl-phenyl)-amine (R)	*	483.13

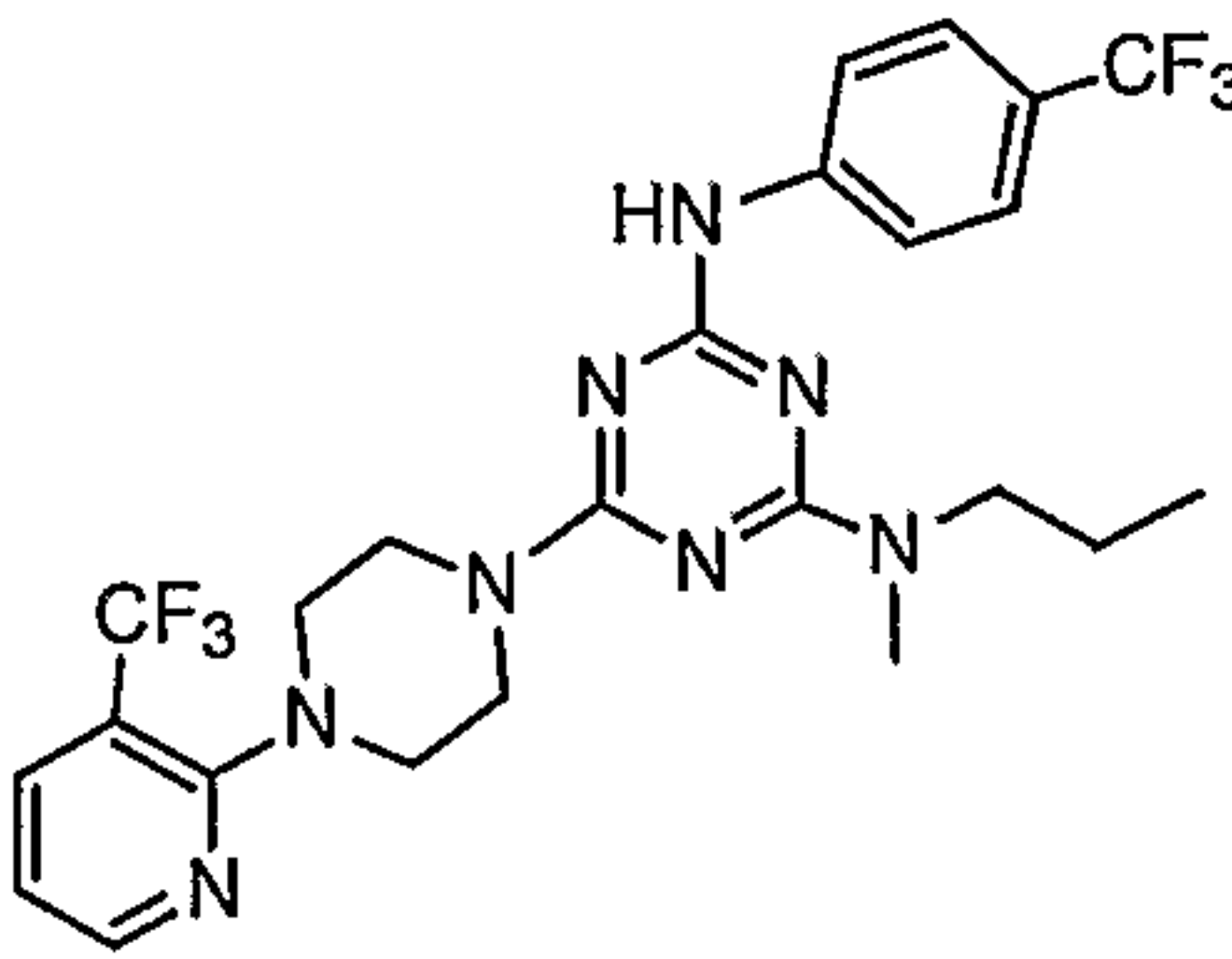
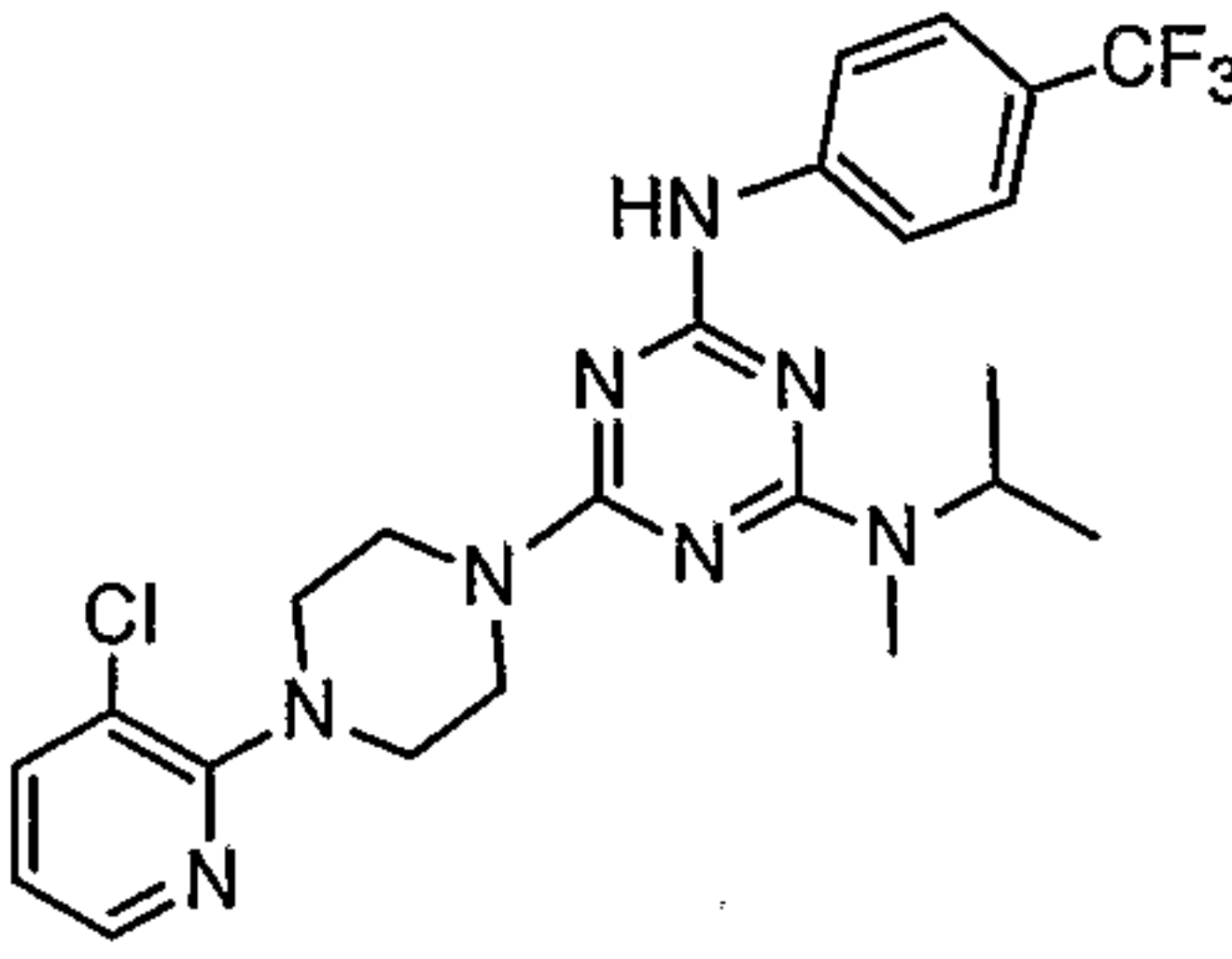
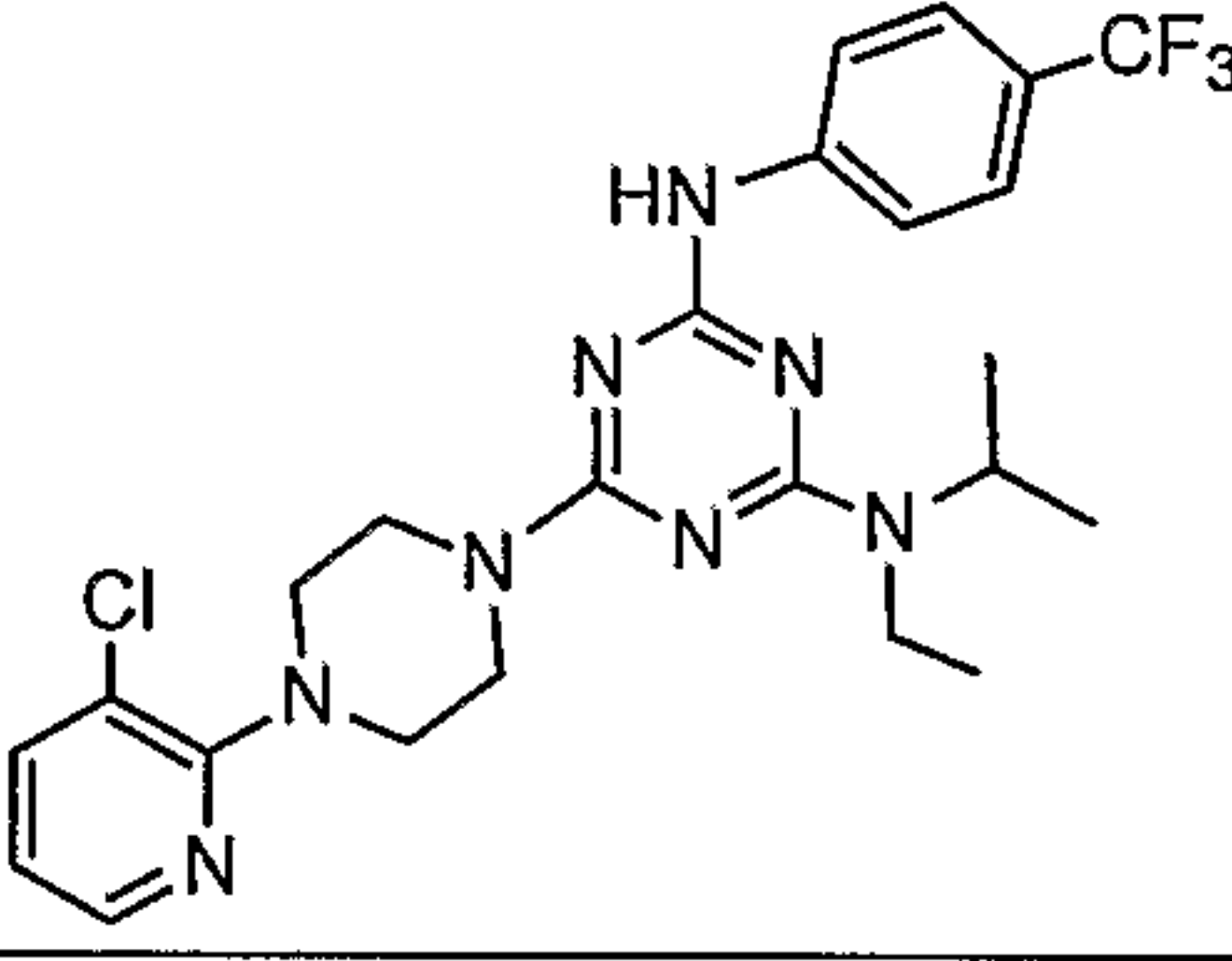
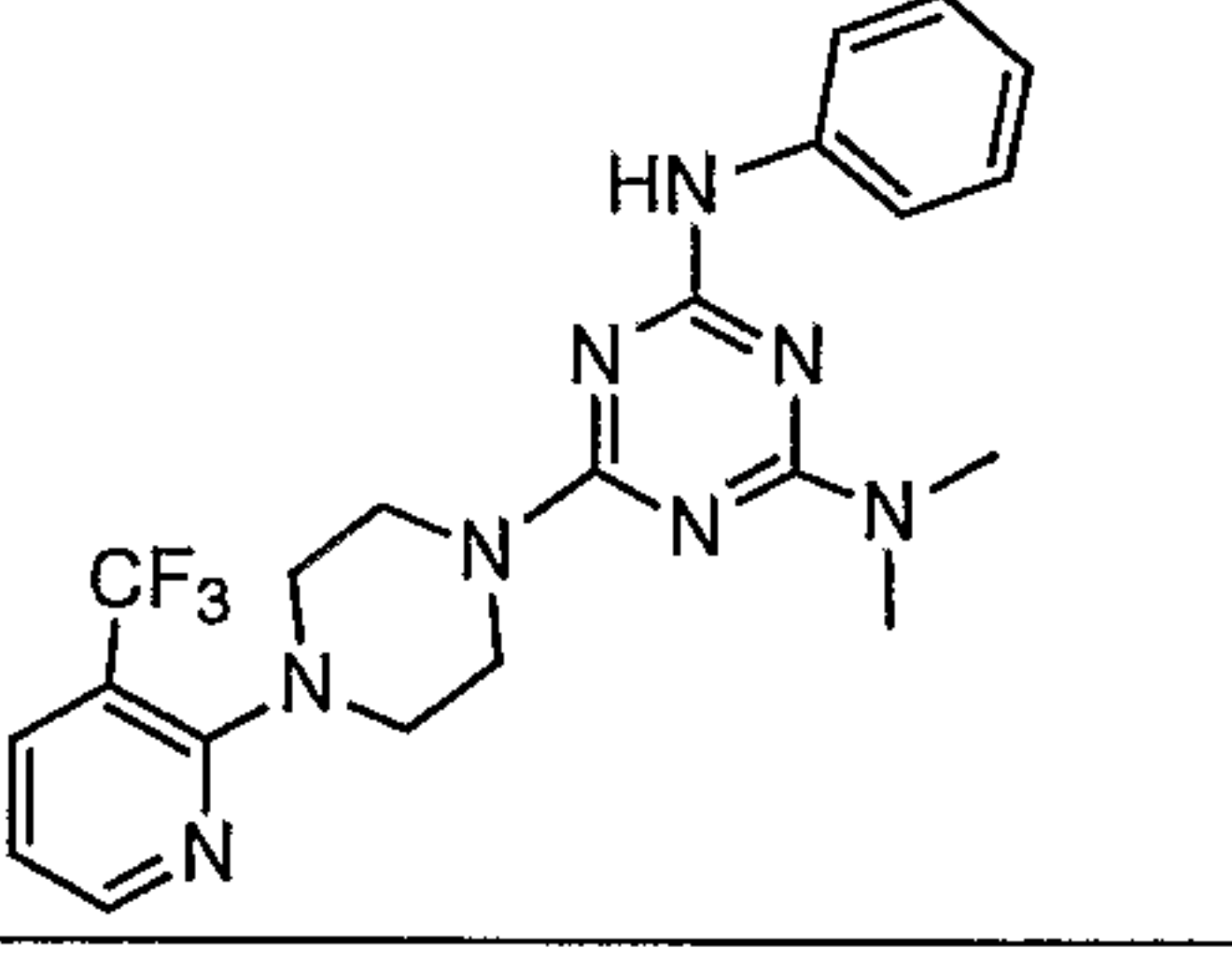
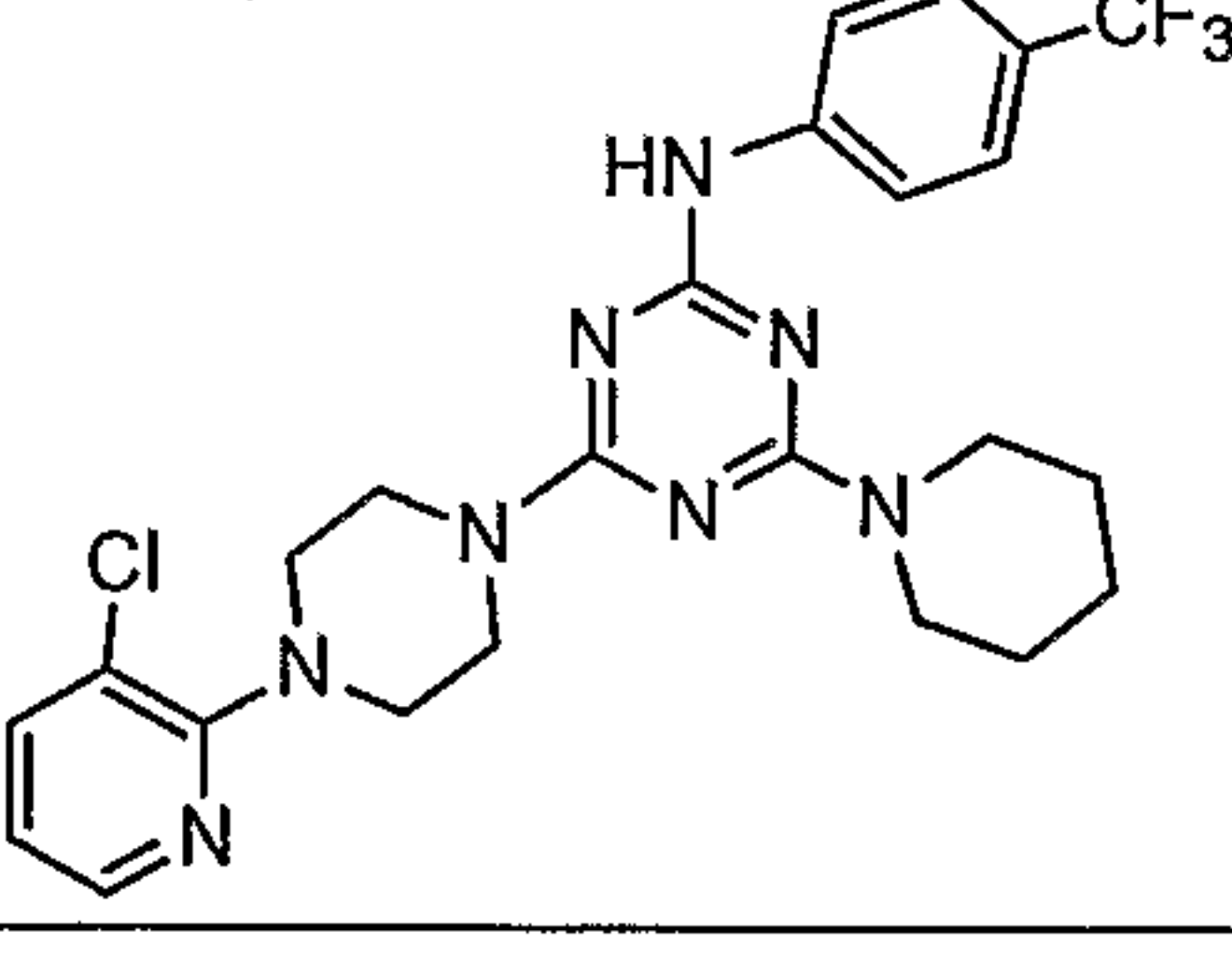
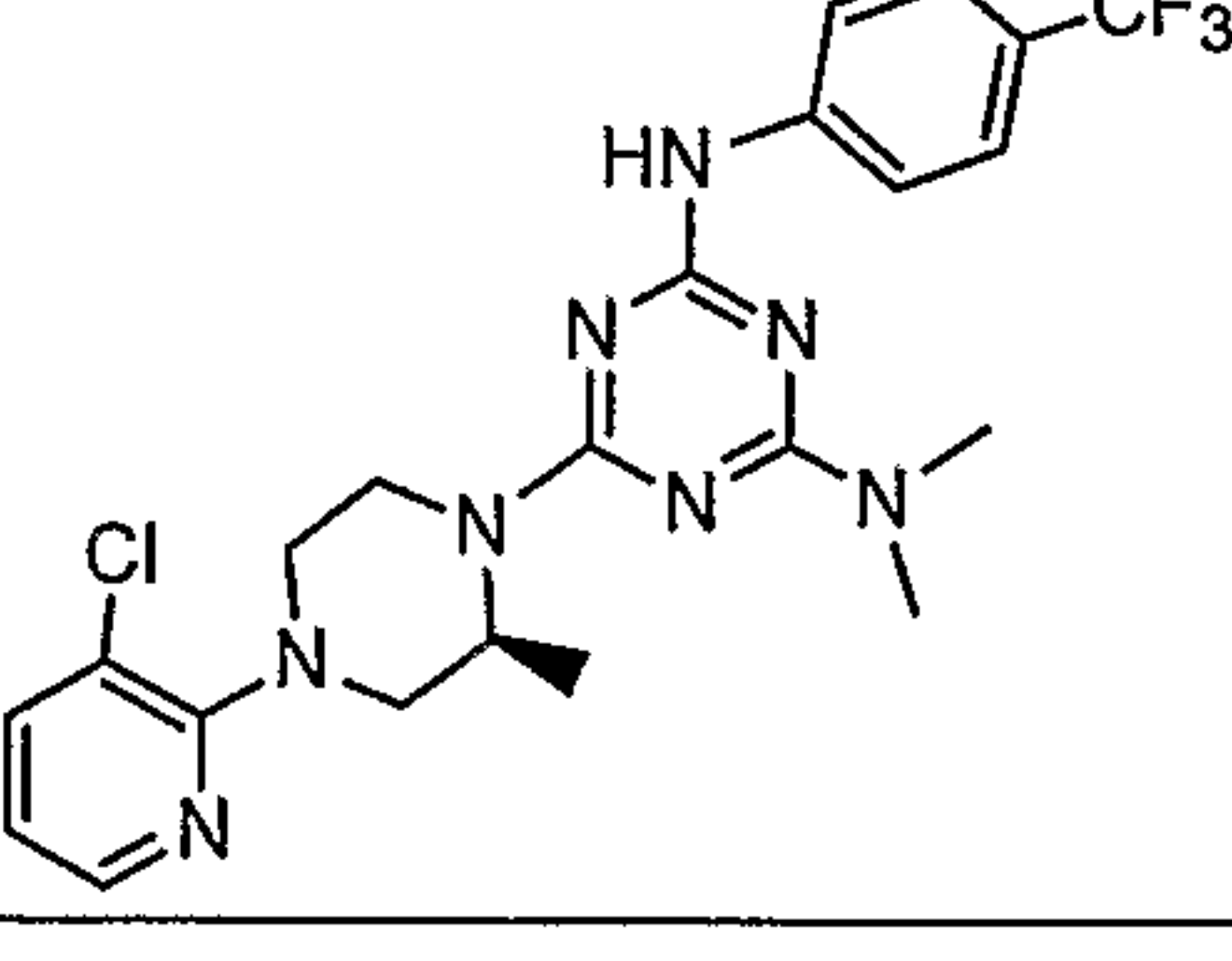
Compound	Name	IC ₅₀	MS
18. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	493.25
19. 	N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	521.29
20. 	N,N-Dimethyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	*	513.25
21. 	N-(3-Methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	*	555.31
22. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	507.27
23. 	{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	555.28

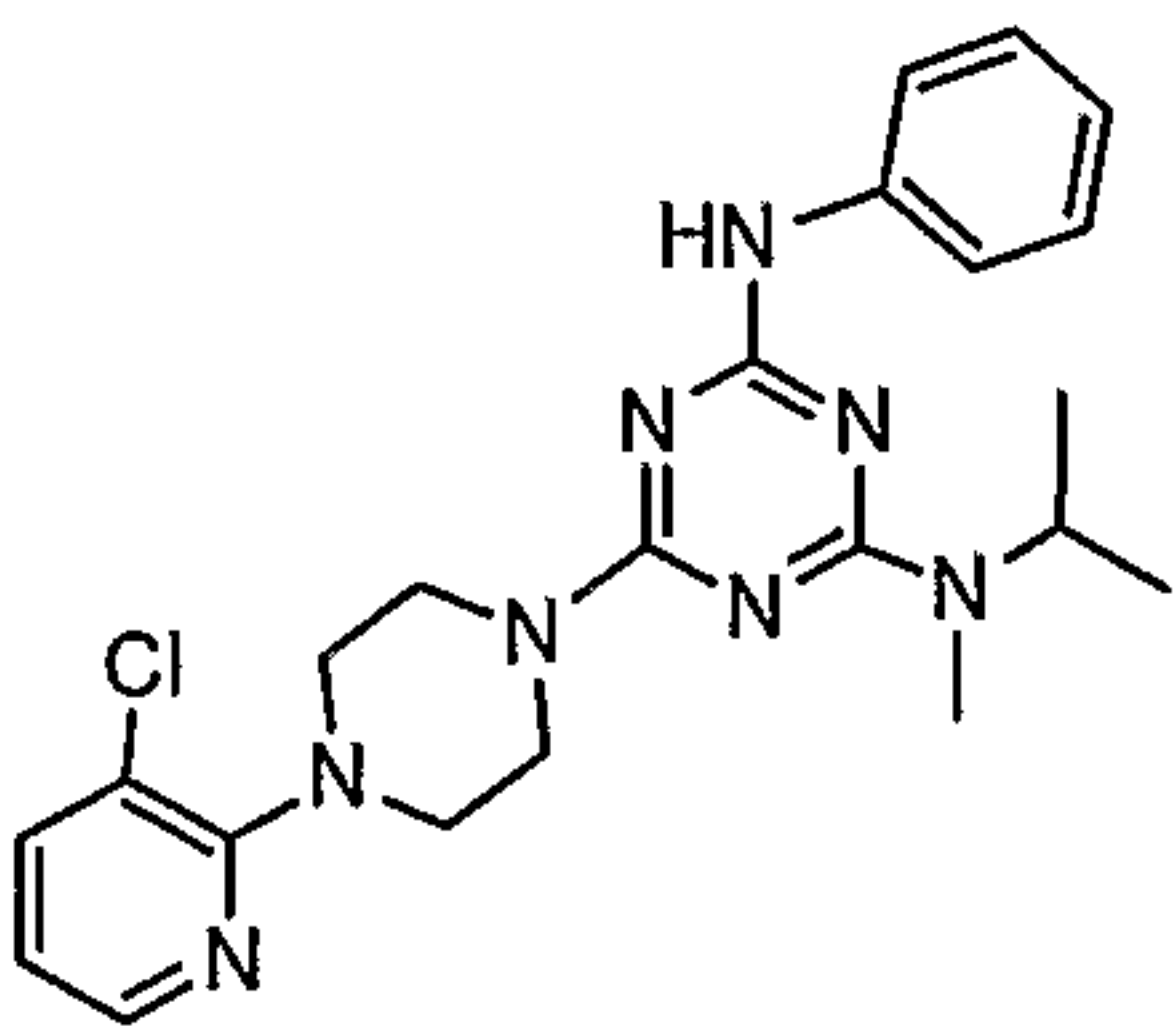
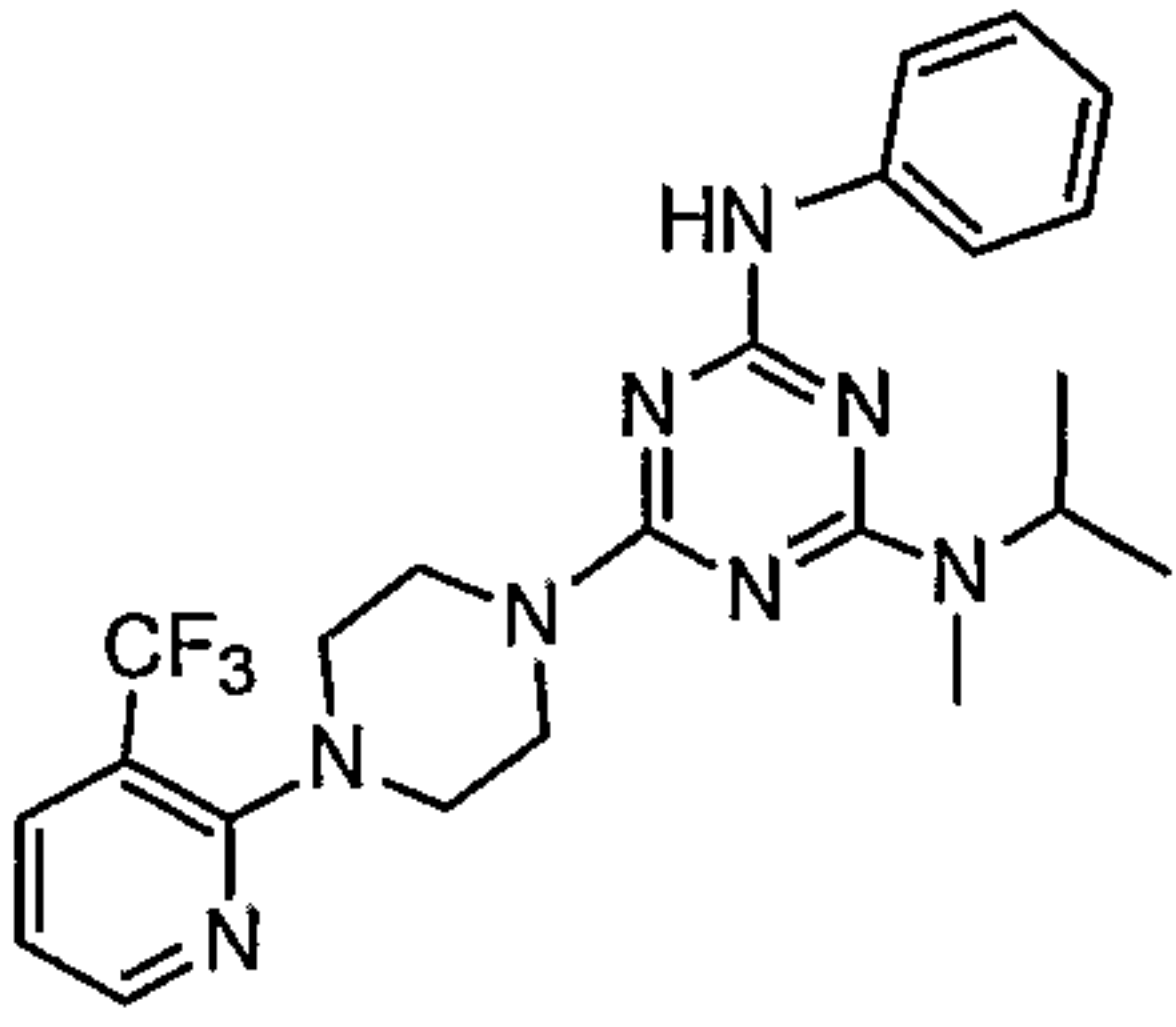
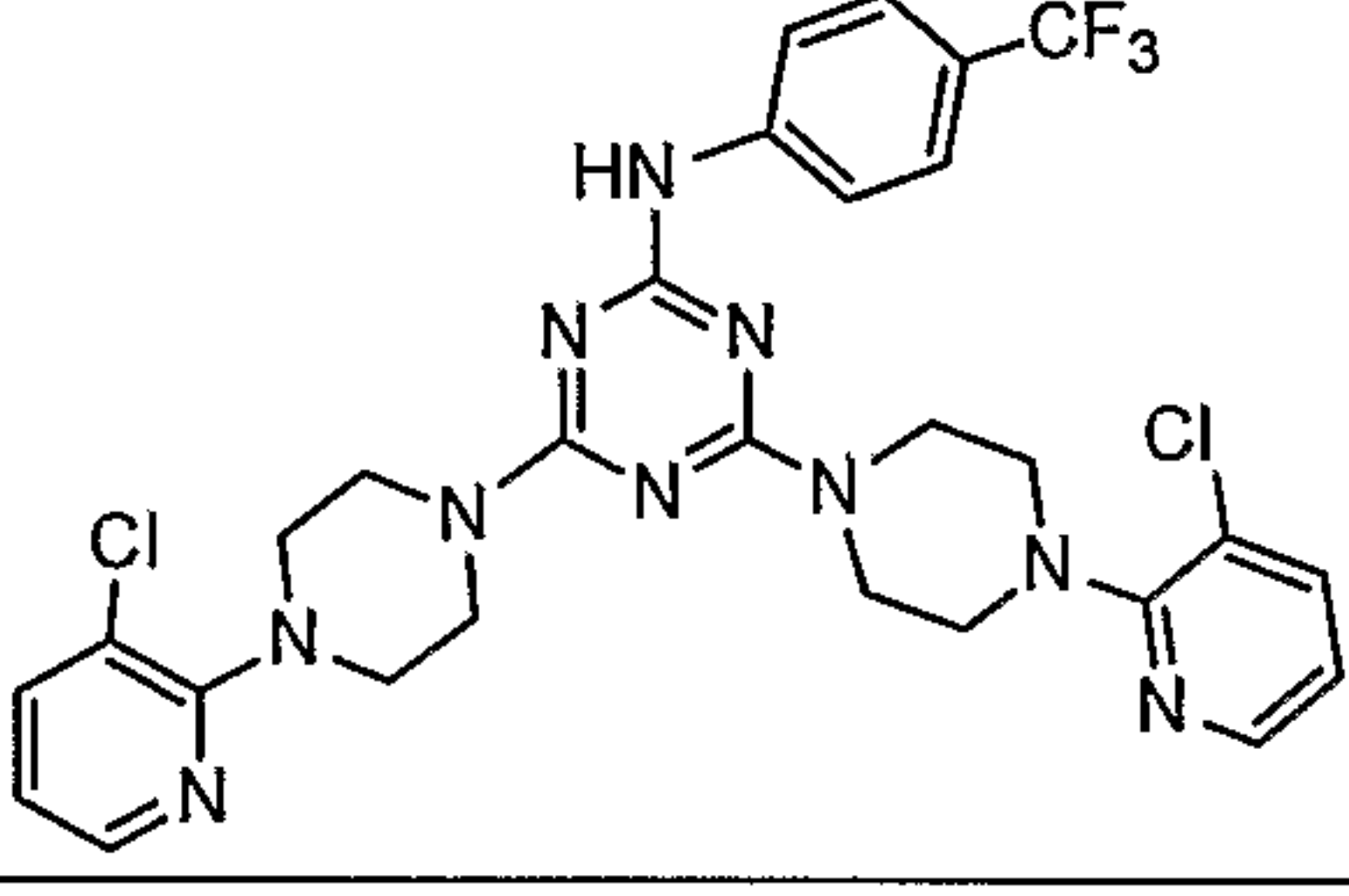
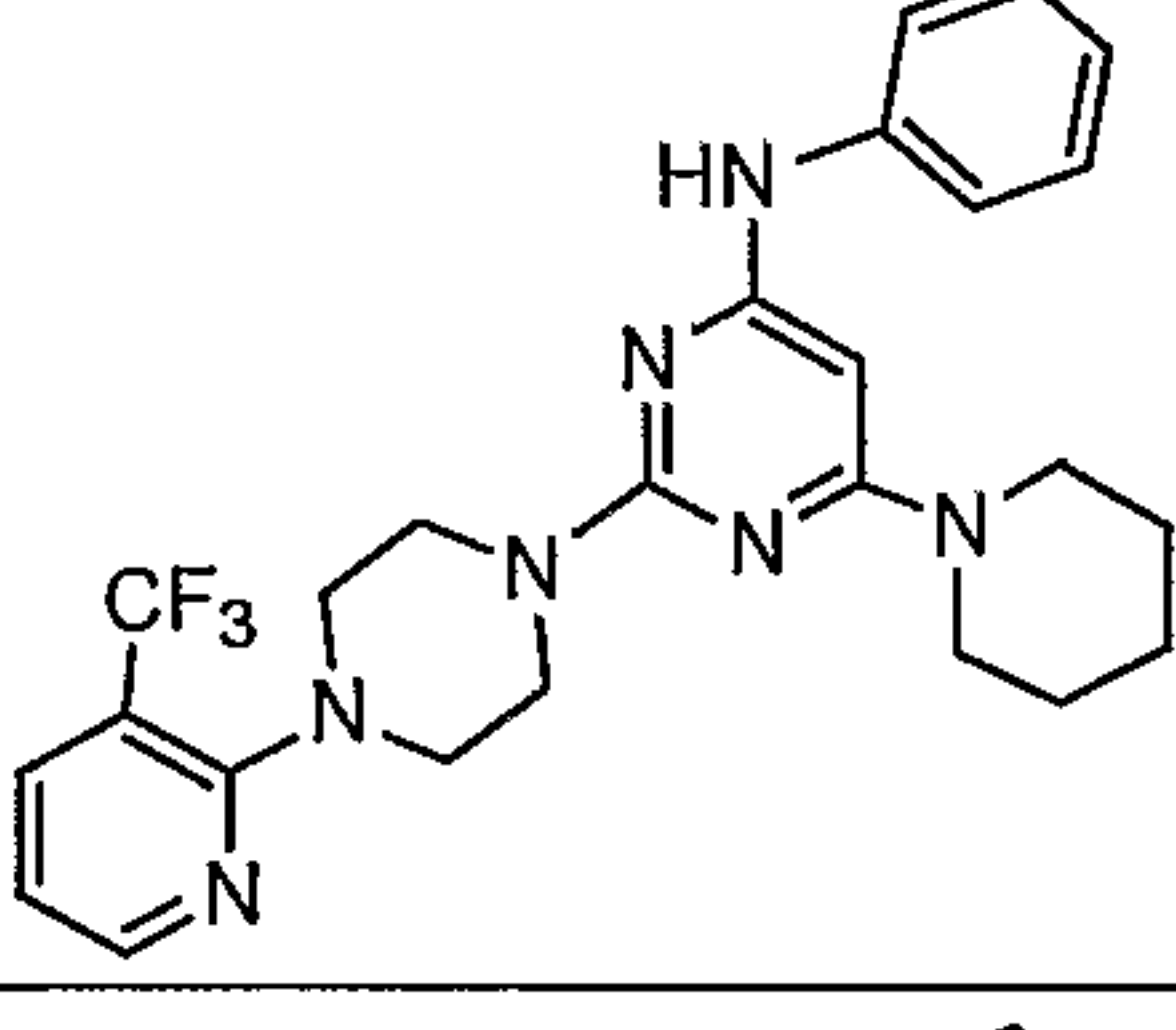
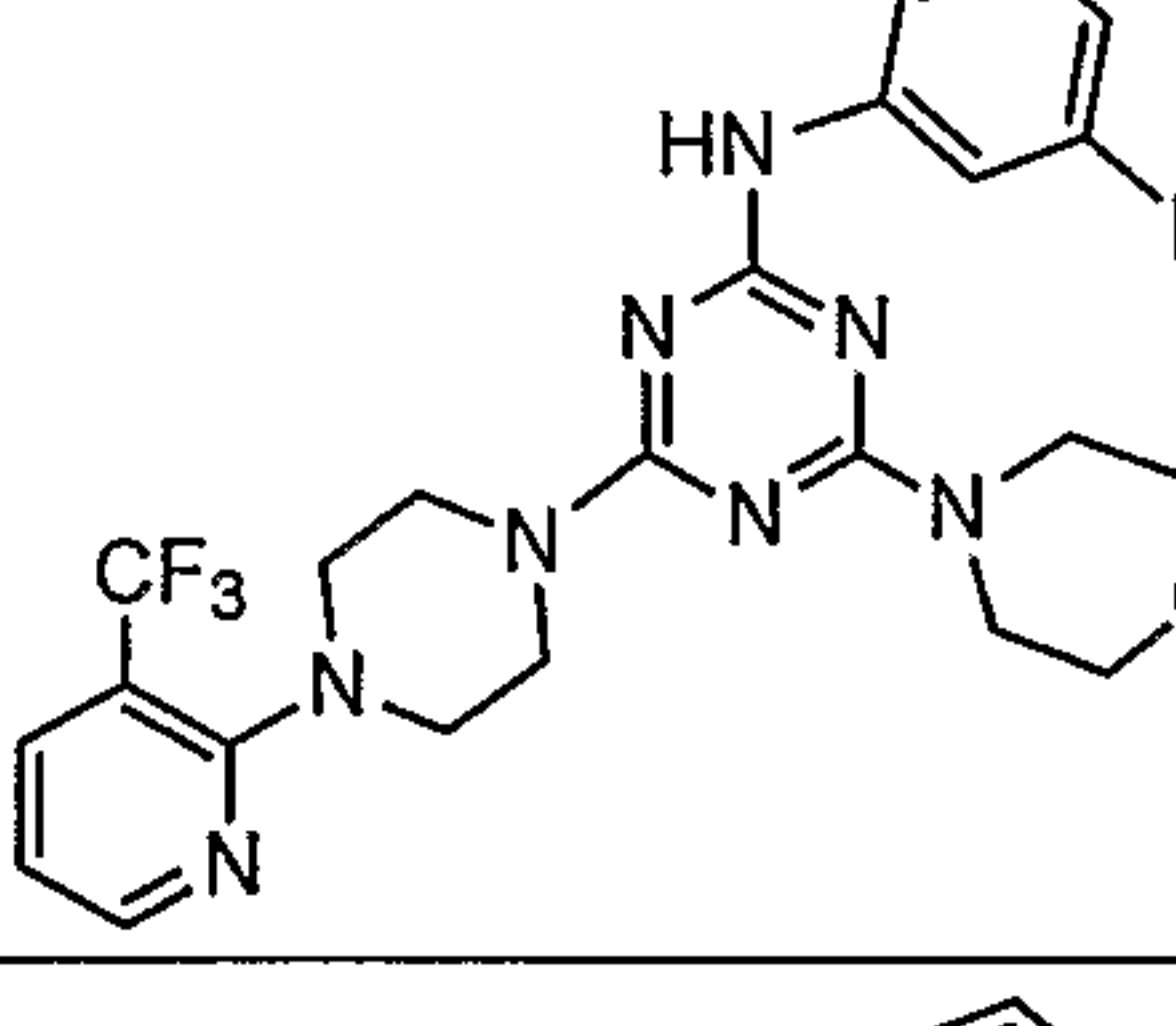
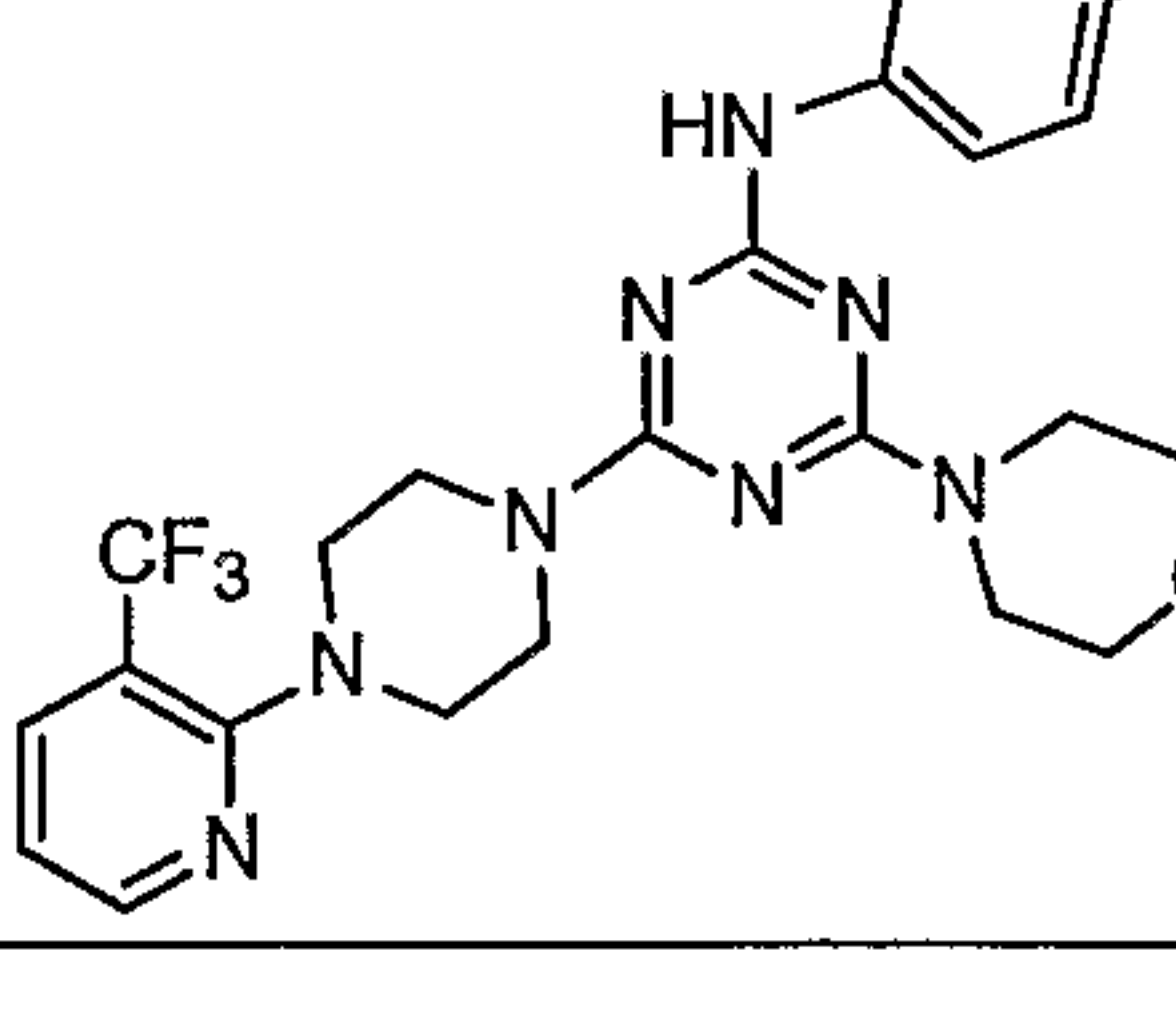
Compound	Name	IC ₅₀	MS
24. 	{4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-amine (R)	*	584.19
25. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R)	*	607.27
26. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R)	*	621.28
27. 	N-sec-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R)	*	621.29
28. 	N-Butyl-6-[4-(2-chloro-phenyl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R)	*	
29. 	N-Butyl-6-[4-(2-chloro-phenyl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R)	*	

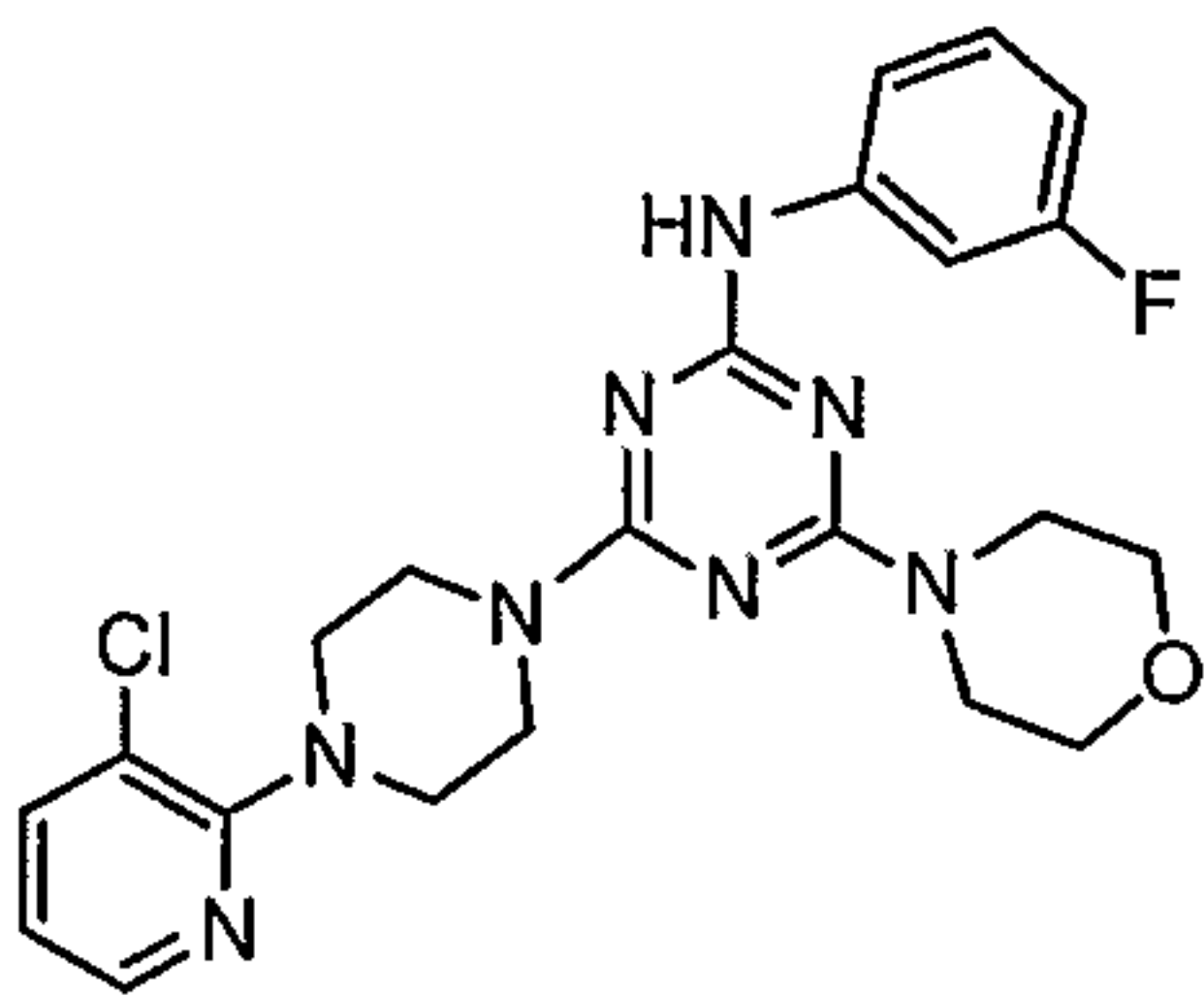
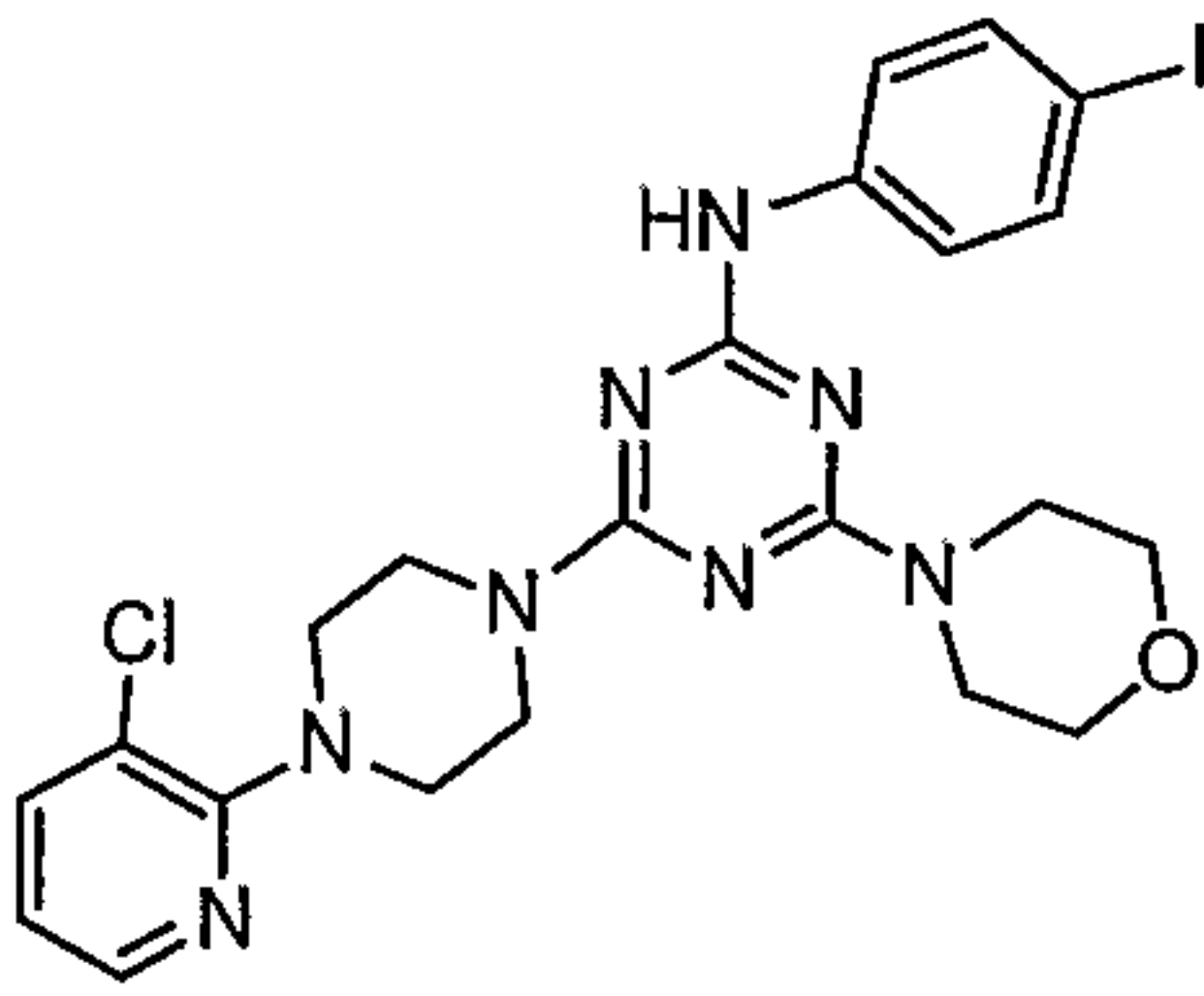
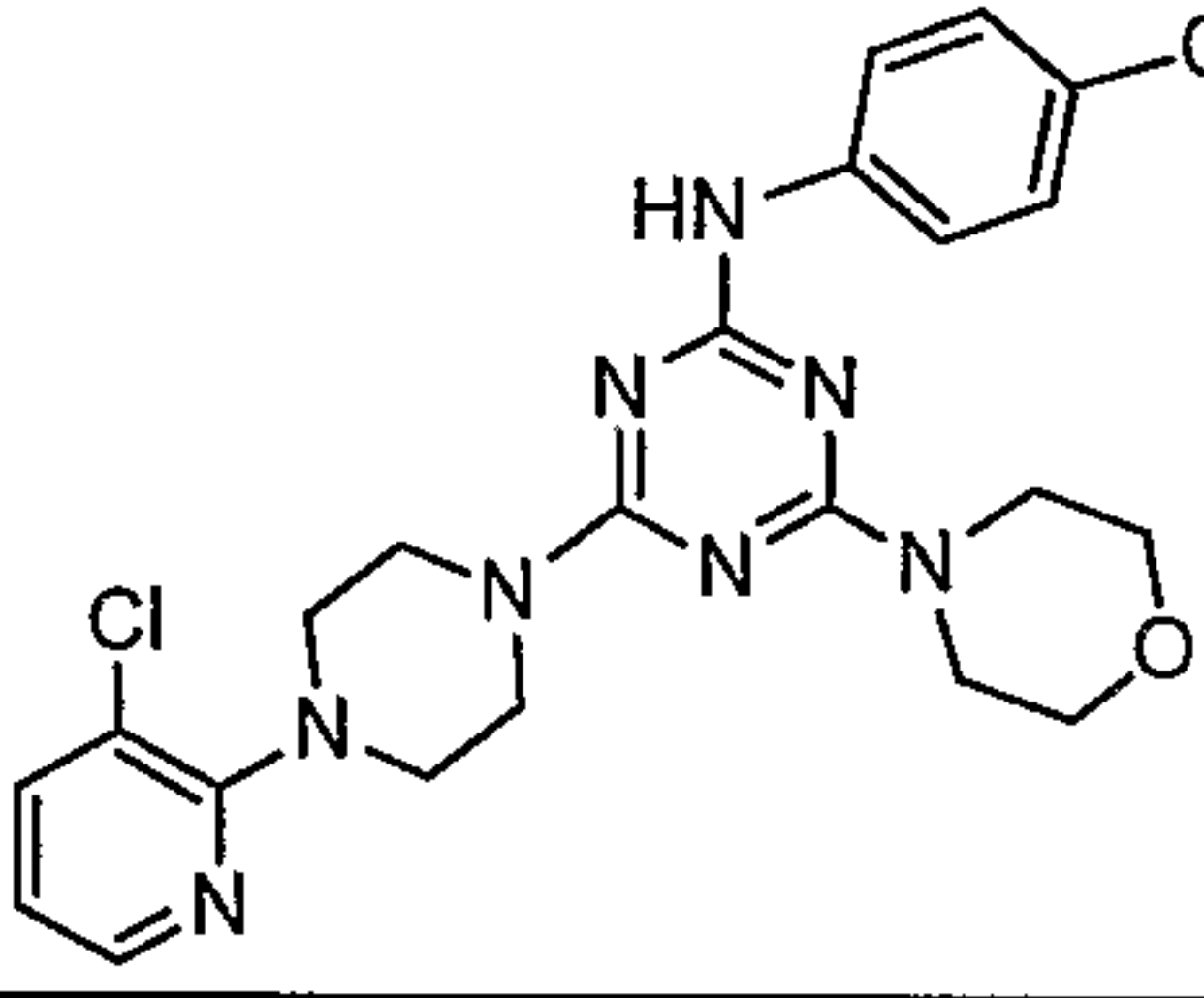
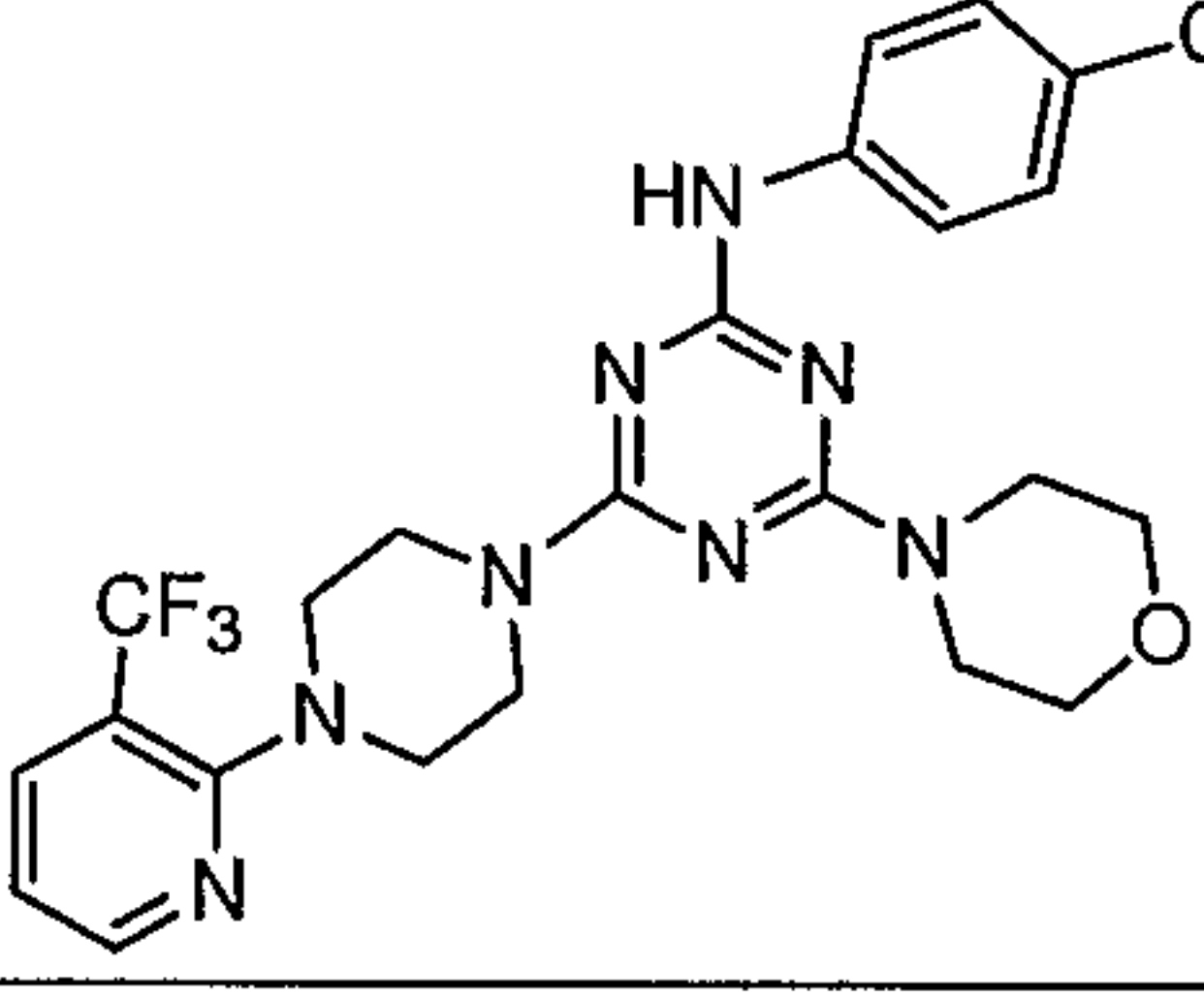
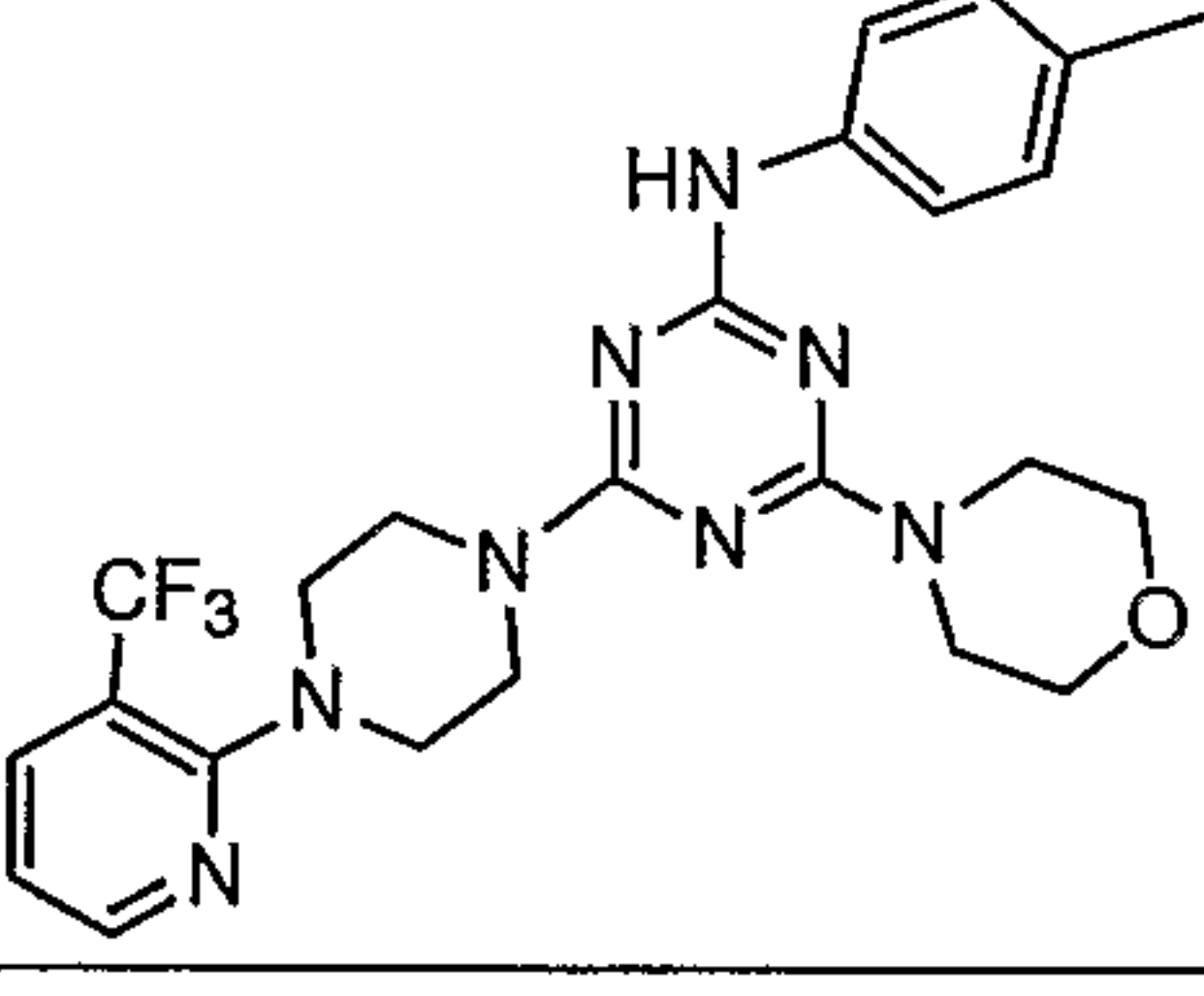
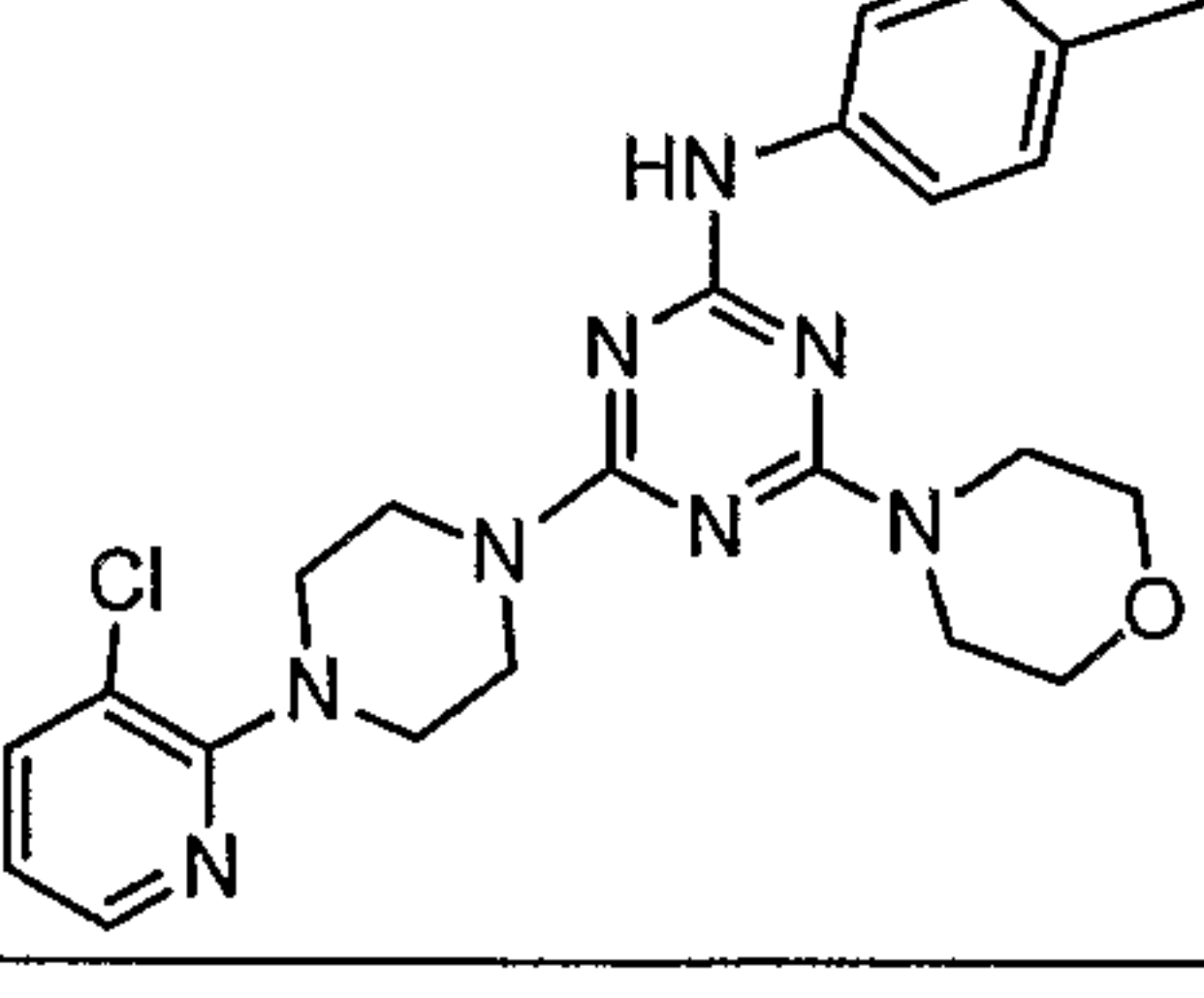
Compound	Name	IC ₅₀	MS
30. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	521.14
31. 	N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	535.16
32. 	N,N-Diallyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	545.15
33. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dipropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	549.18
34. 	N,N-Dibutyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	577.22
35. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	521.14

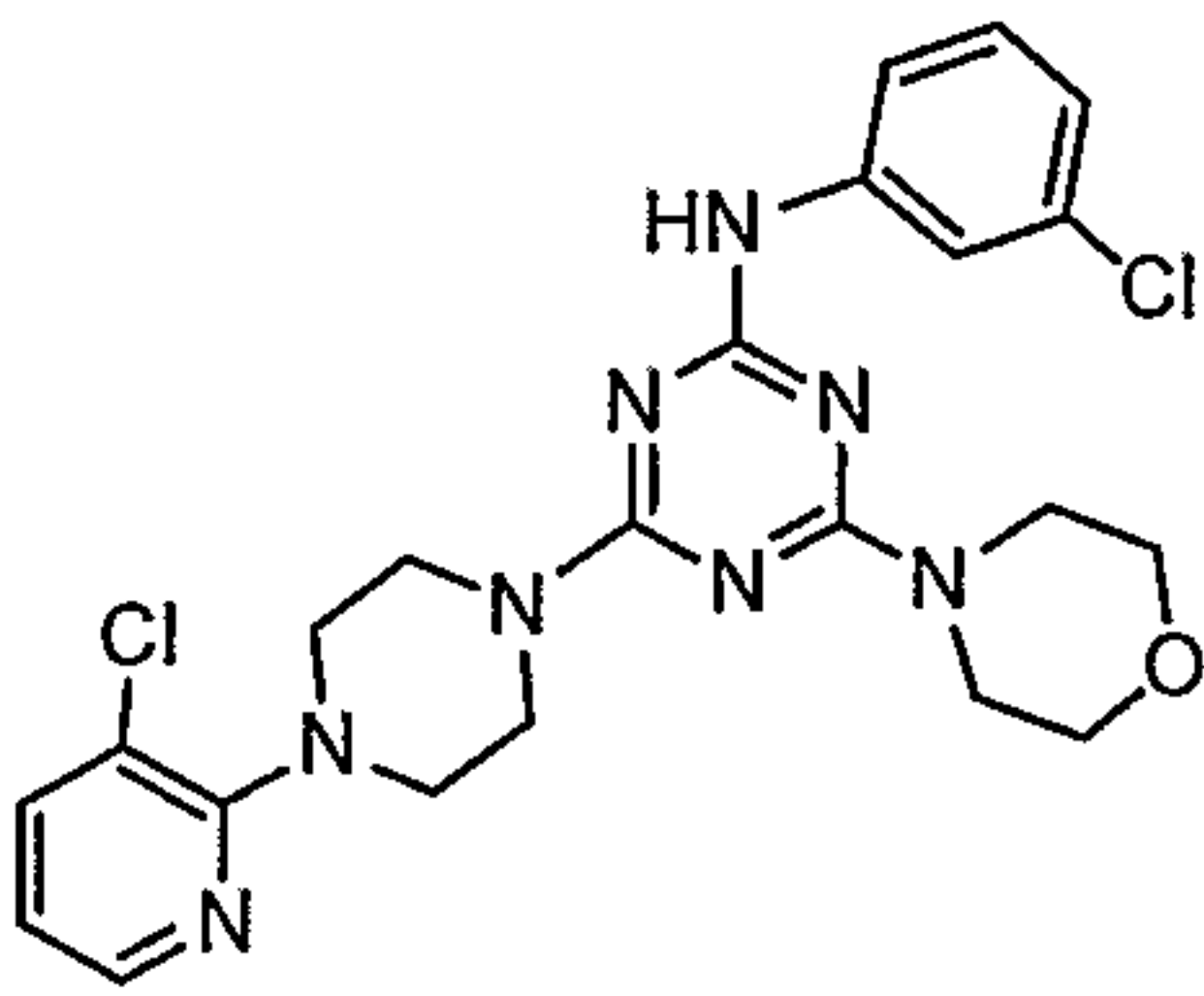
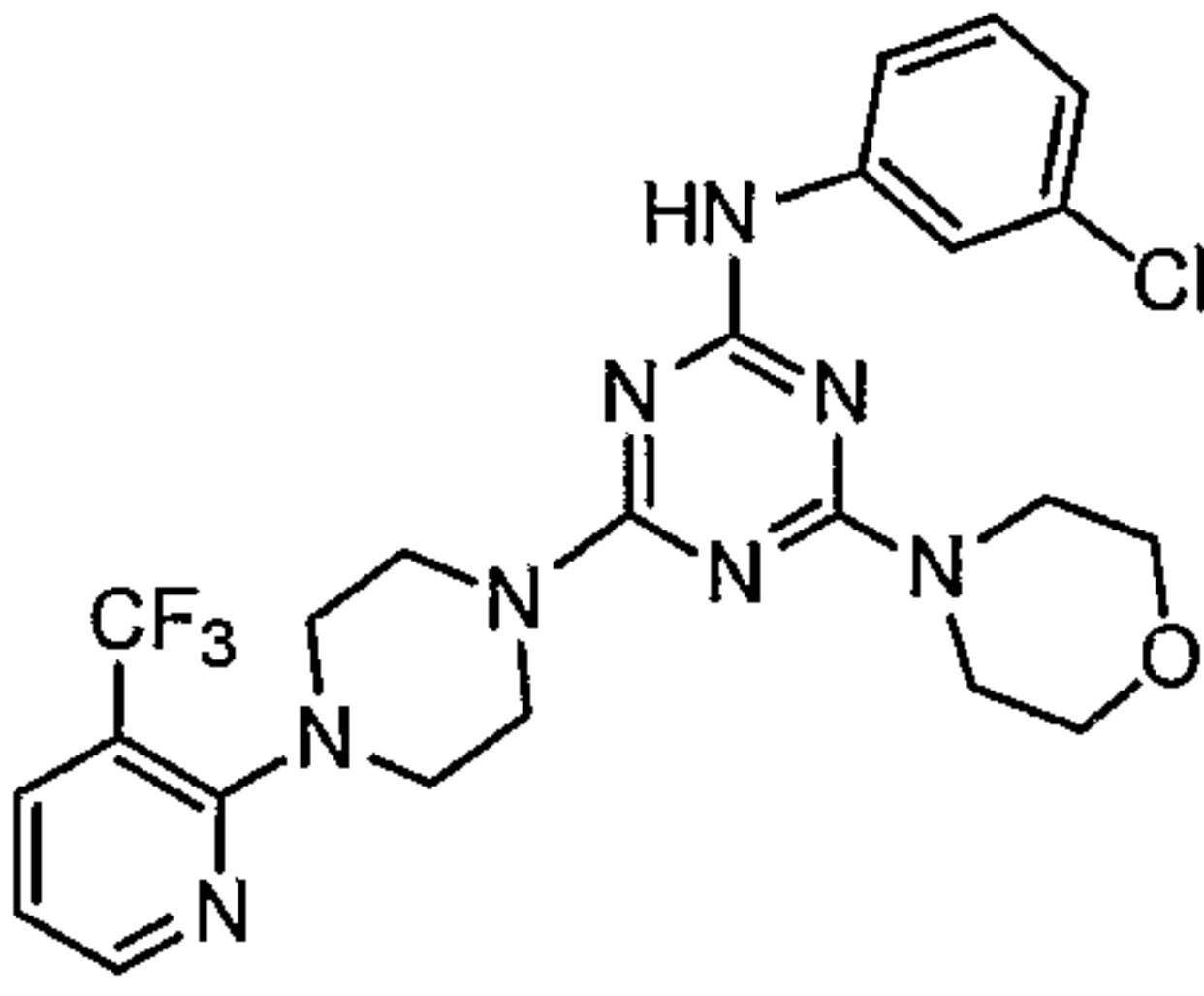
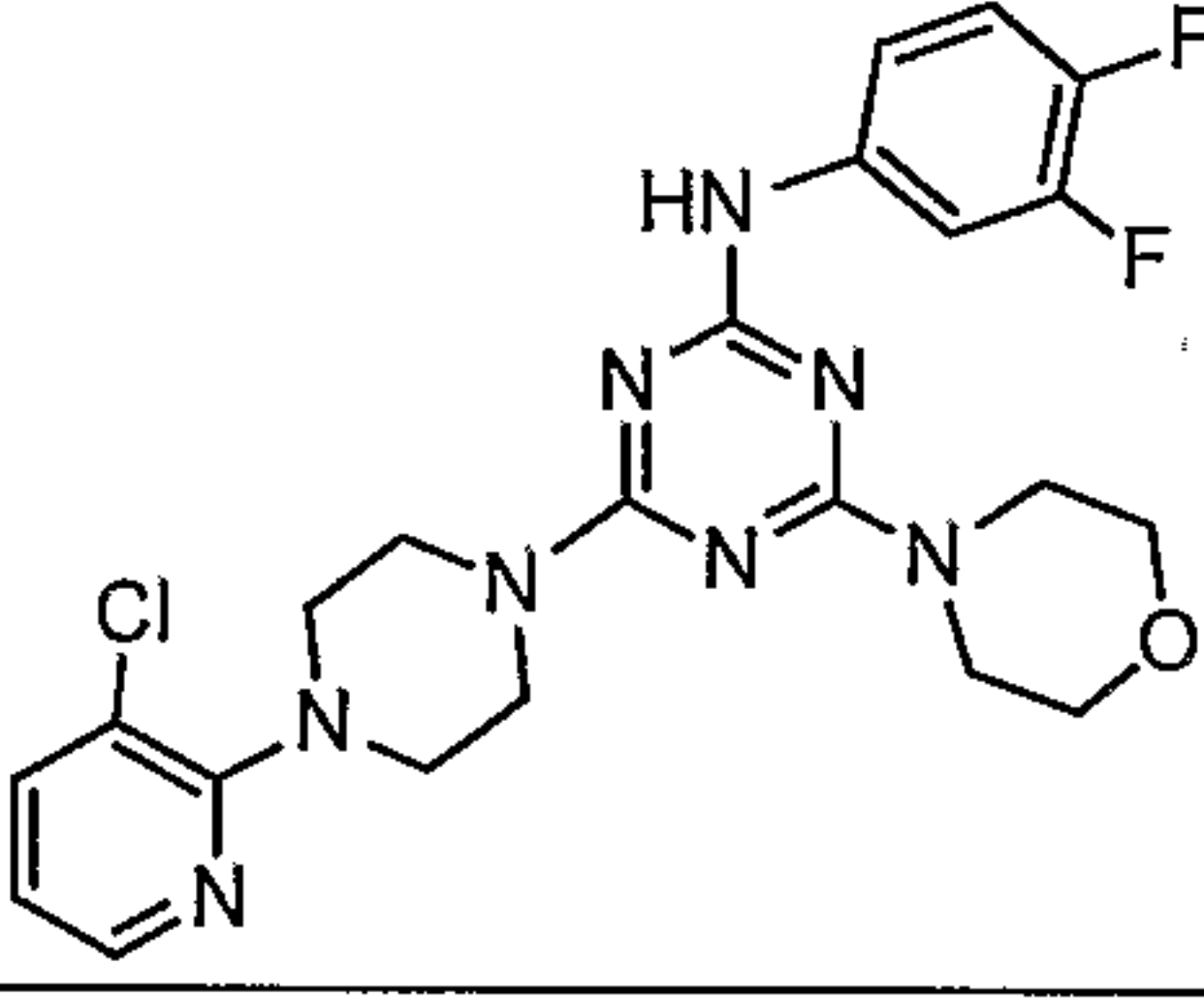
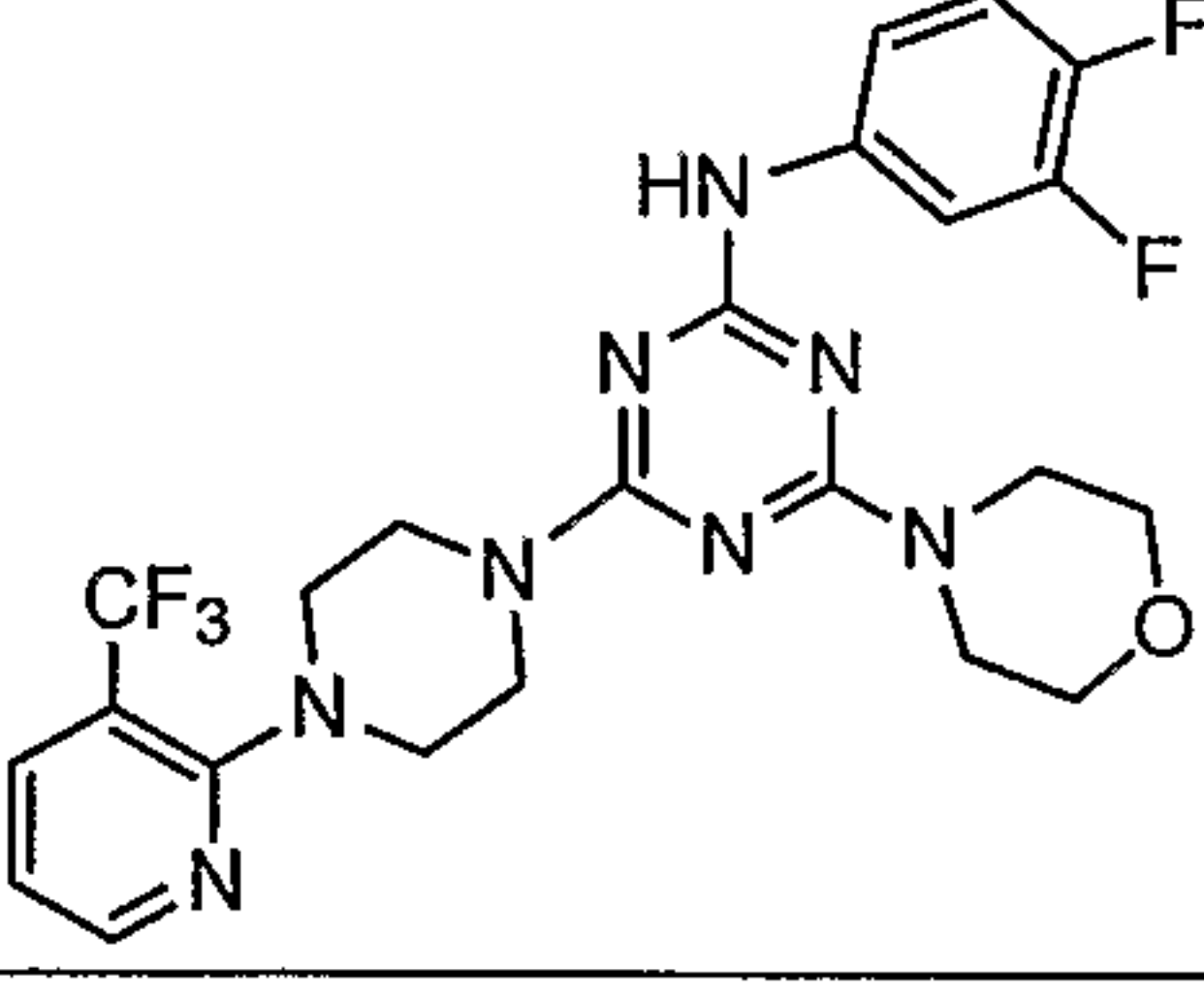
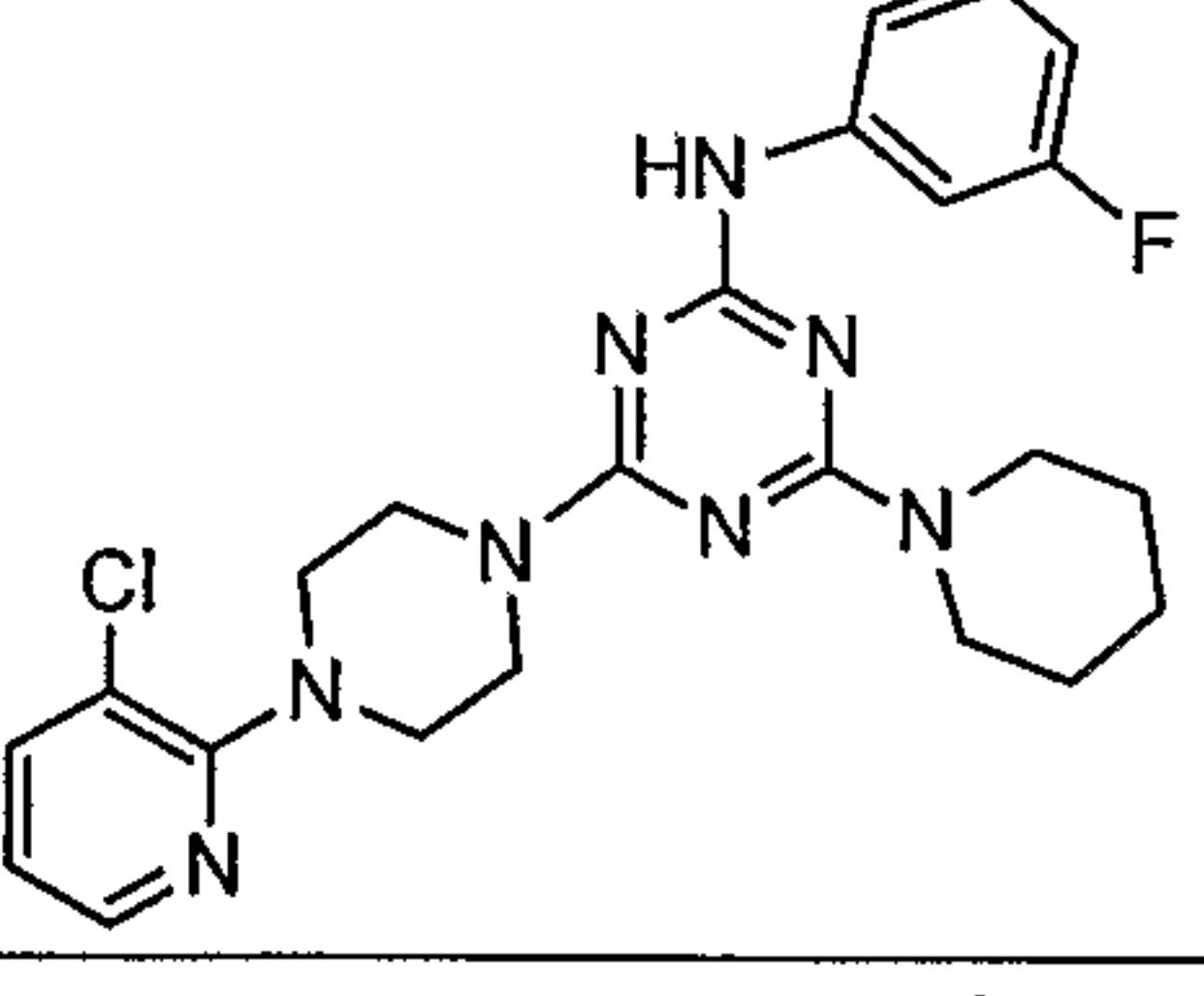
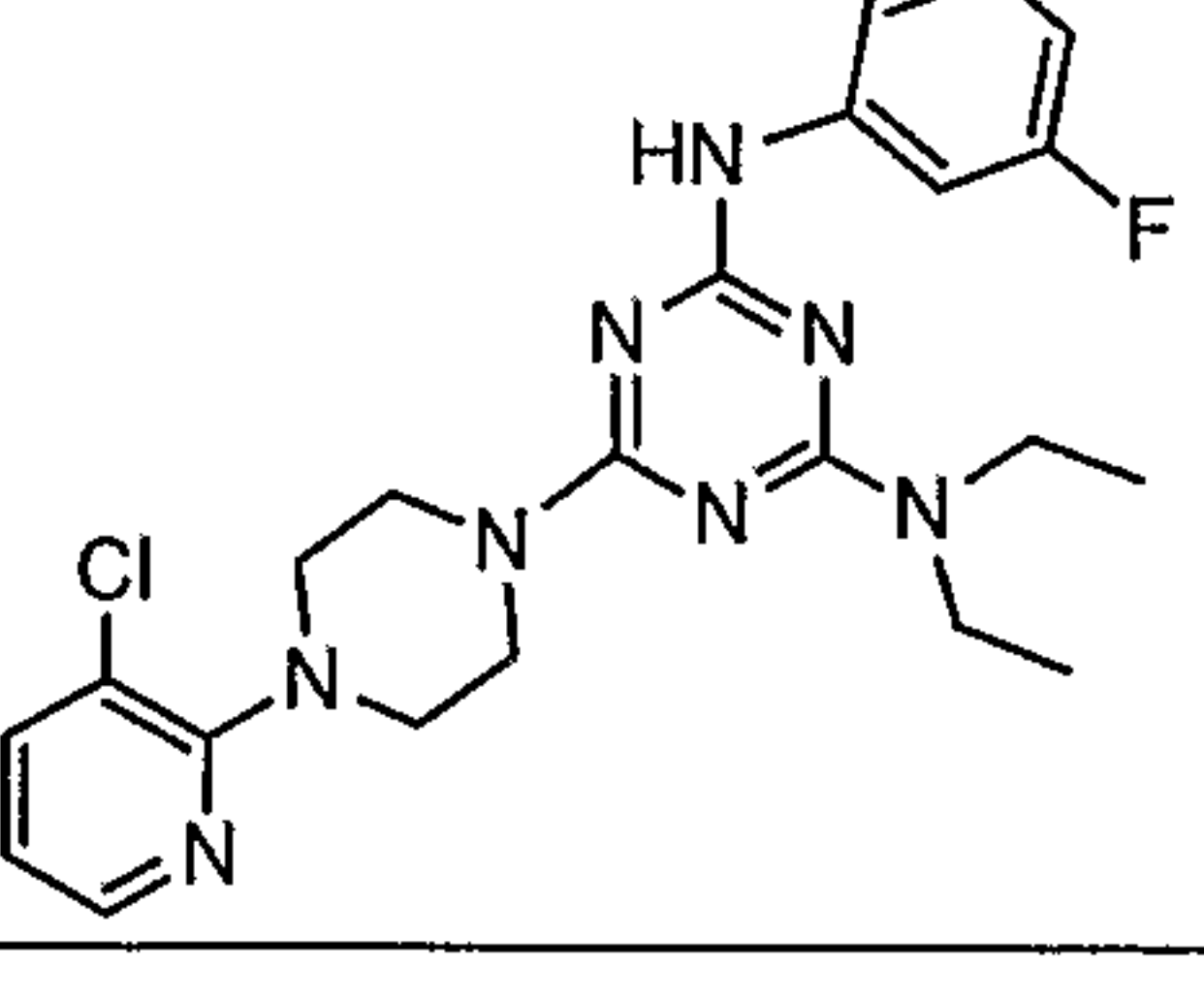
Compound	Name	IC ₅₀	MS	
36.		N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	535.17
37.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-trifluoromethyl-benzyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	623.17
38.		N-Benzyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	
39.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	
40.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	
41.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-phenyl-propyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R)	*	583.19

Compound	Name	IC ₅₀	MS
42. 	N,N-Dimethyl-6-(4-phenyl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	*	444.35
43. 	N,N-Dimethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	*	445.35
44. 	6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	*	479.35
45. 	{4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	470.28
46. 	6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	*	465.33
47. 	N-Isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	*	541.45

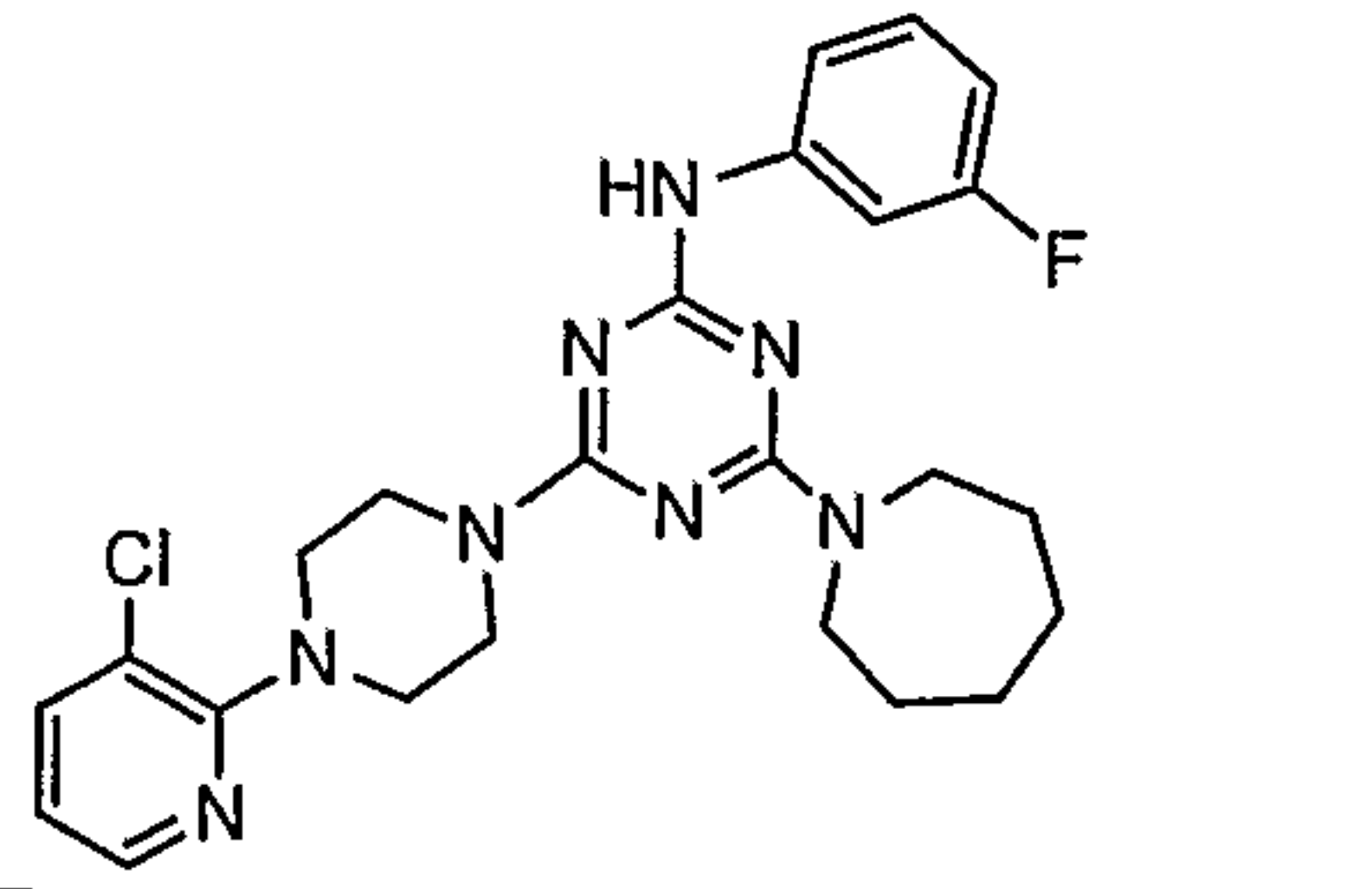
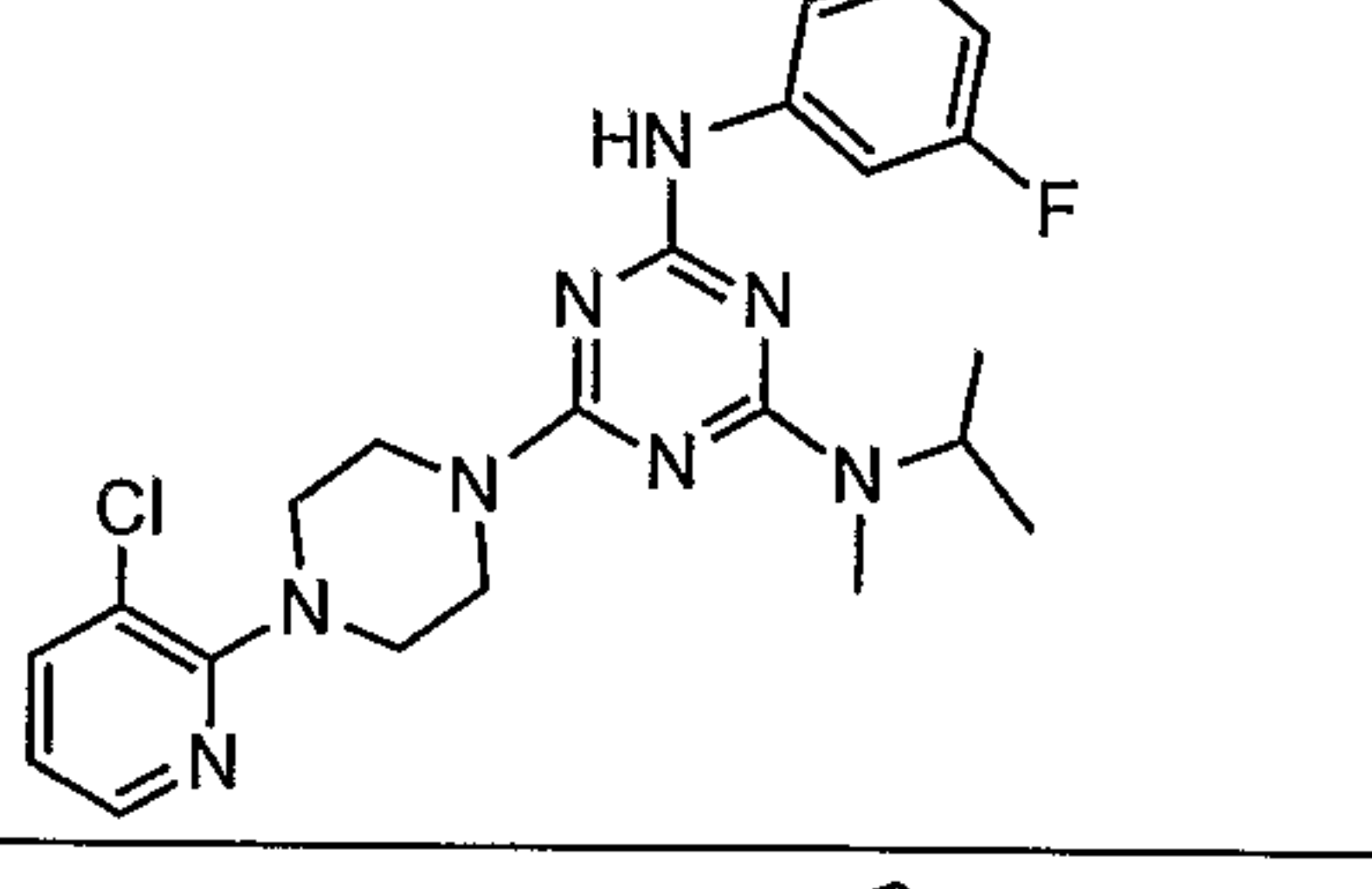
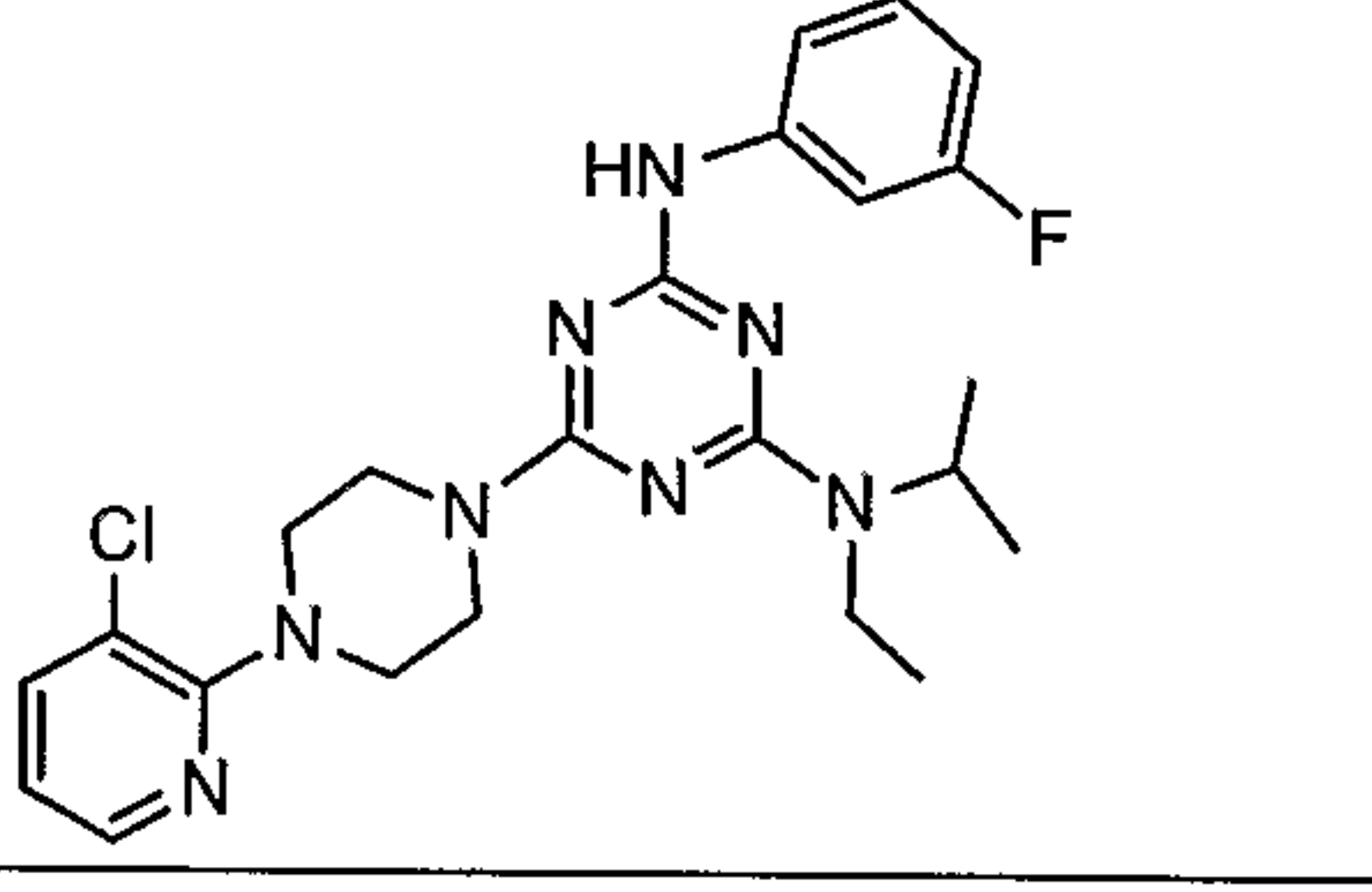
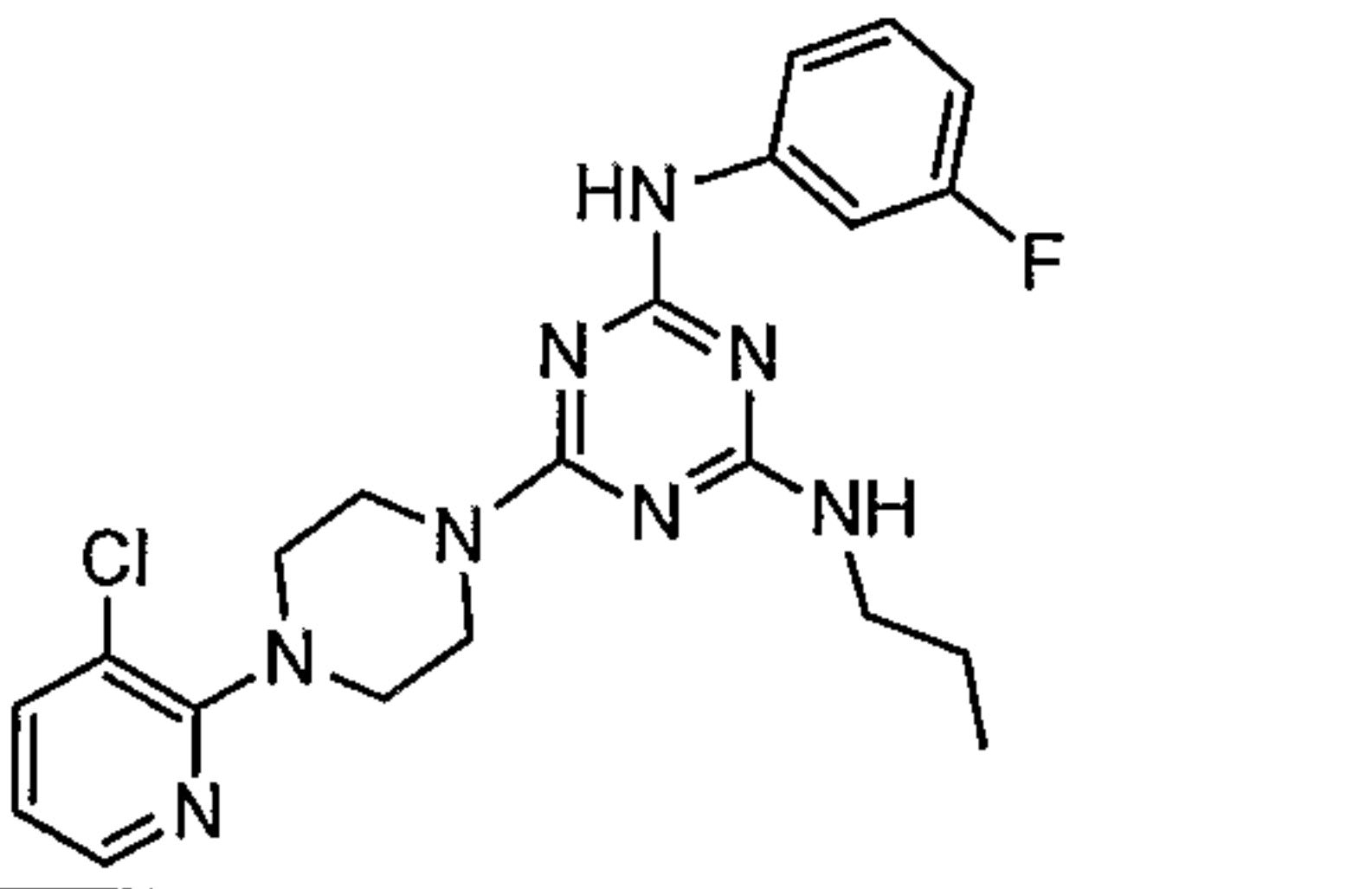
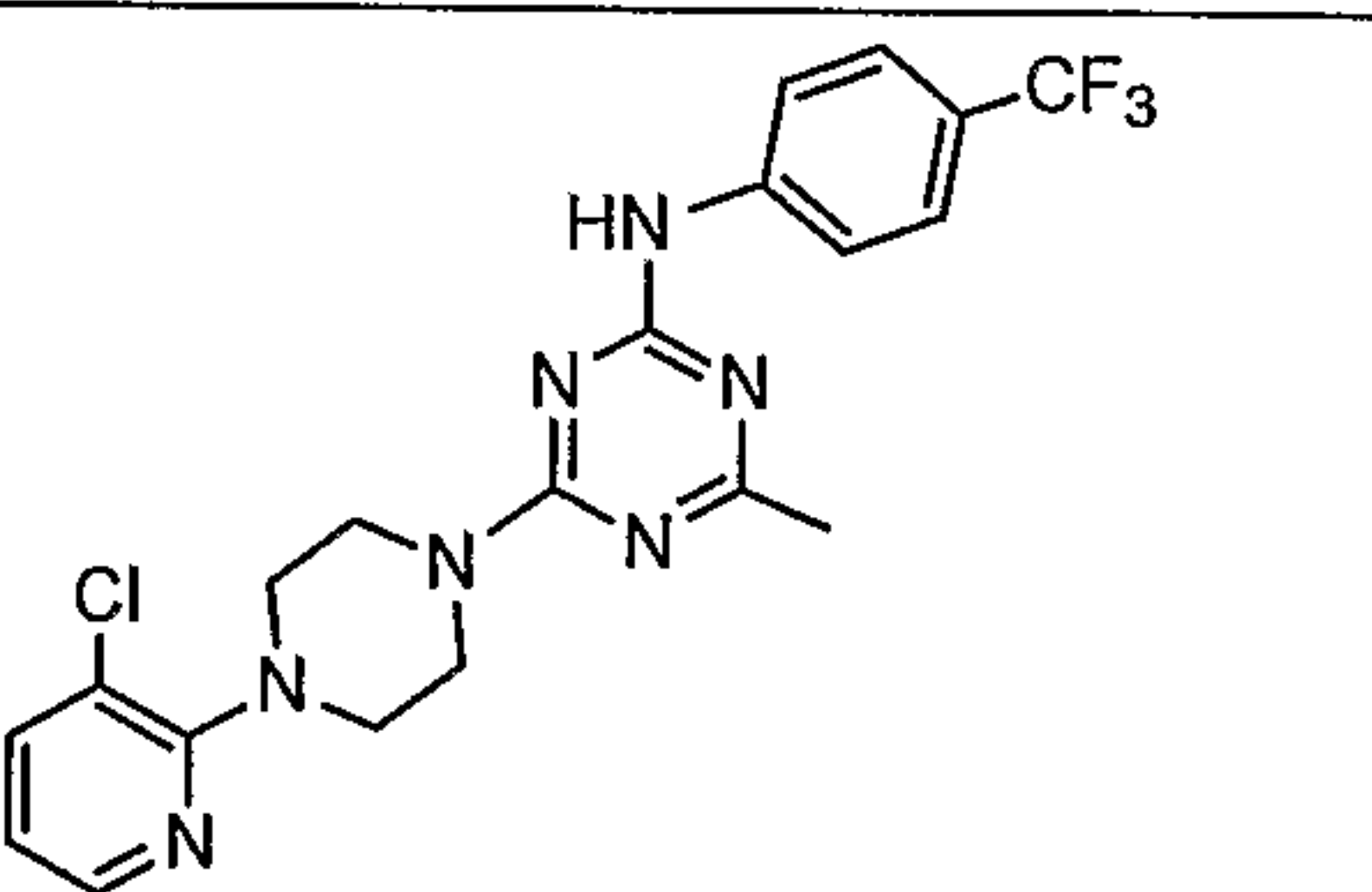
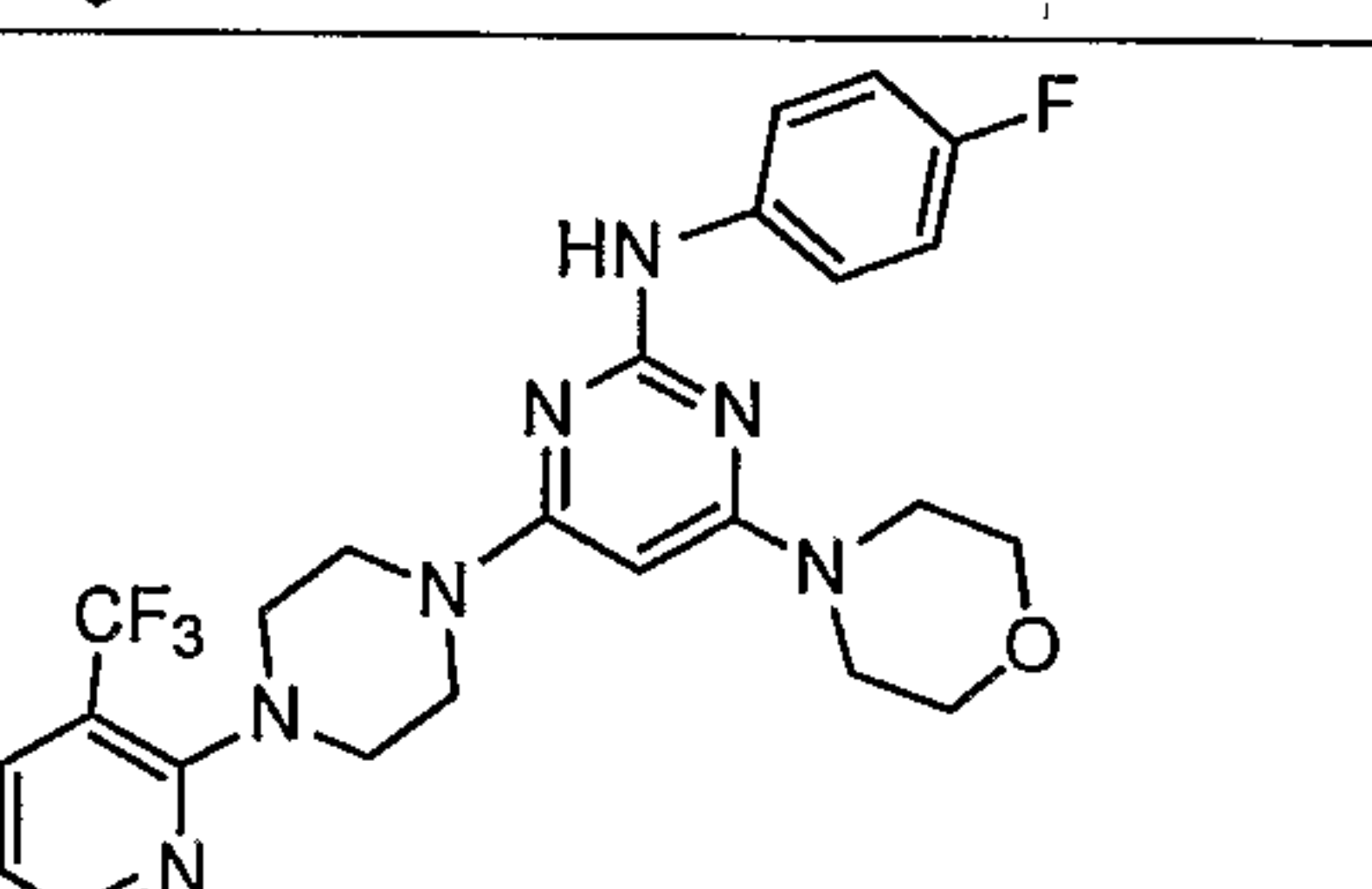
Compound	Name	IC ₅₀	MS
48. 	N-Methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	*	541.45
49. 	6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	*	507.40
50. 	6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N-isopropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine	*	521.43
51. 	N,N-Dimethyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	*	445.36
52. 	{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	519.41
53. 	6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S)	*	493.38

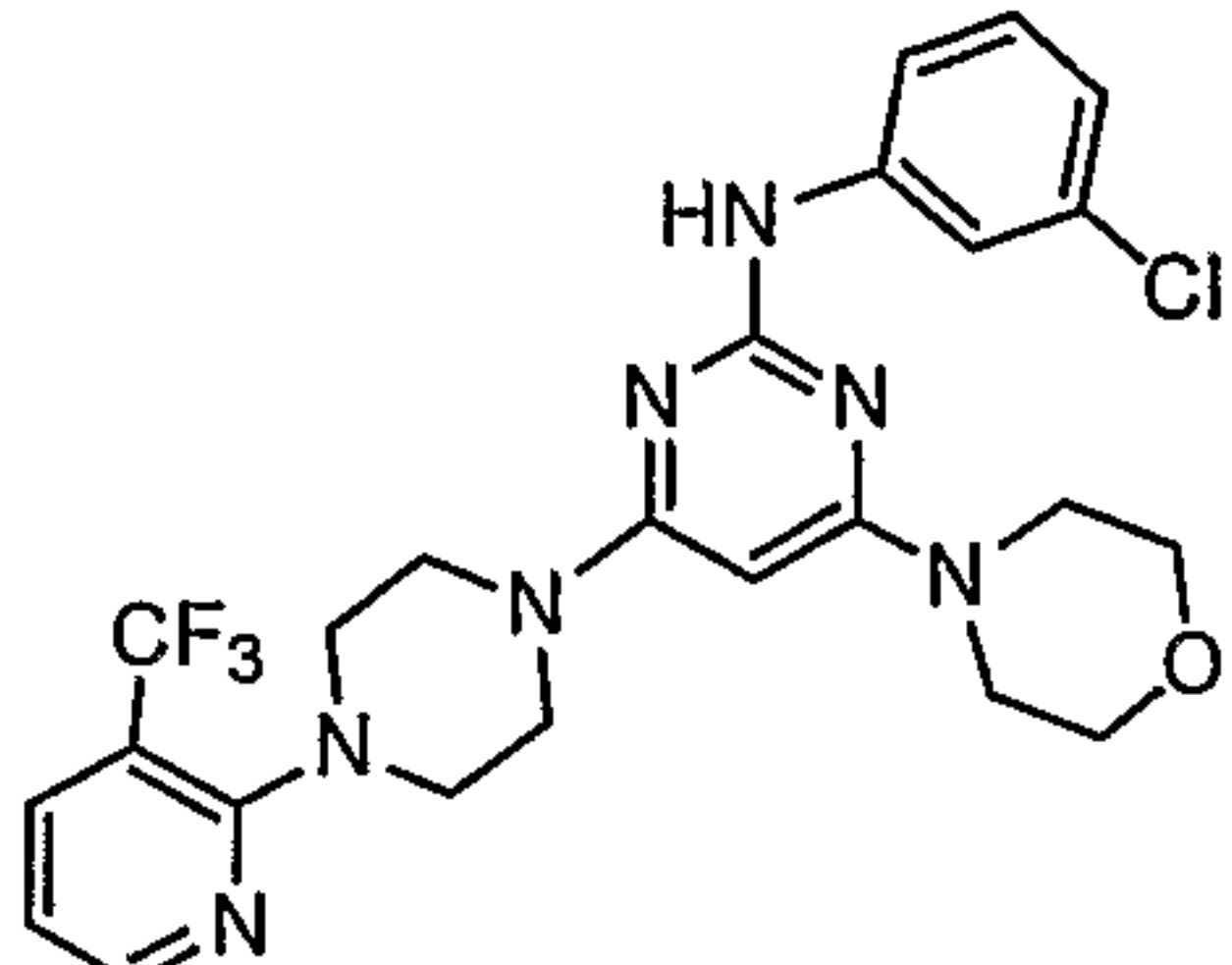
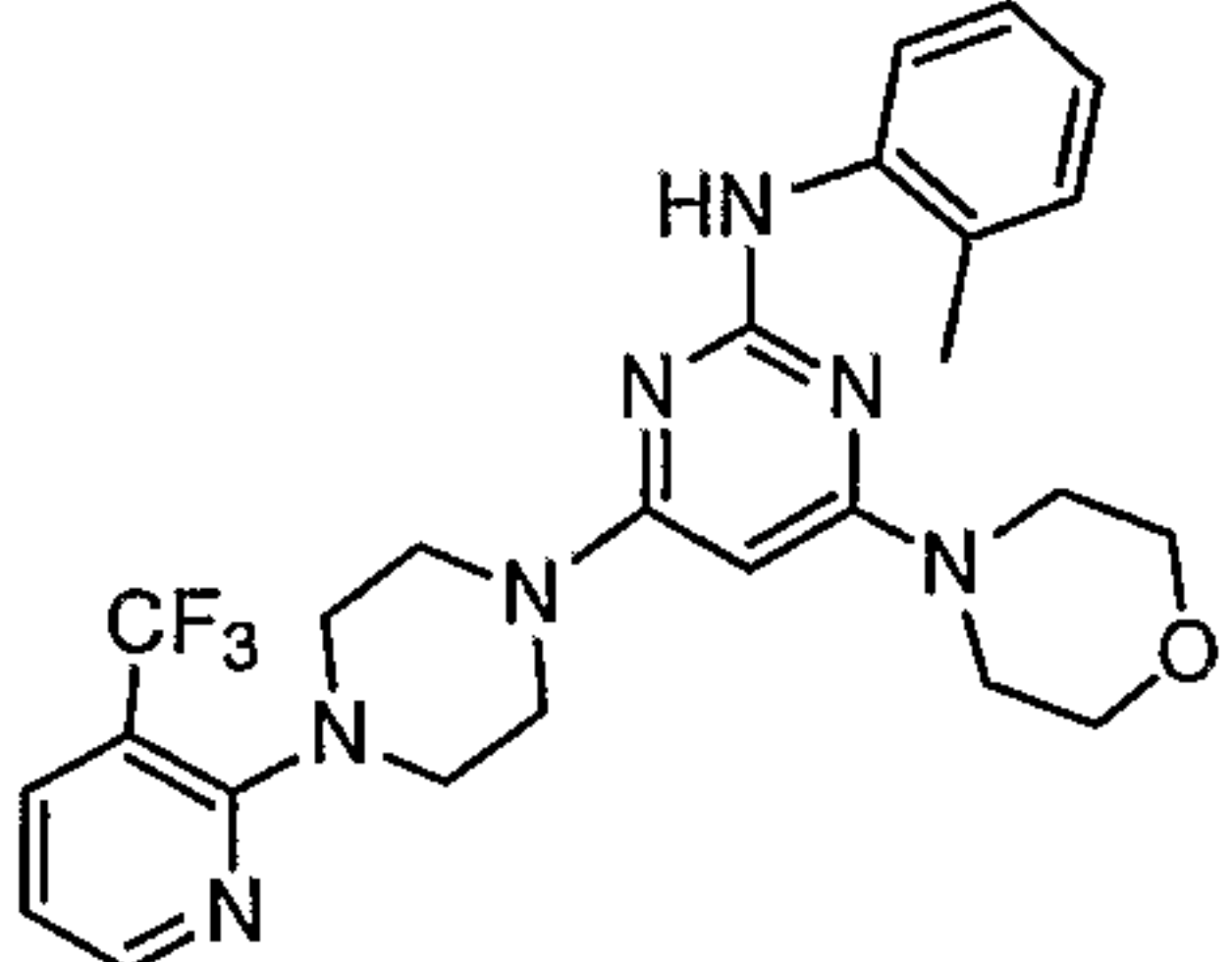
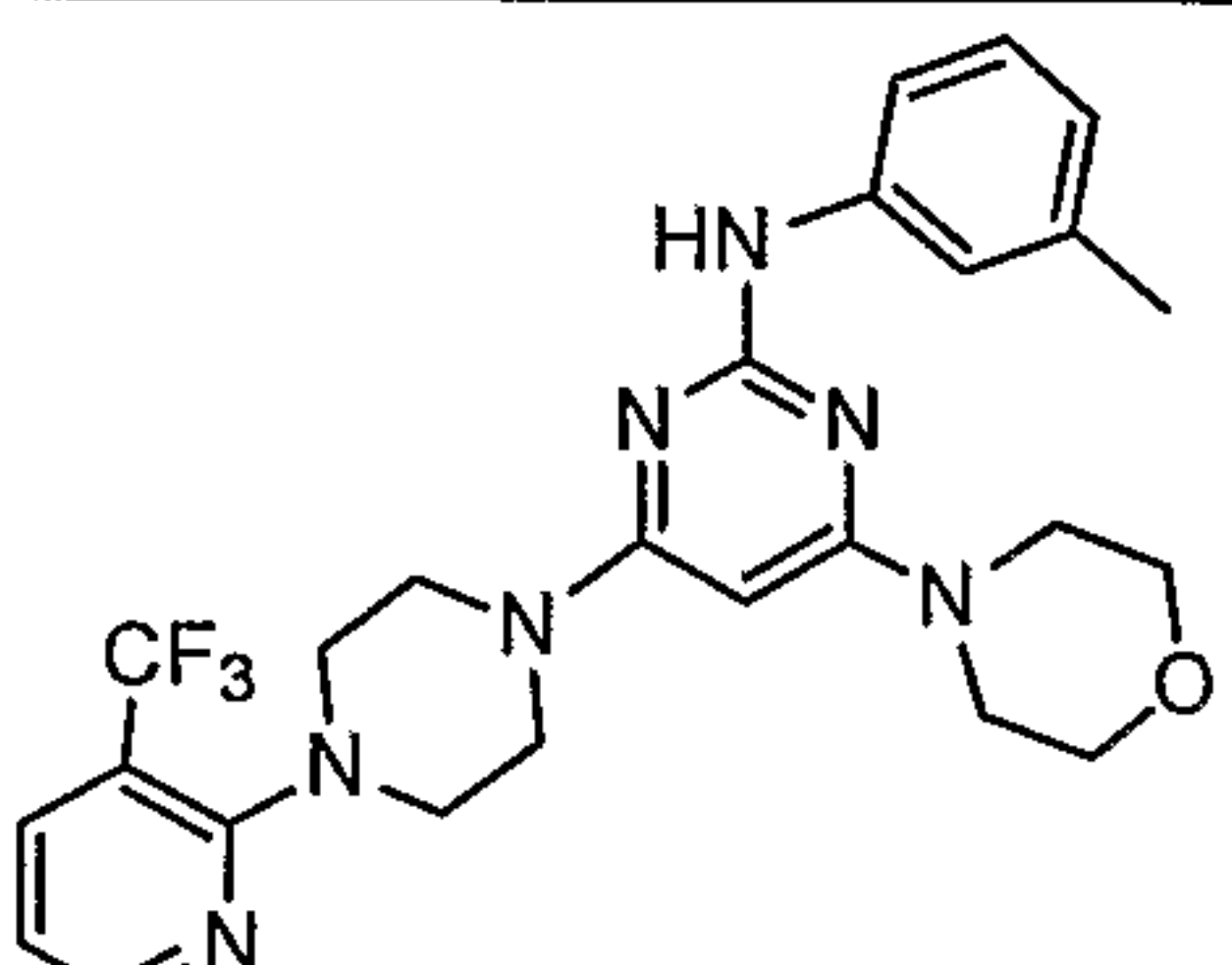
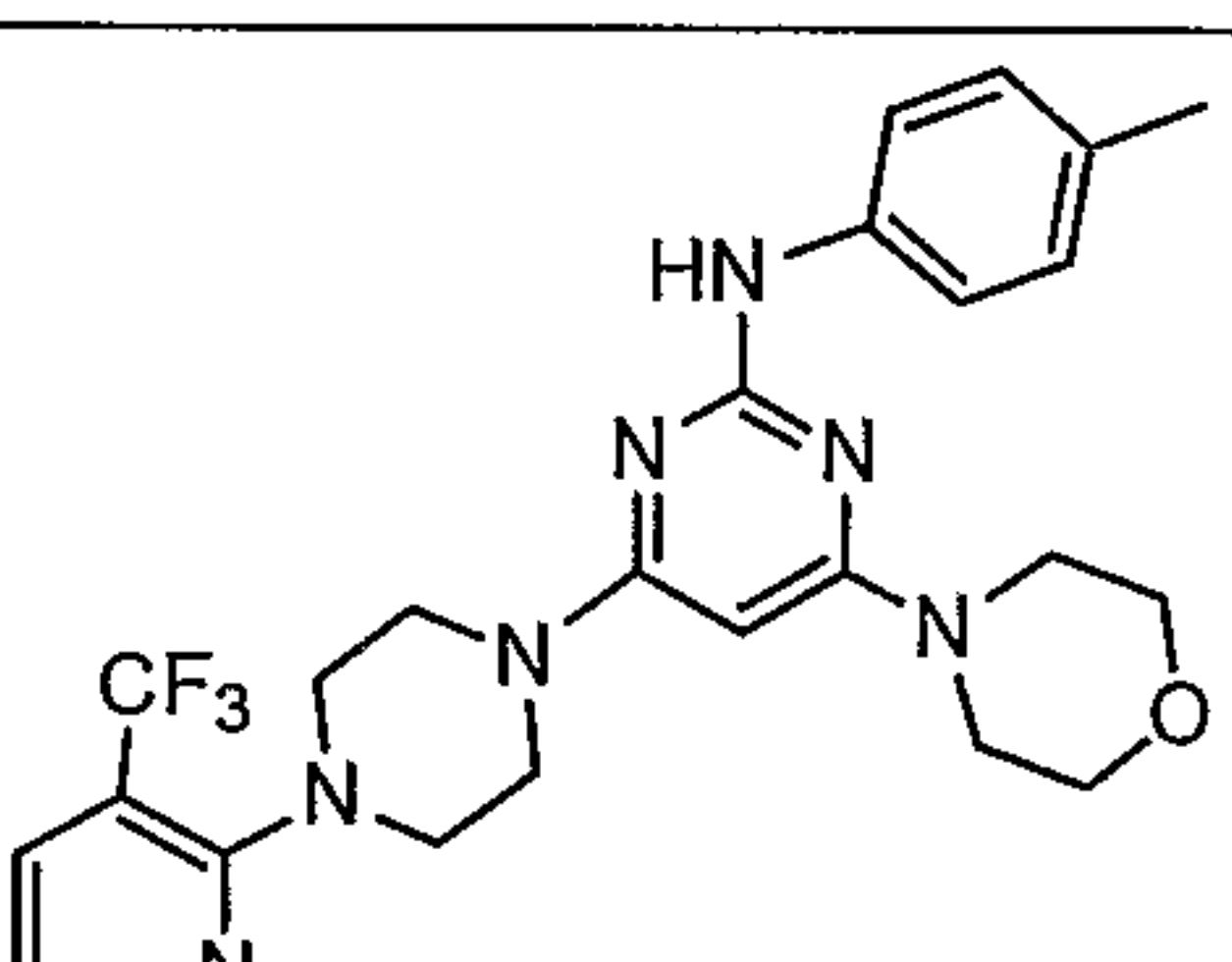
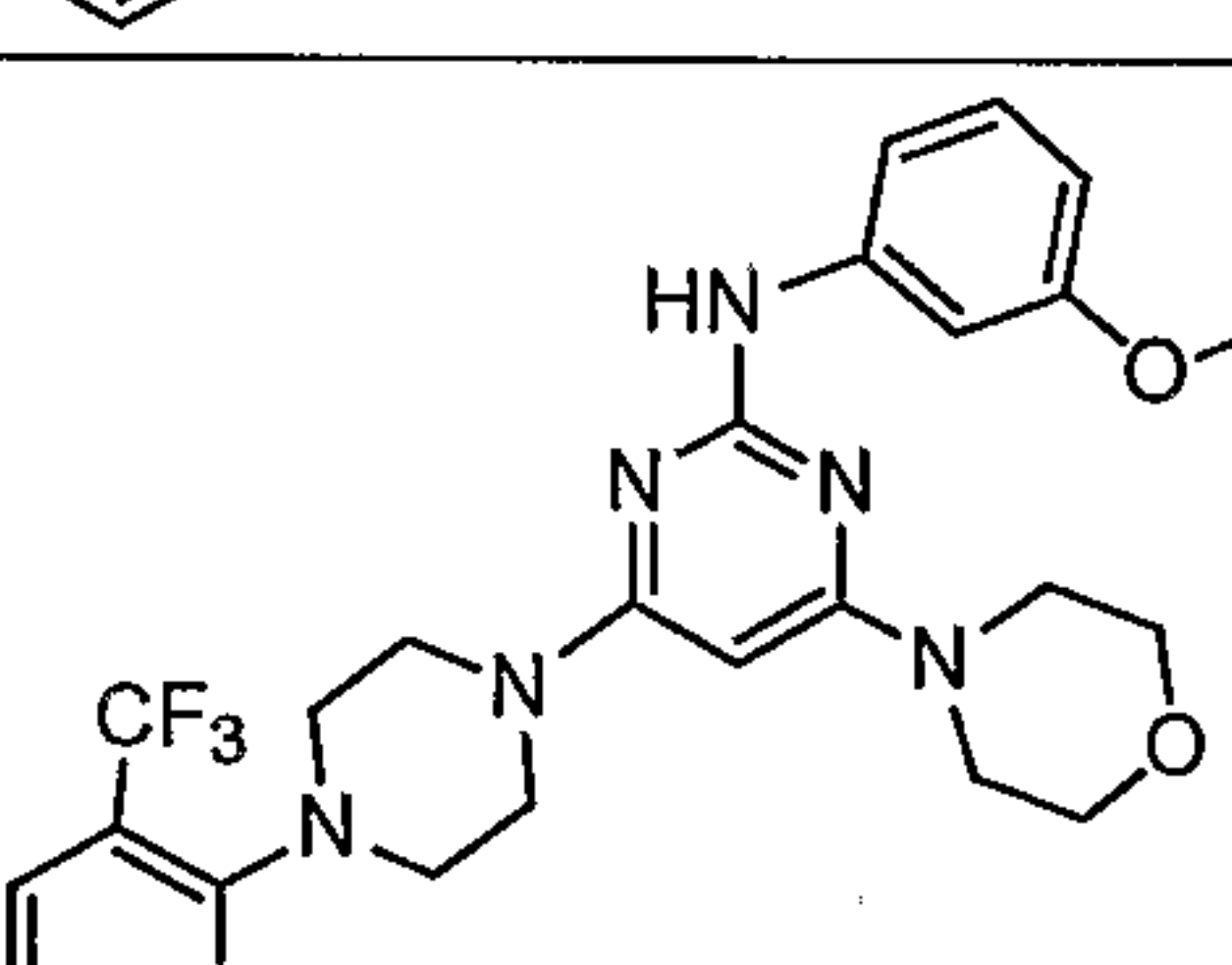
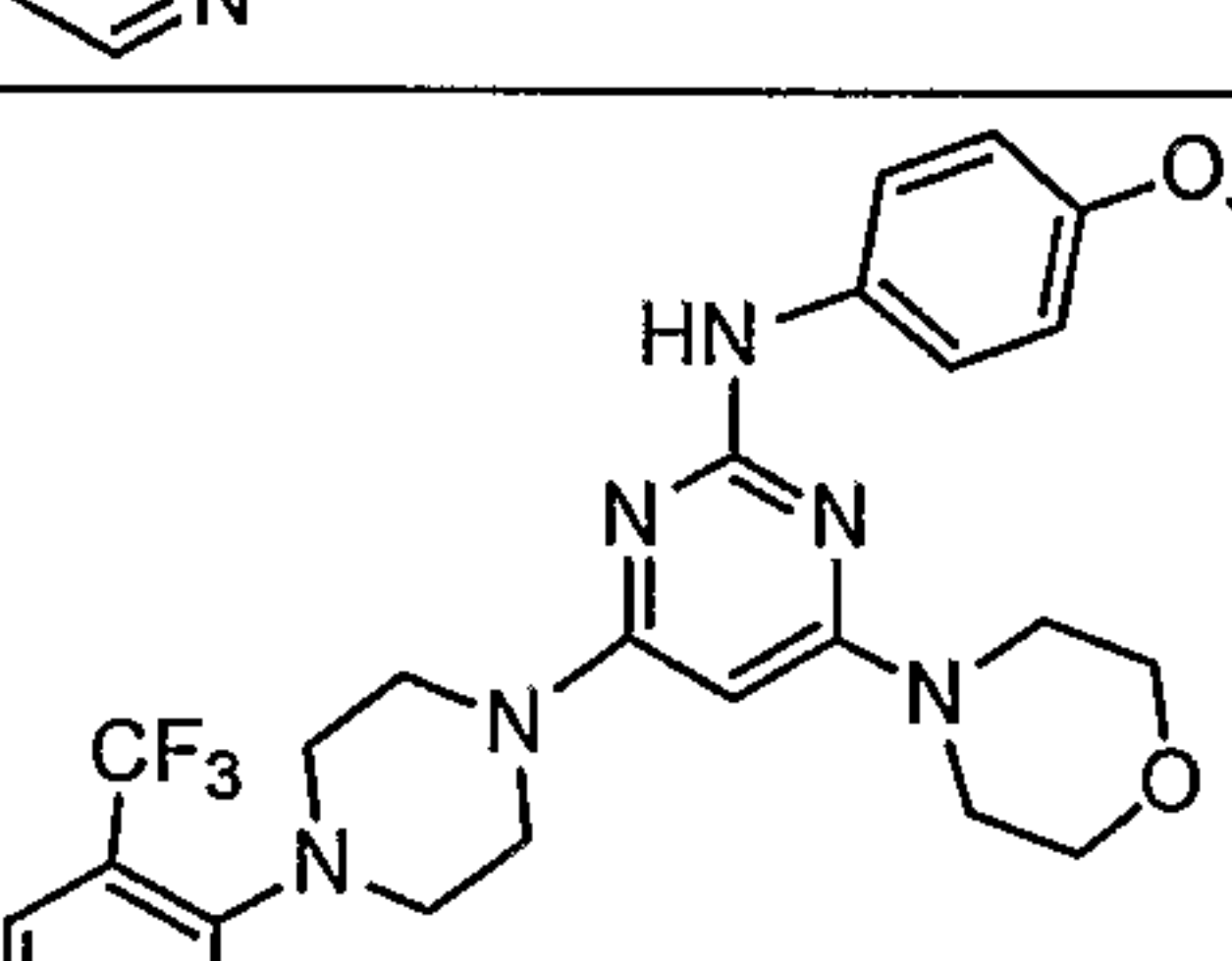
Compound	Name	IC ₅₀	MS
54. 	6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-phenyl-[1,3,5]triazine-2,4-diamine	*	439.20
55. 	N-Isopropyl-N-methyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine	*	473.22
56. 	{4,6-Bis-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	631.19
57. 	Phenyl-{6-piperidin-1-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine	*	484.23
58. 	(3-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	*	505.21
59. 	(4-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	*	505.21

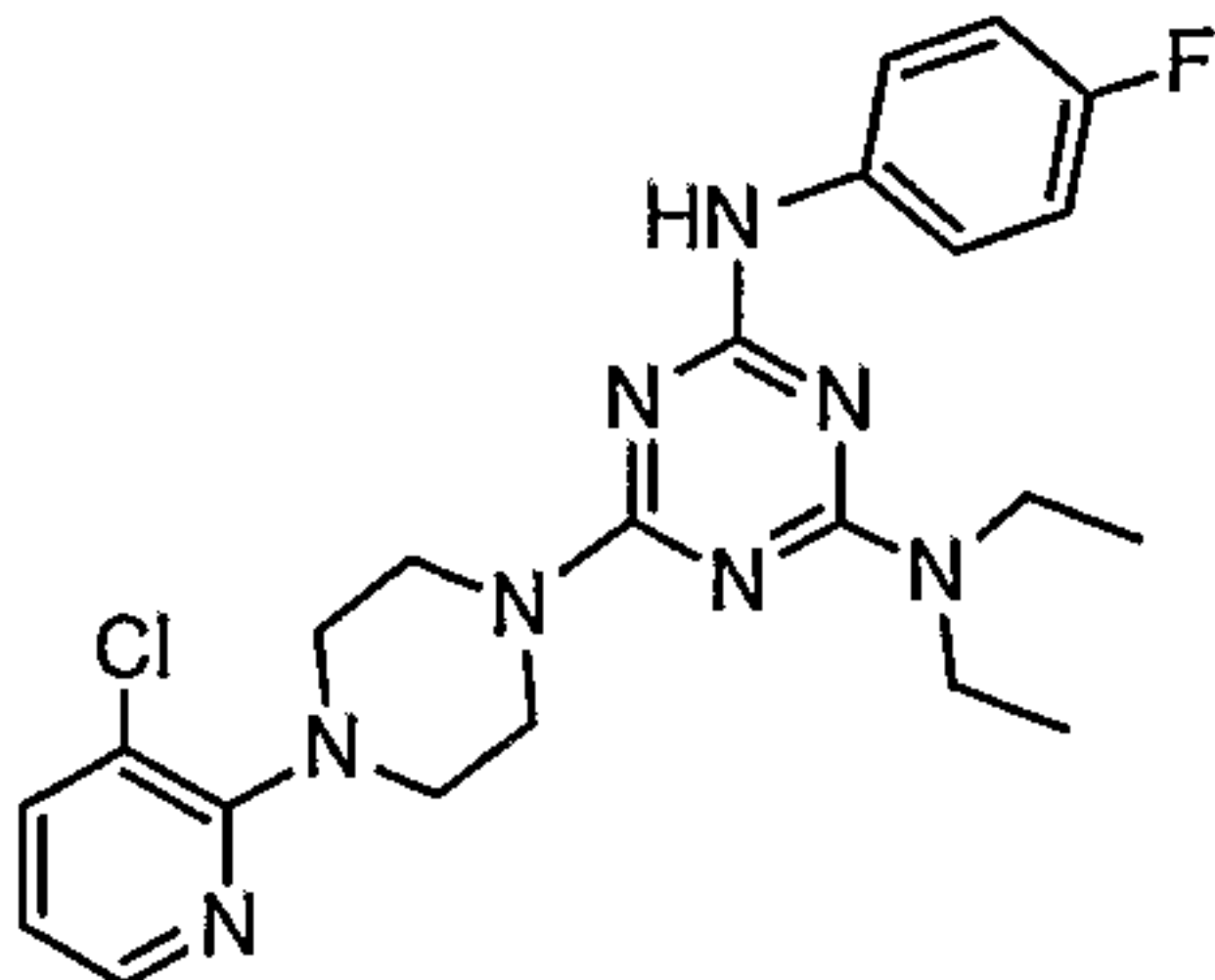
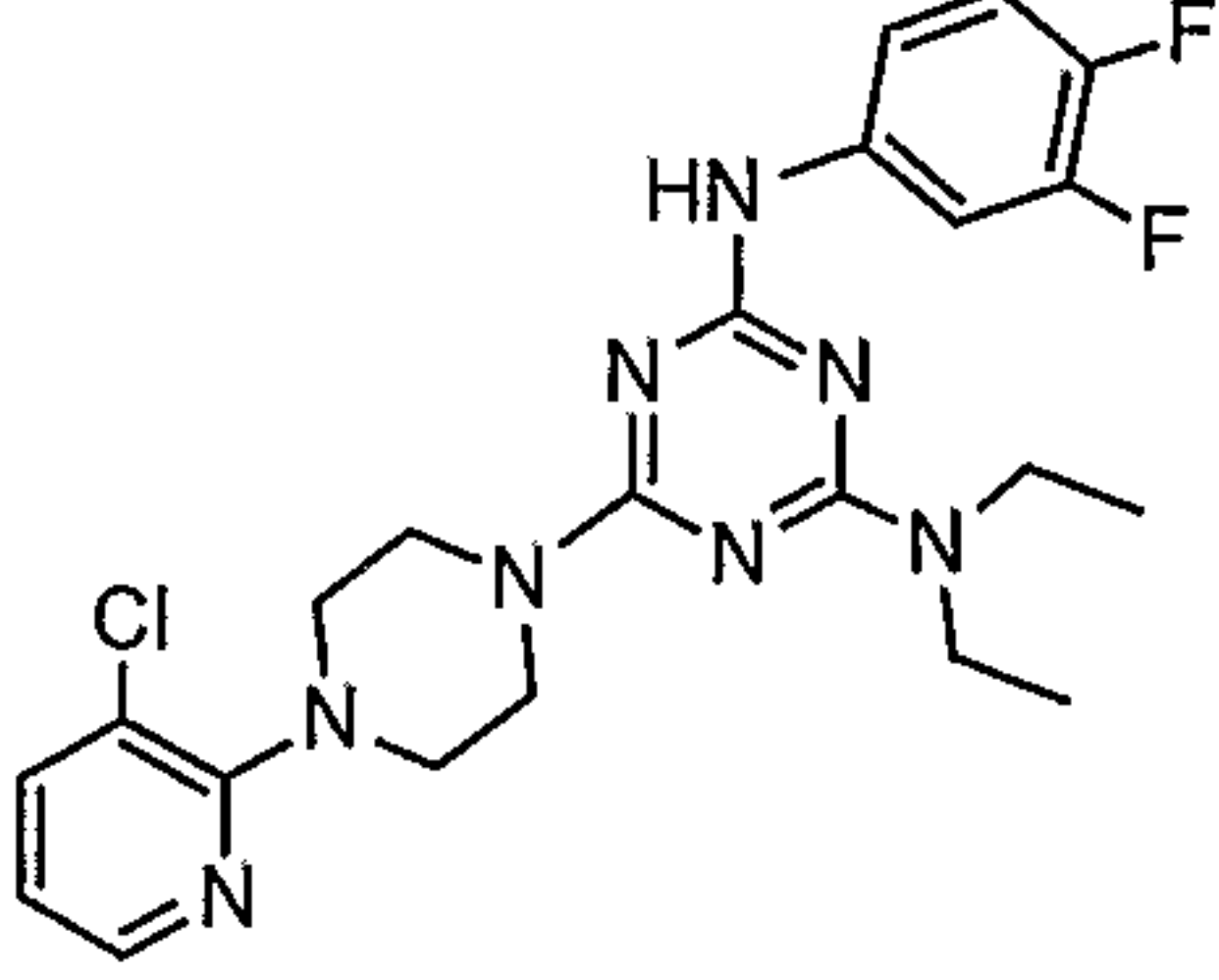
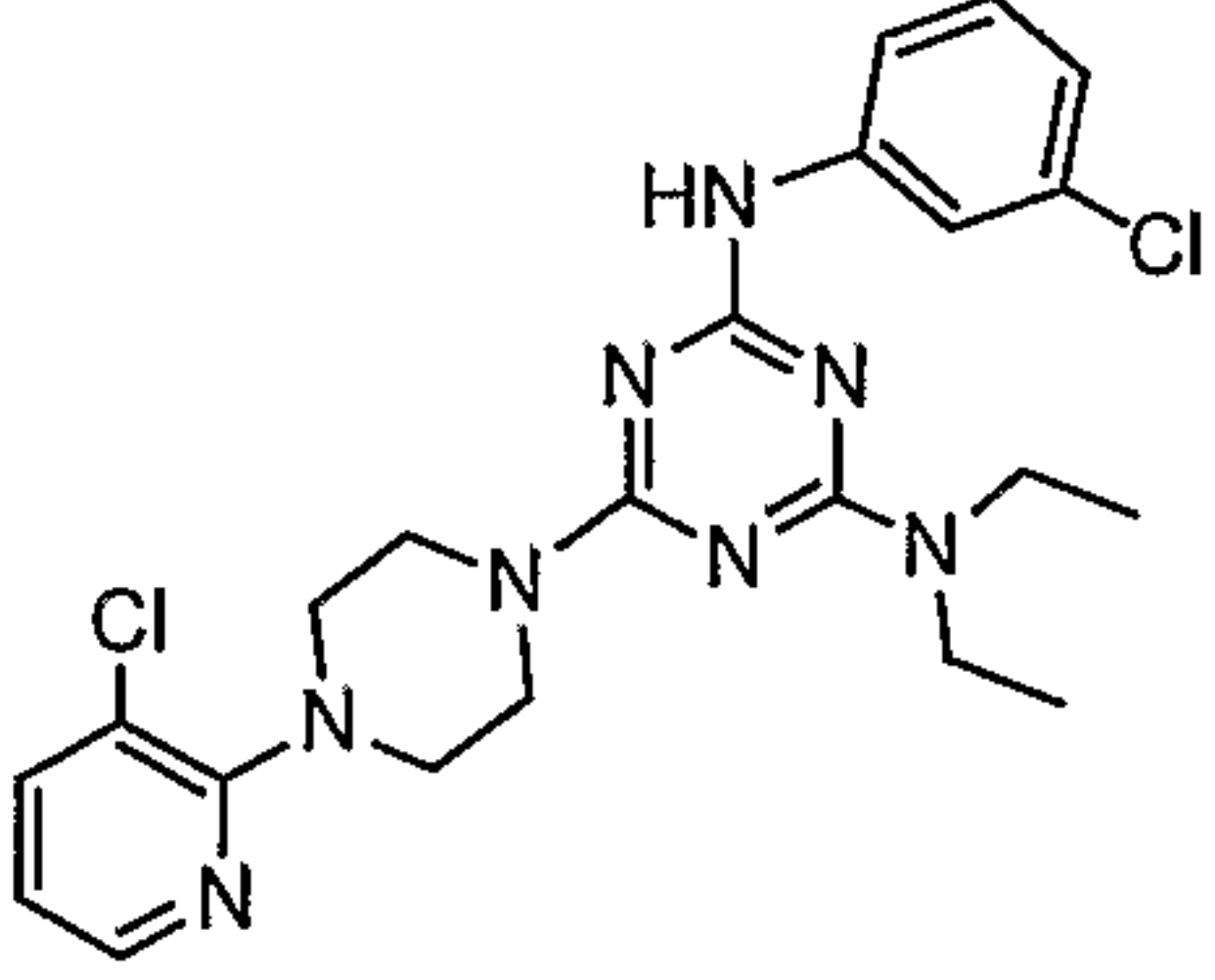
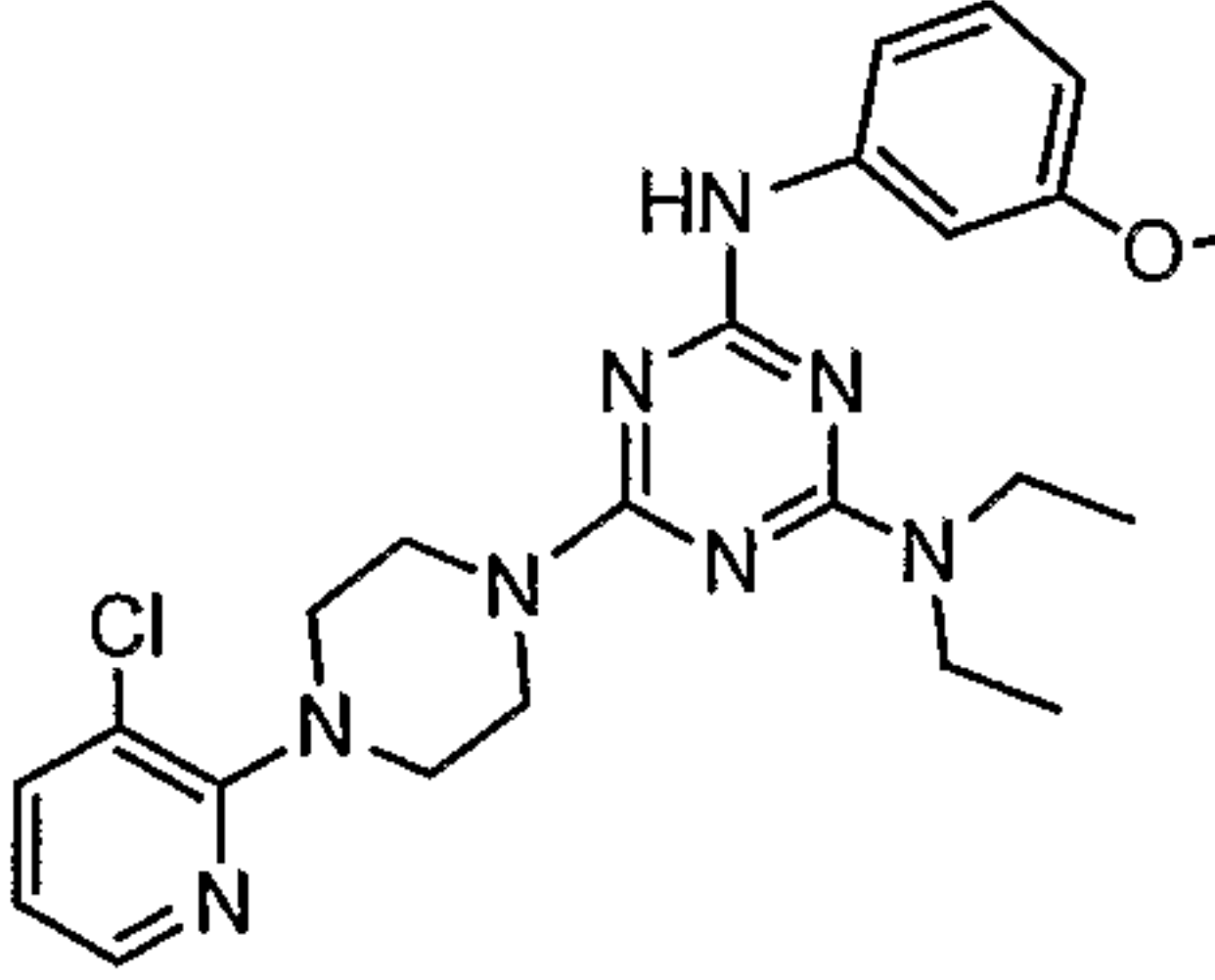
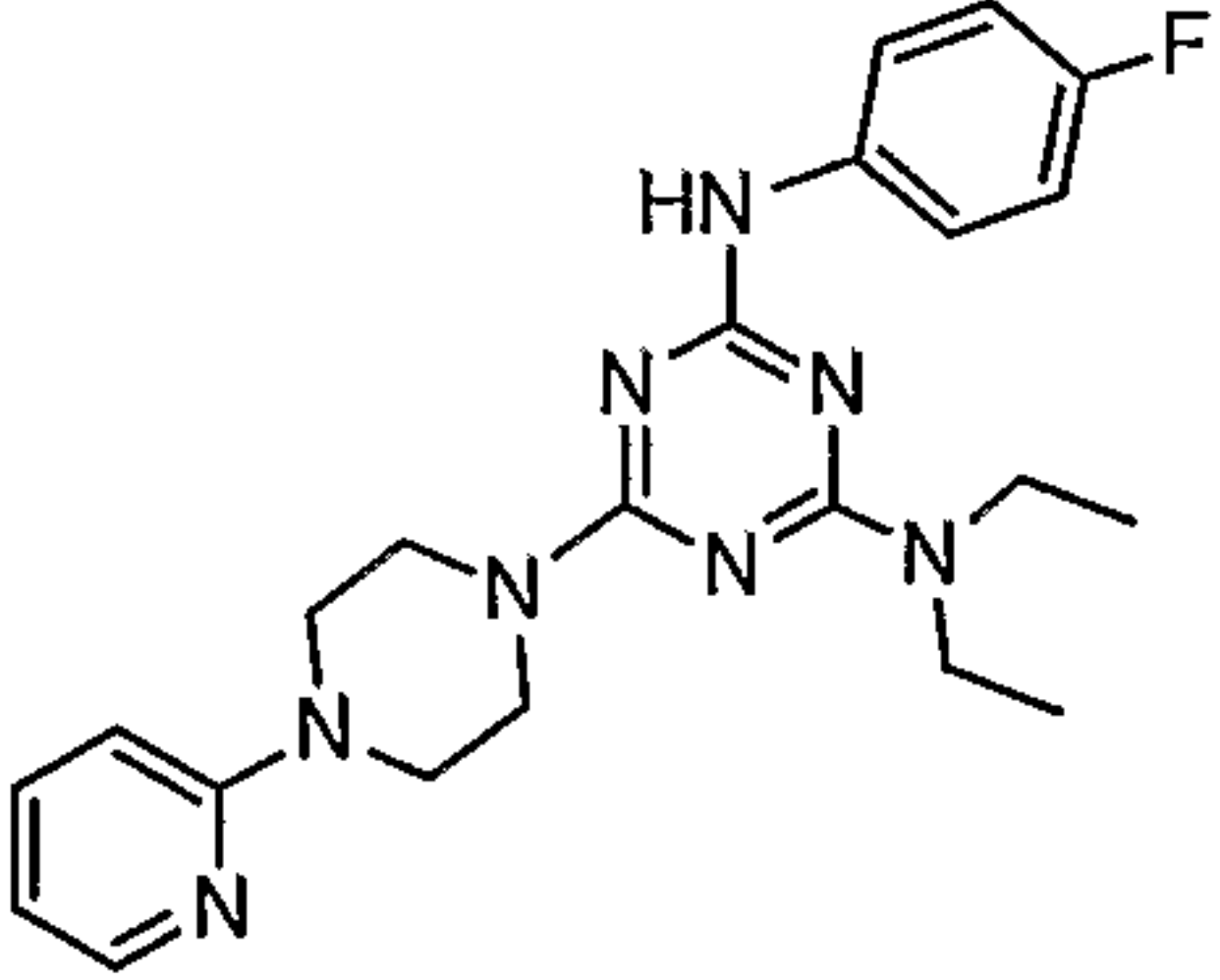
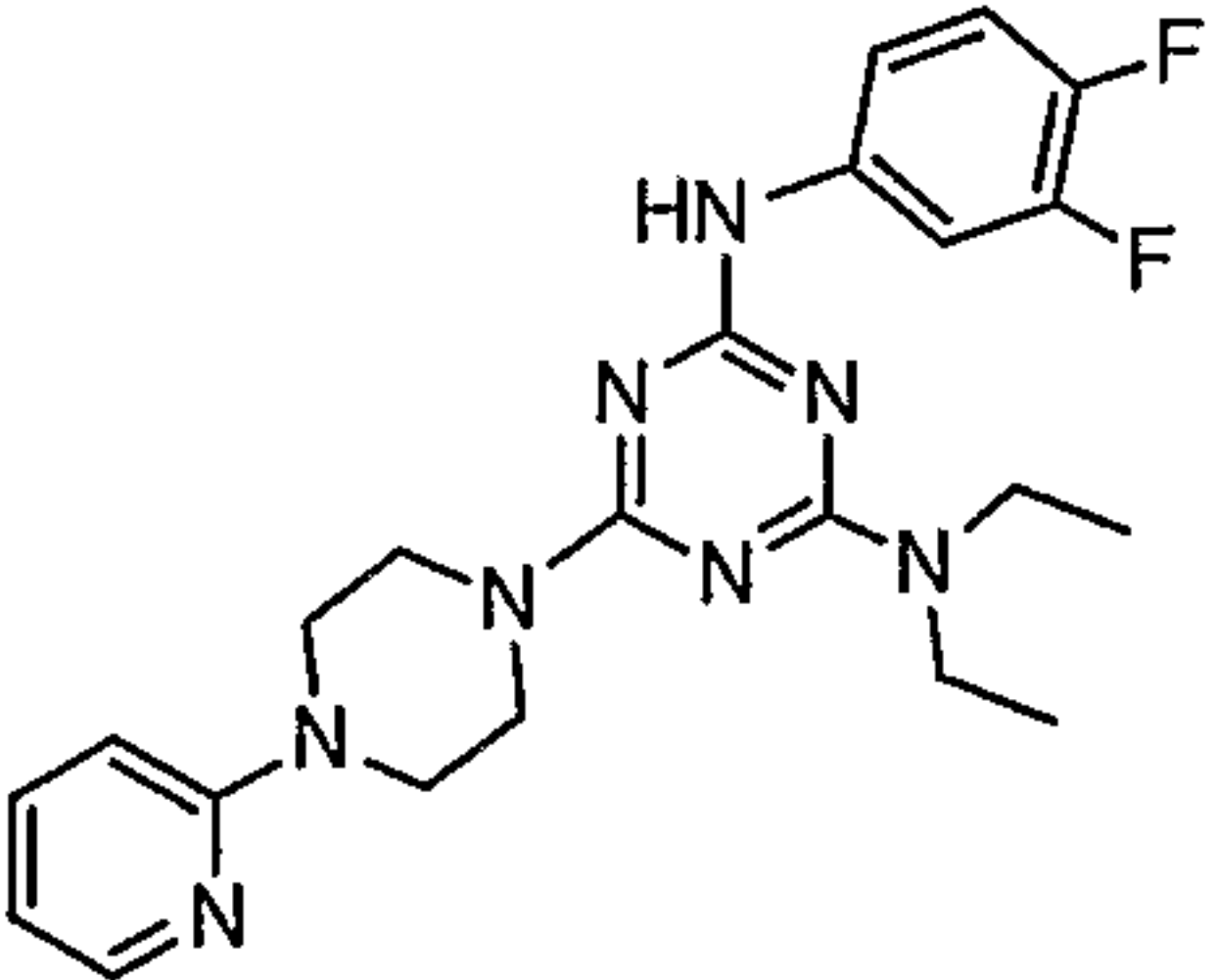
Compound	Name	IC ₅₀	MS
60. 	{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine	*	471.19
61. 	{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(4-fluoro-phenyl)-amine	*	471.19
62. 	(4-Chloro-phenyl)-{4-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine	*	487.36
63. 	(4-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	*	521.40
64. 	{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-p-tolyl-amine	*	501.44
65. 	{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-p-tolyl-amine	*	467.39

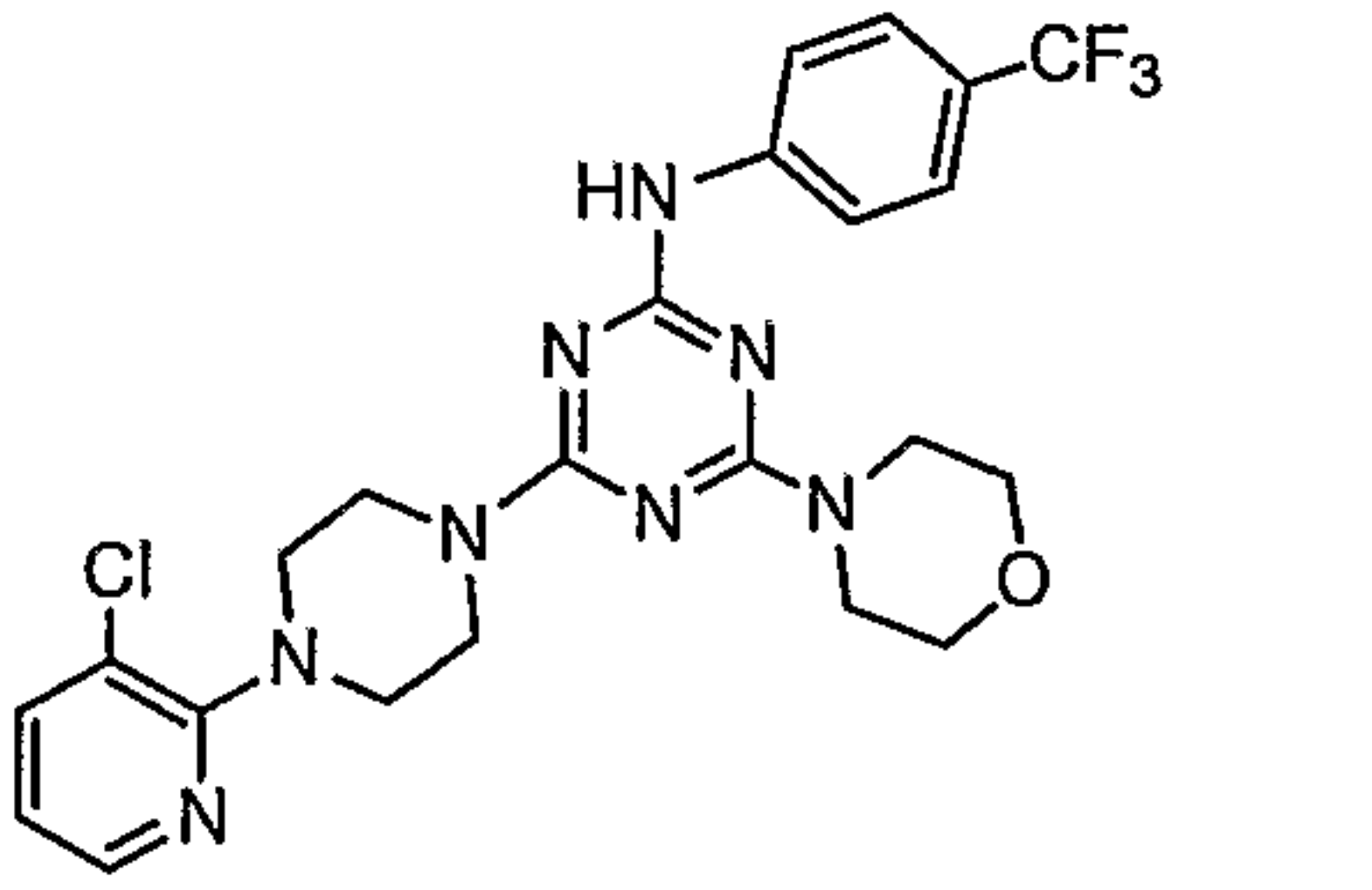
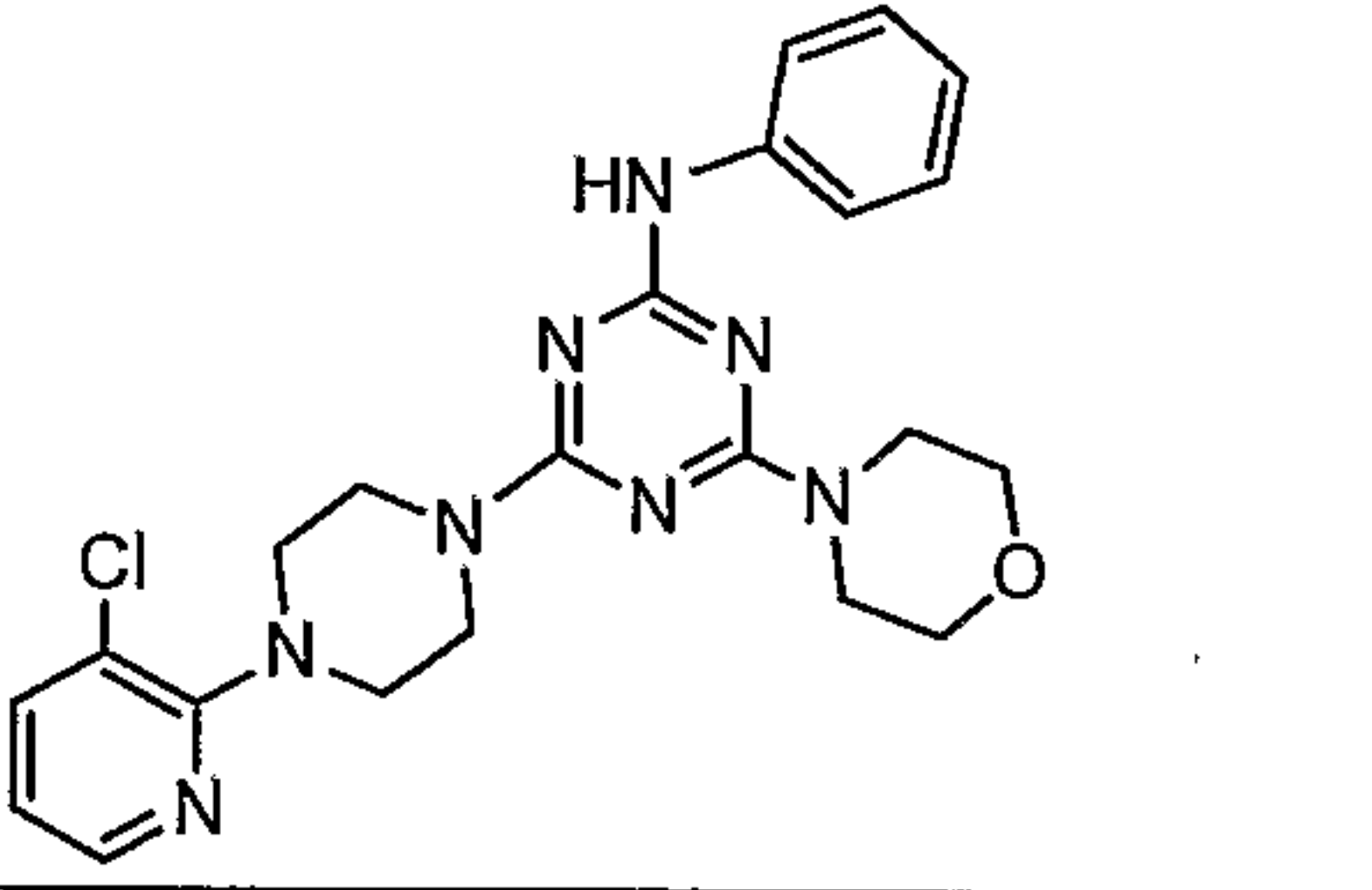
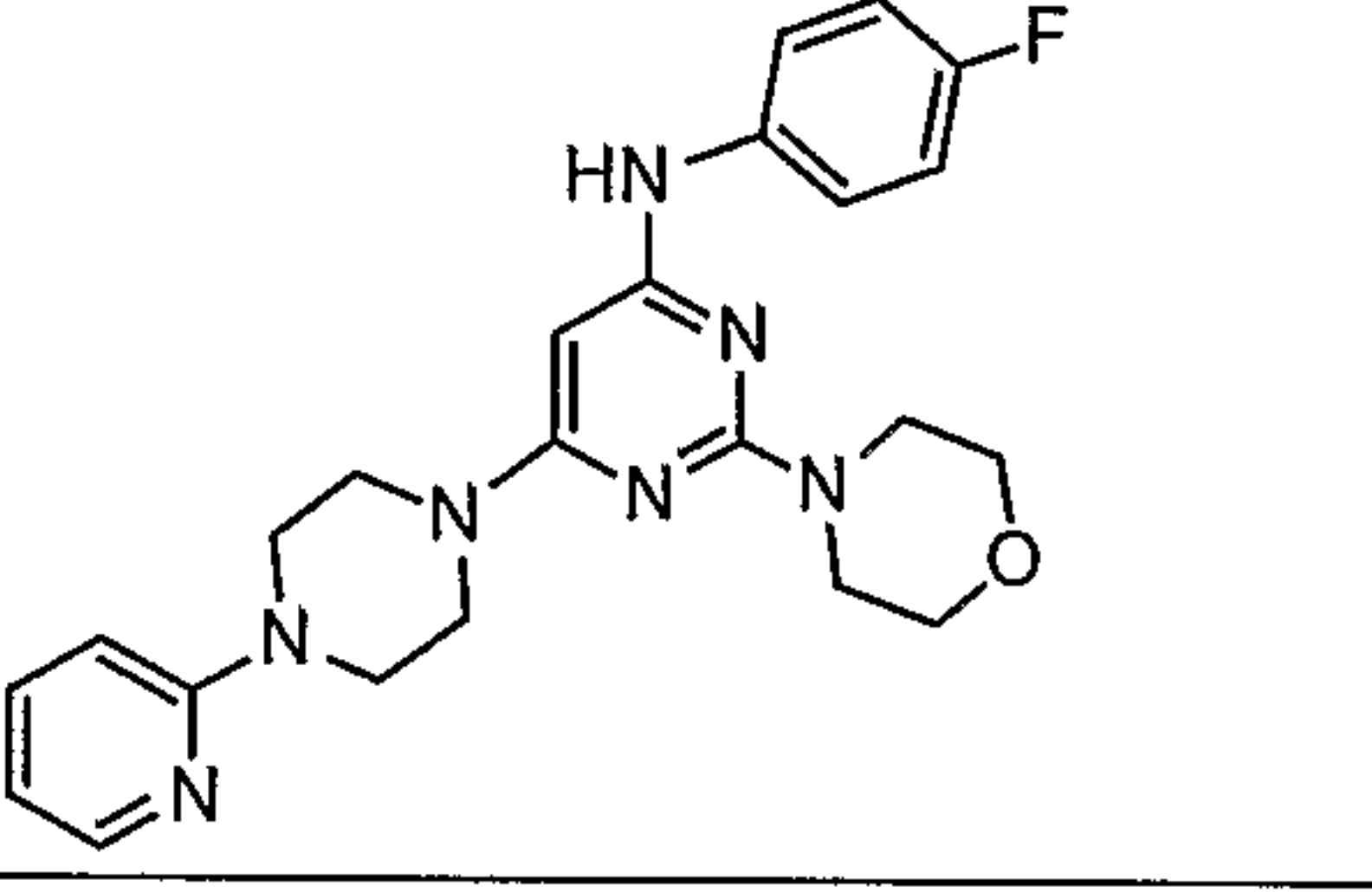
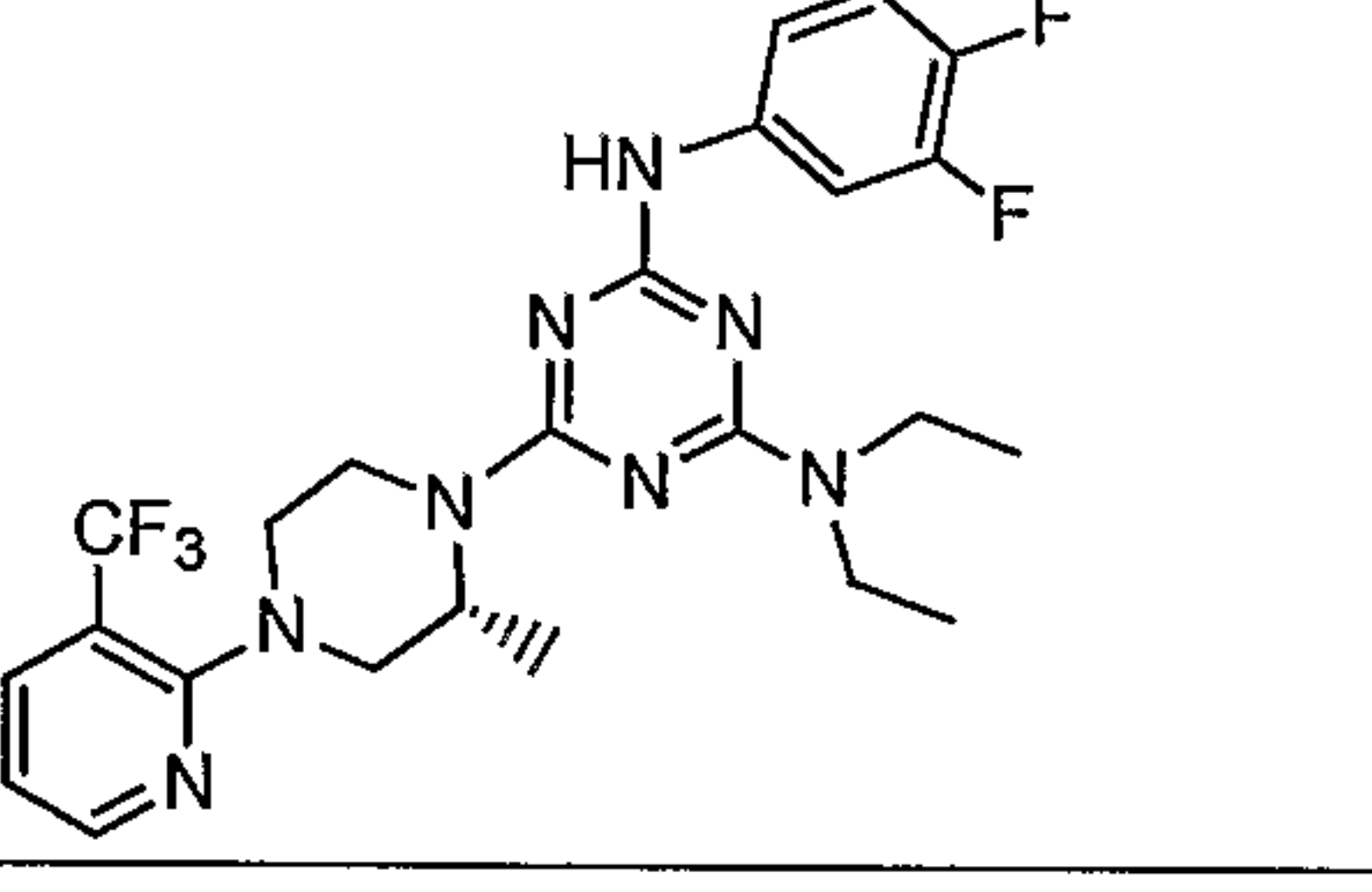
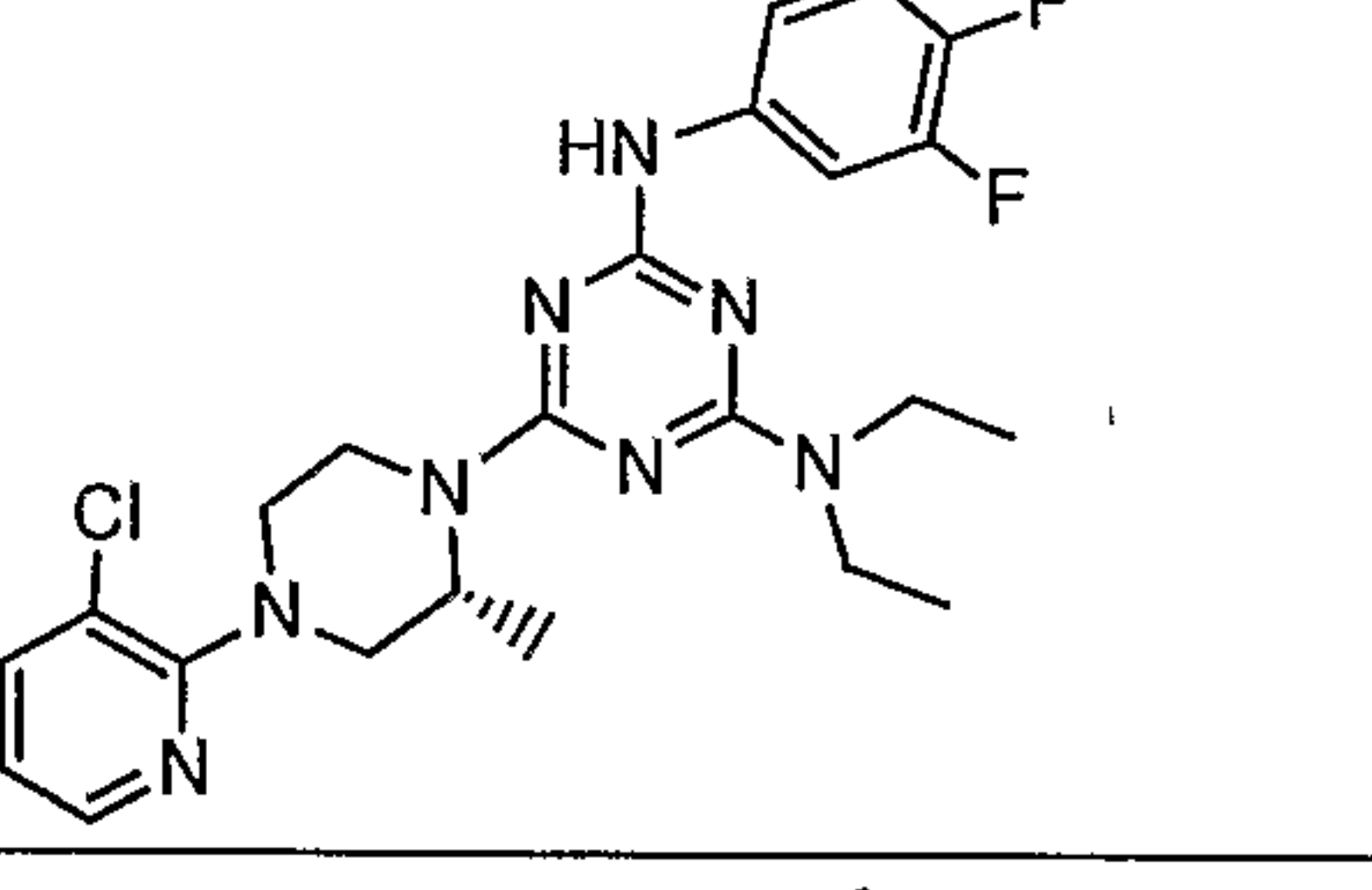
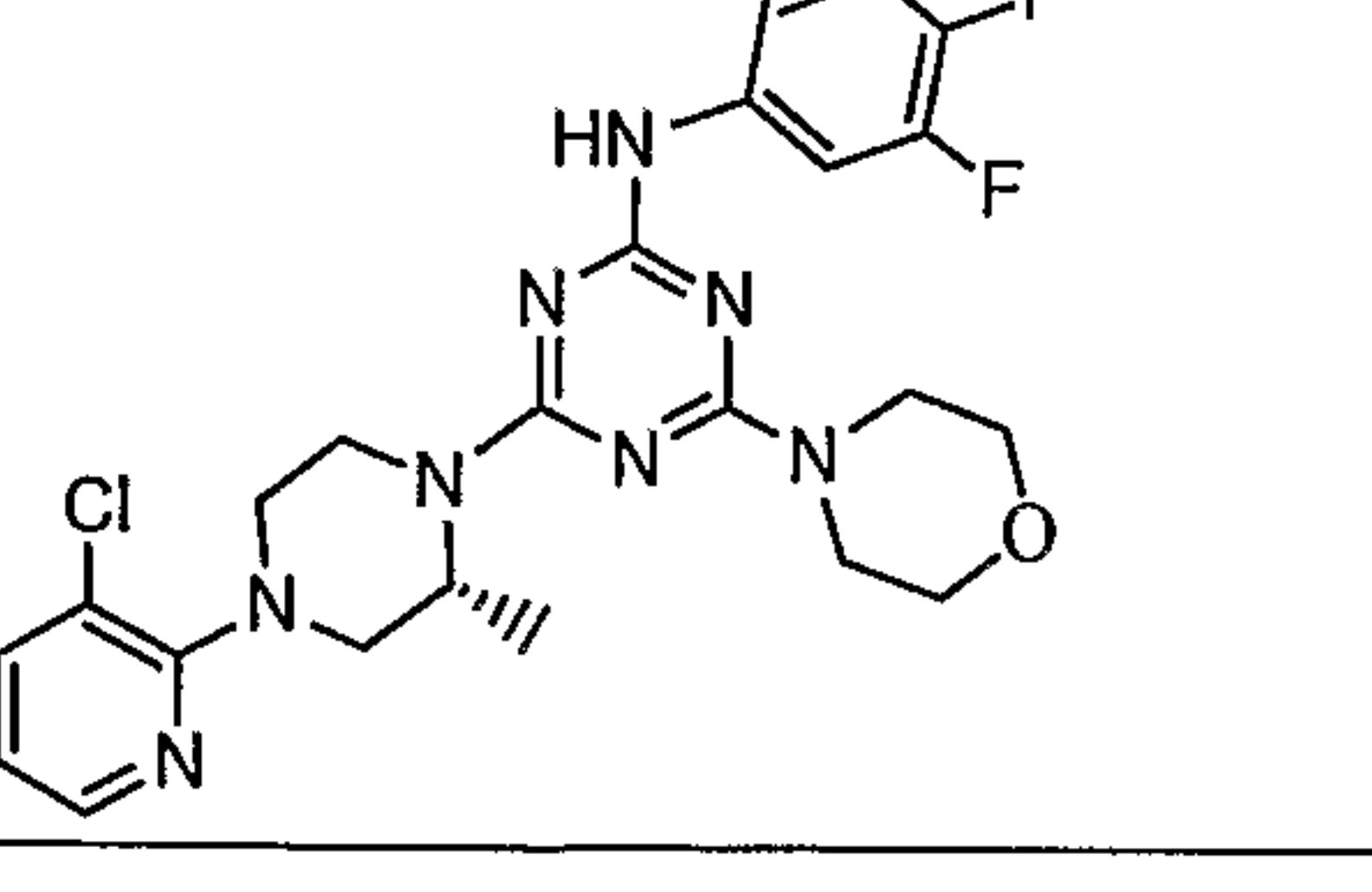
Compound	Name	IC ₅₀	MS
66. 	(3-Chloro-phenyl)-{4-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine	*	487.36
67. 	(3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	*	521.41
68. 	{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3,4-difluoro-phenyl)-amine	*	489.38
69. 	(3,4-Difluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine	*	523.42
70. 	{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine	*	469.39
71. 	6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine	*	457.37

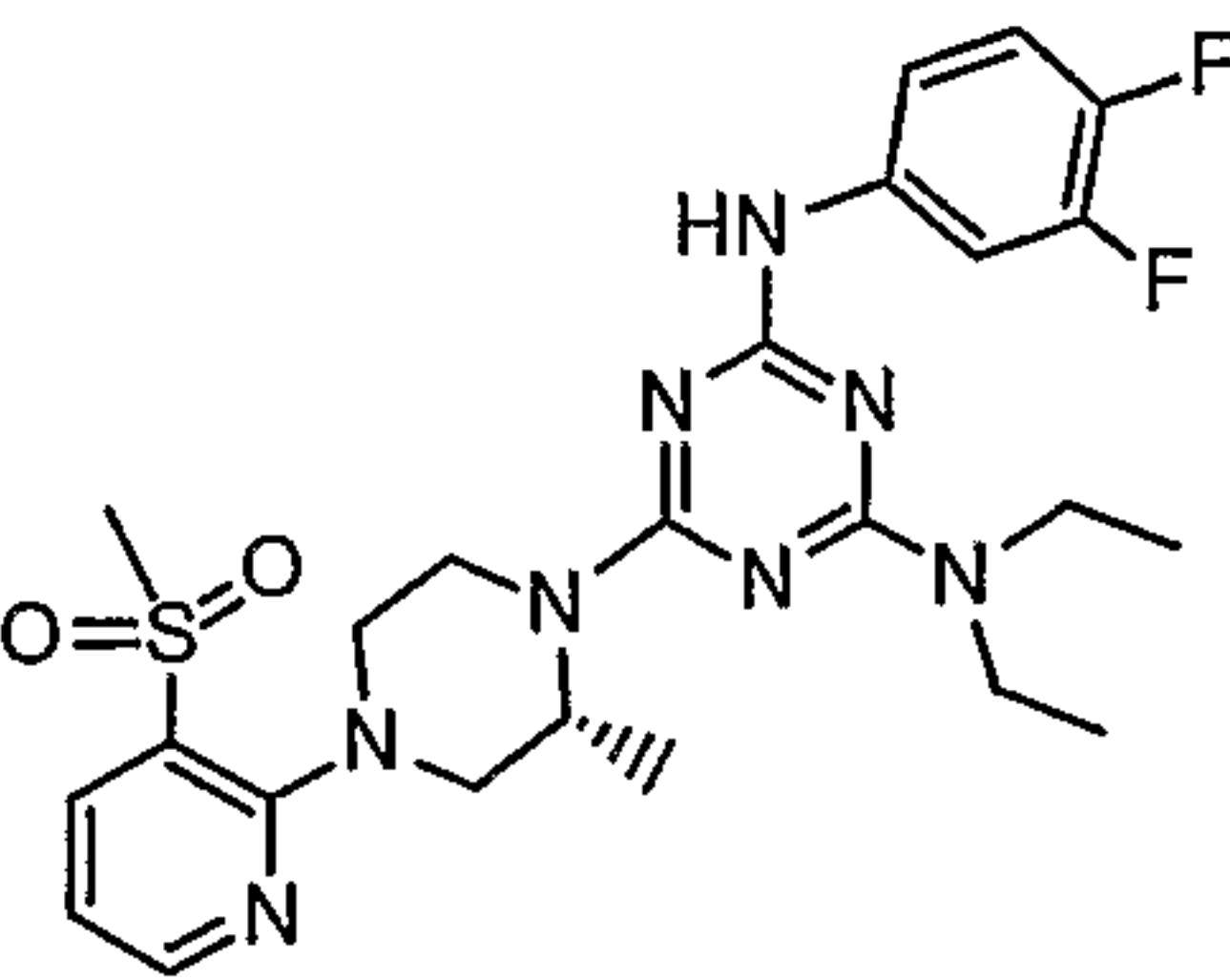
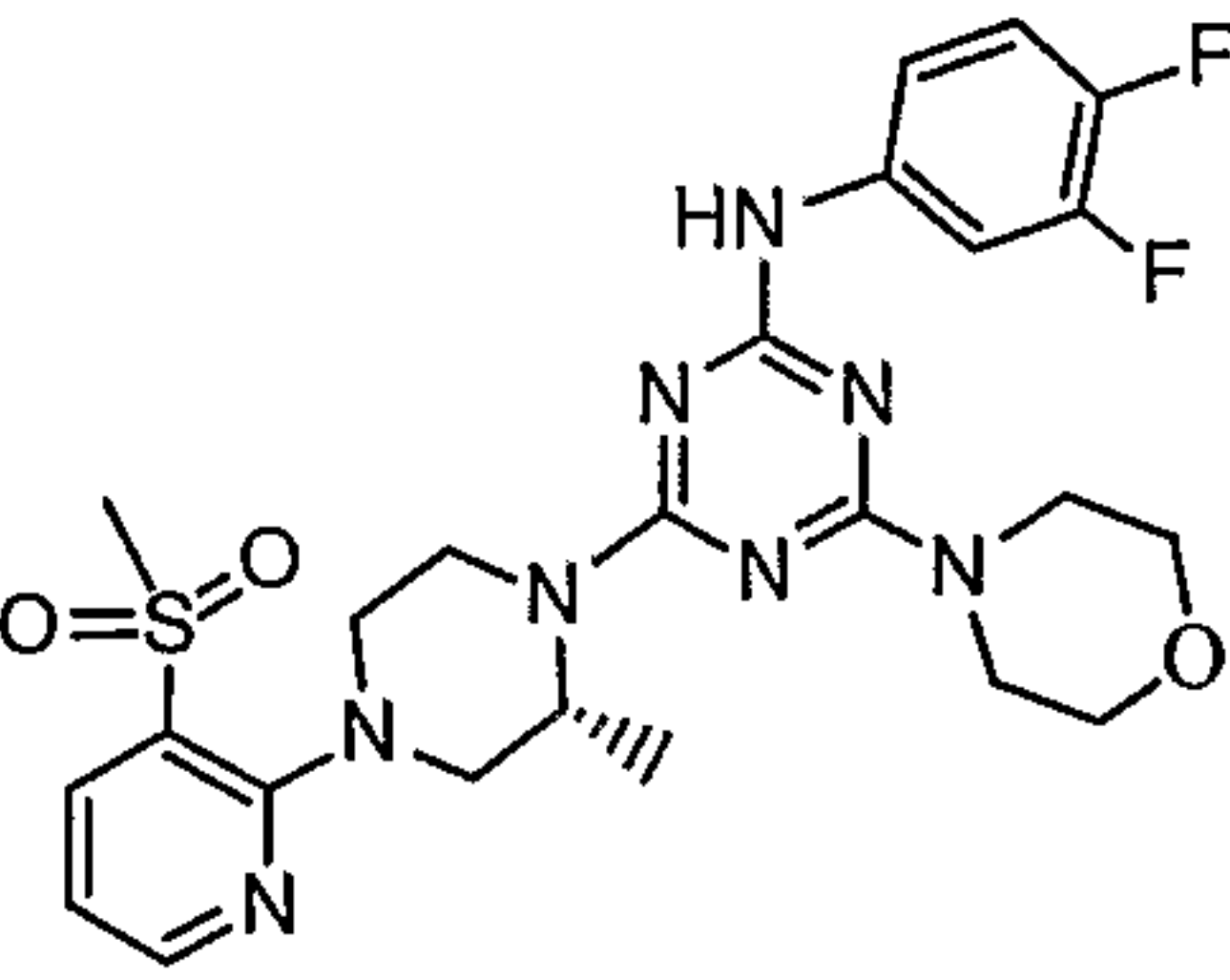
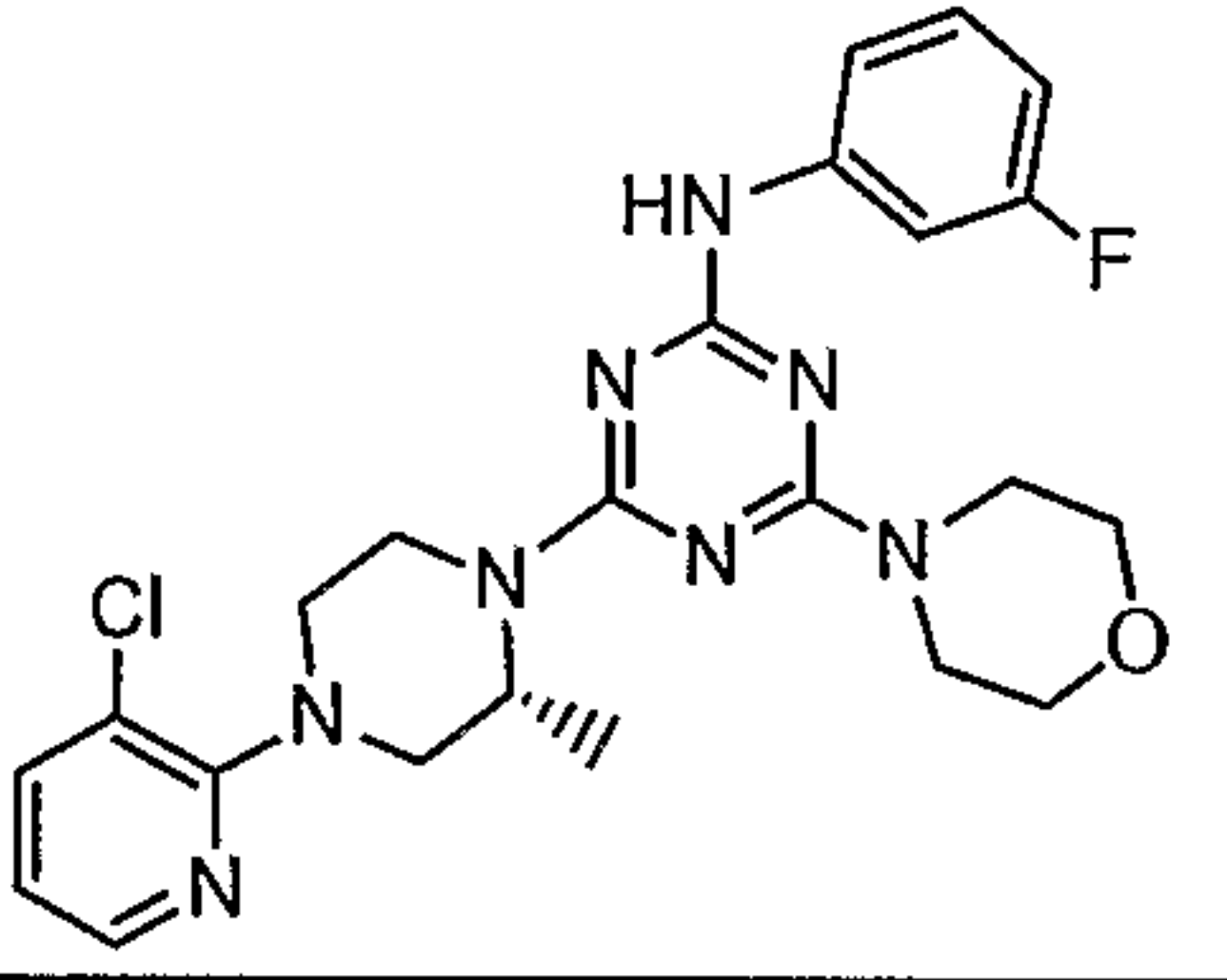
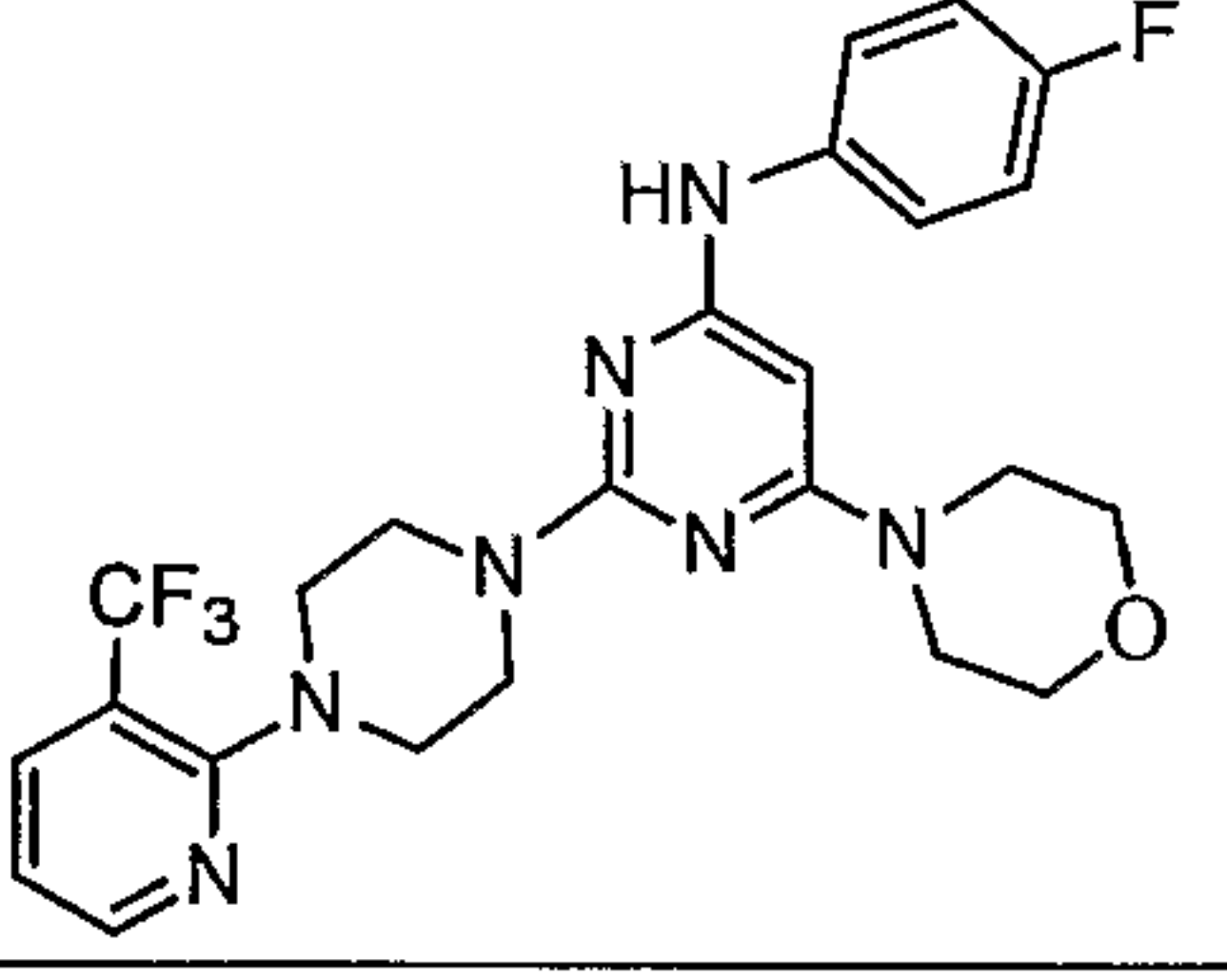
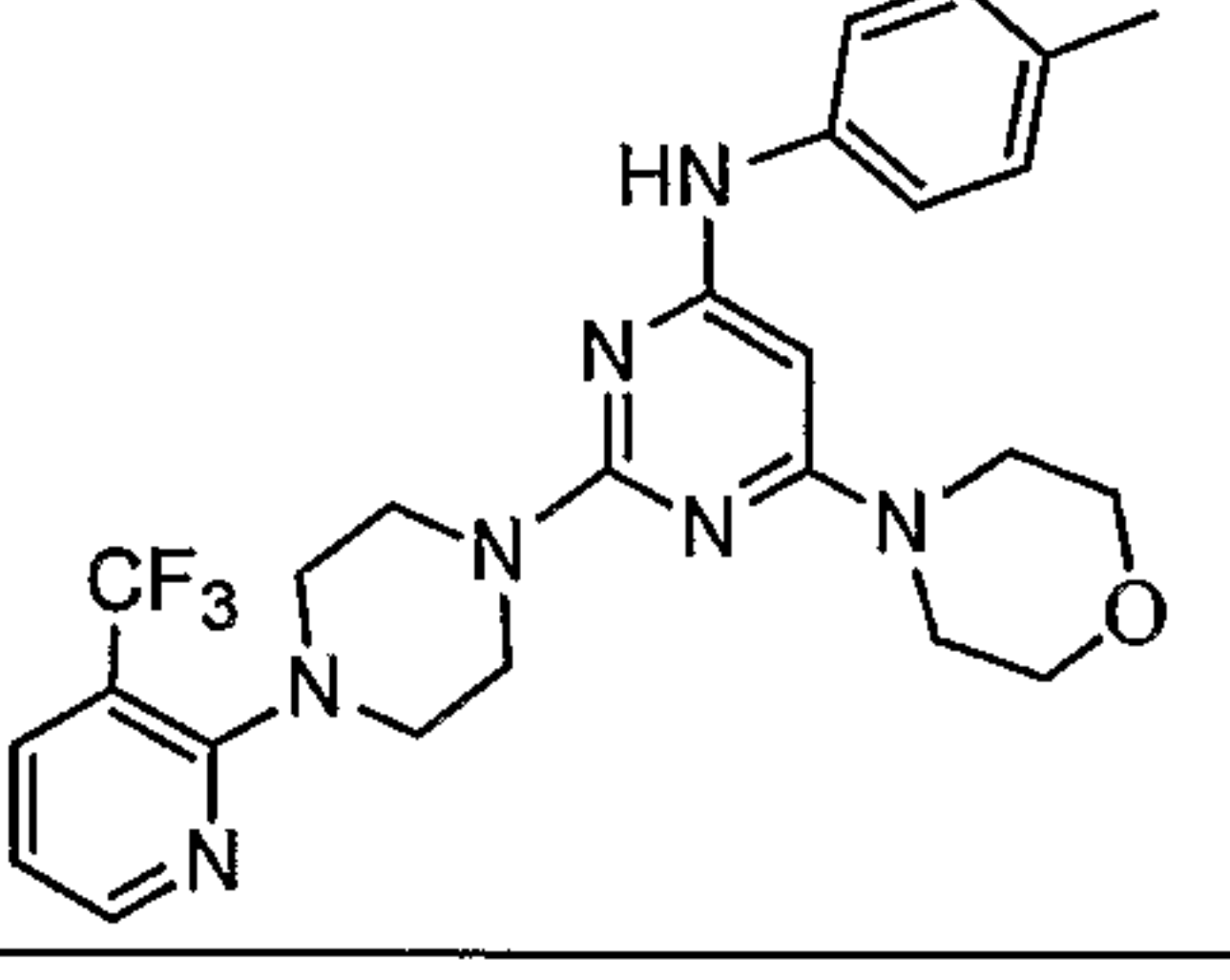
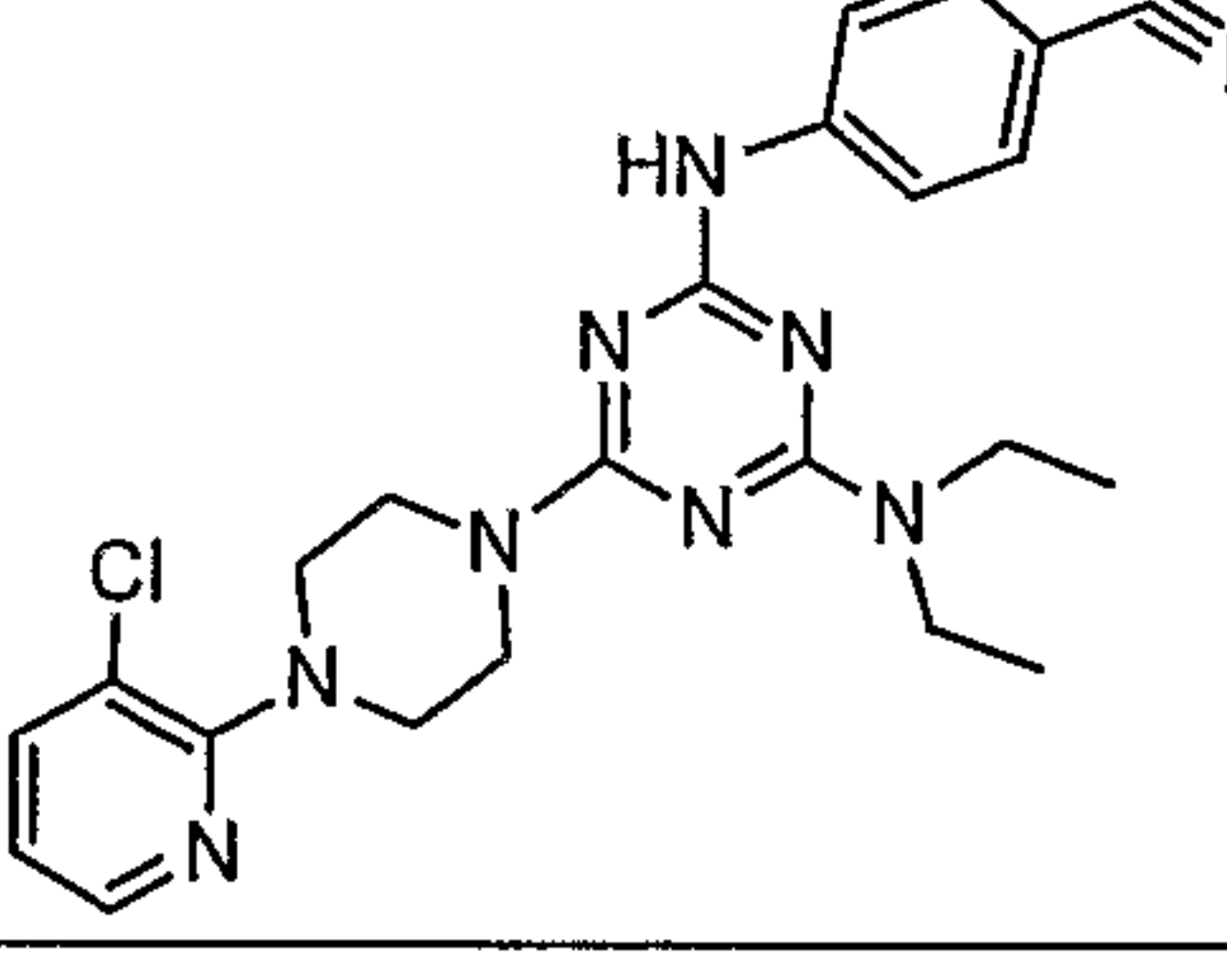
	Compound	Name	IC ₅₀	MS
72.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine	*	443.35
73.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-pyrrolidin-1-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine	*	455.17
74.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-methyl-N'-propyl-[1,3,5]triazine-2,4-diamine	*	457.19
75.		N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine	*	471.20
76.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N',N'-dimethyl-[1,3,5]triazine-2,4-diamine	*	429.16
77.		[4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-(2-methyl-pyrrolidin-1-yl)-[1,3,5]triazin-2-yl]-(3-fluoro-phenyl)-amine	*	469.19

	Compound	Name	IC ₅₀	MS
78.		{4-Azepan-1-yl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine	*	483.21
79.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-isopropyl-N'-methyl-[1,3,5]triazine-2,4-diamine	*	457.19
80.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-isopropyl-[1,3,5]triazine-2,4-diamine	*	471.20
81.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-propyl-[1,3,5]triazine-2,4-diamine	*	443.18
82.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-methyl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	450.22
83.		(4-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine	*	504.34

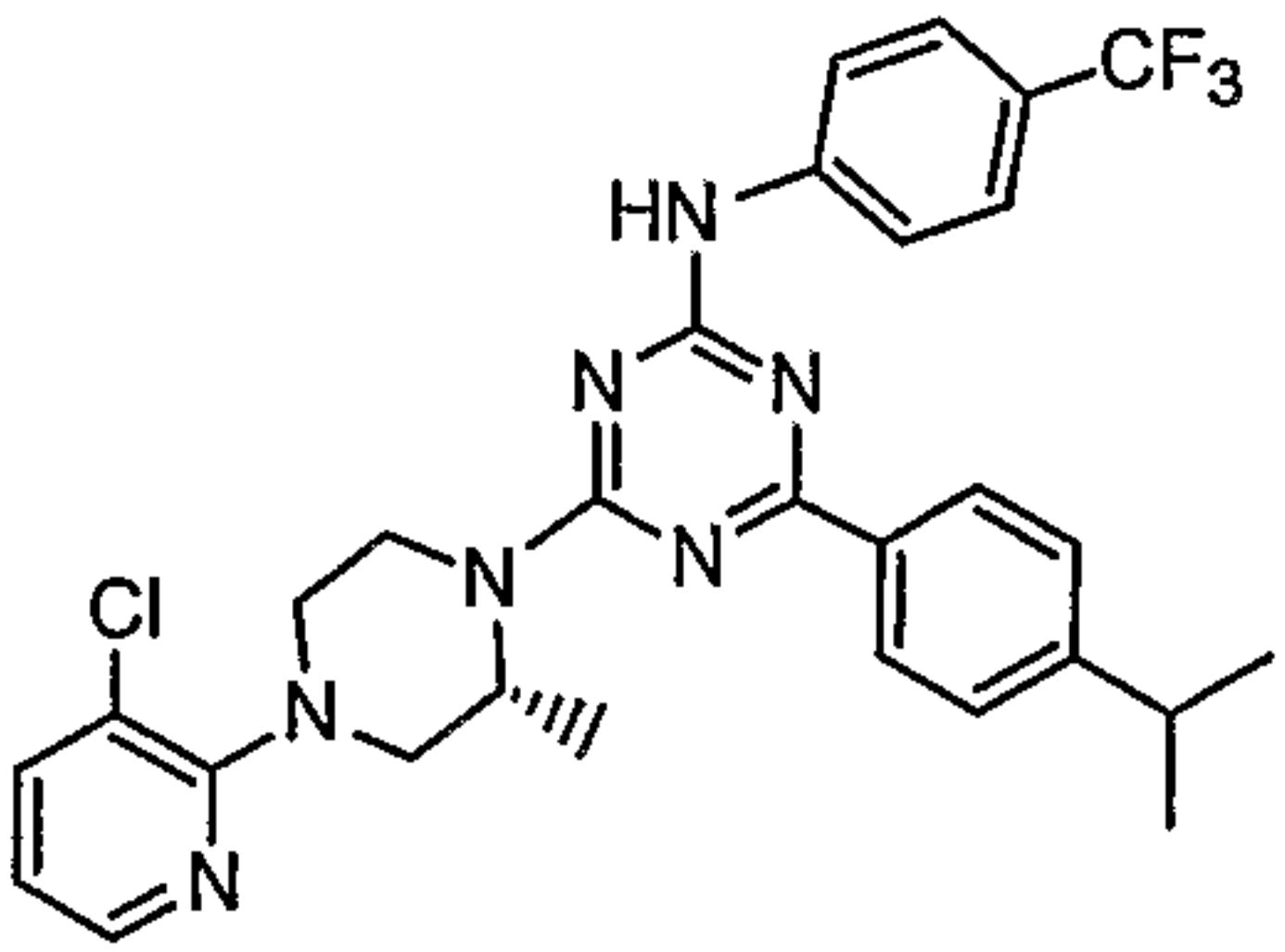
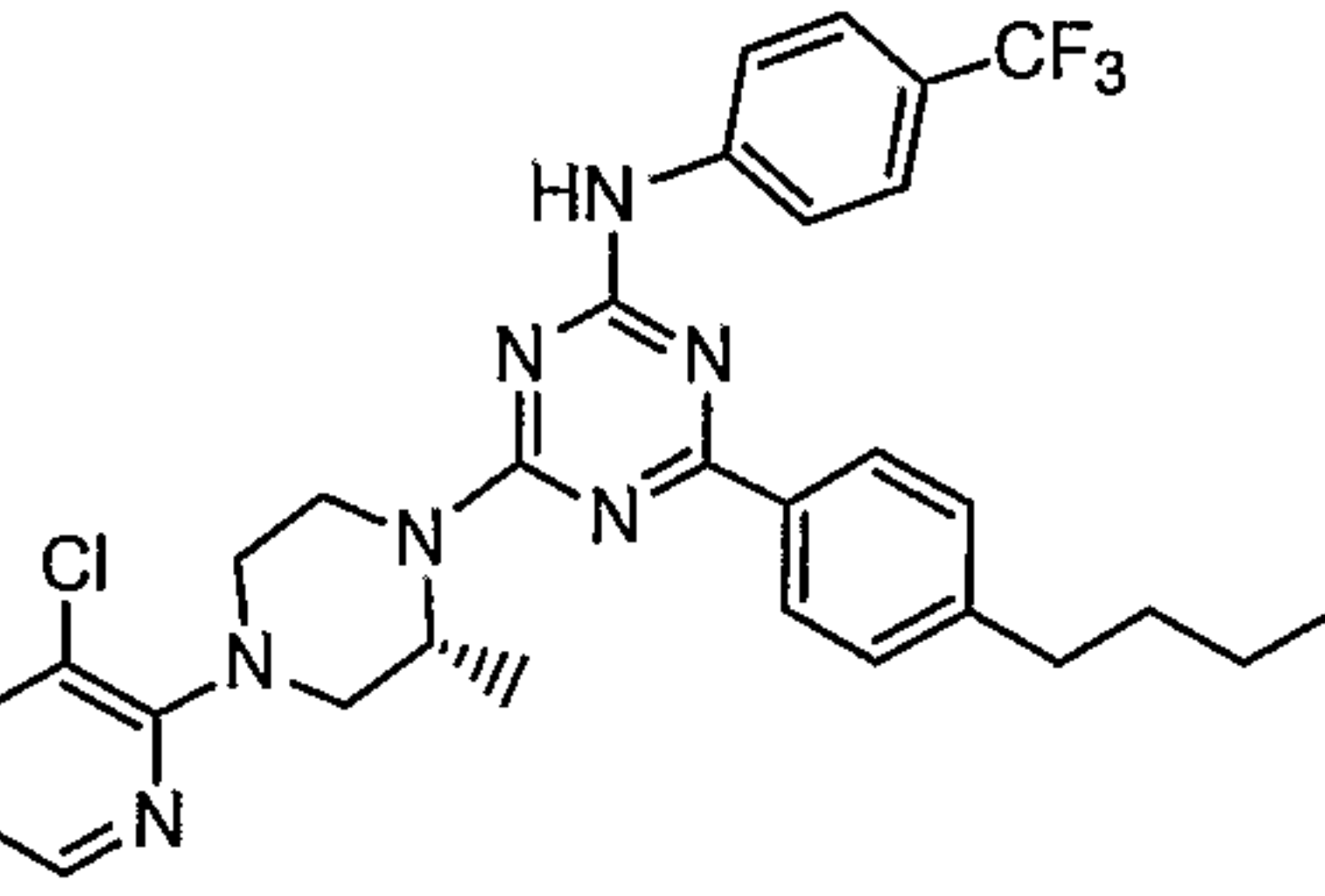
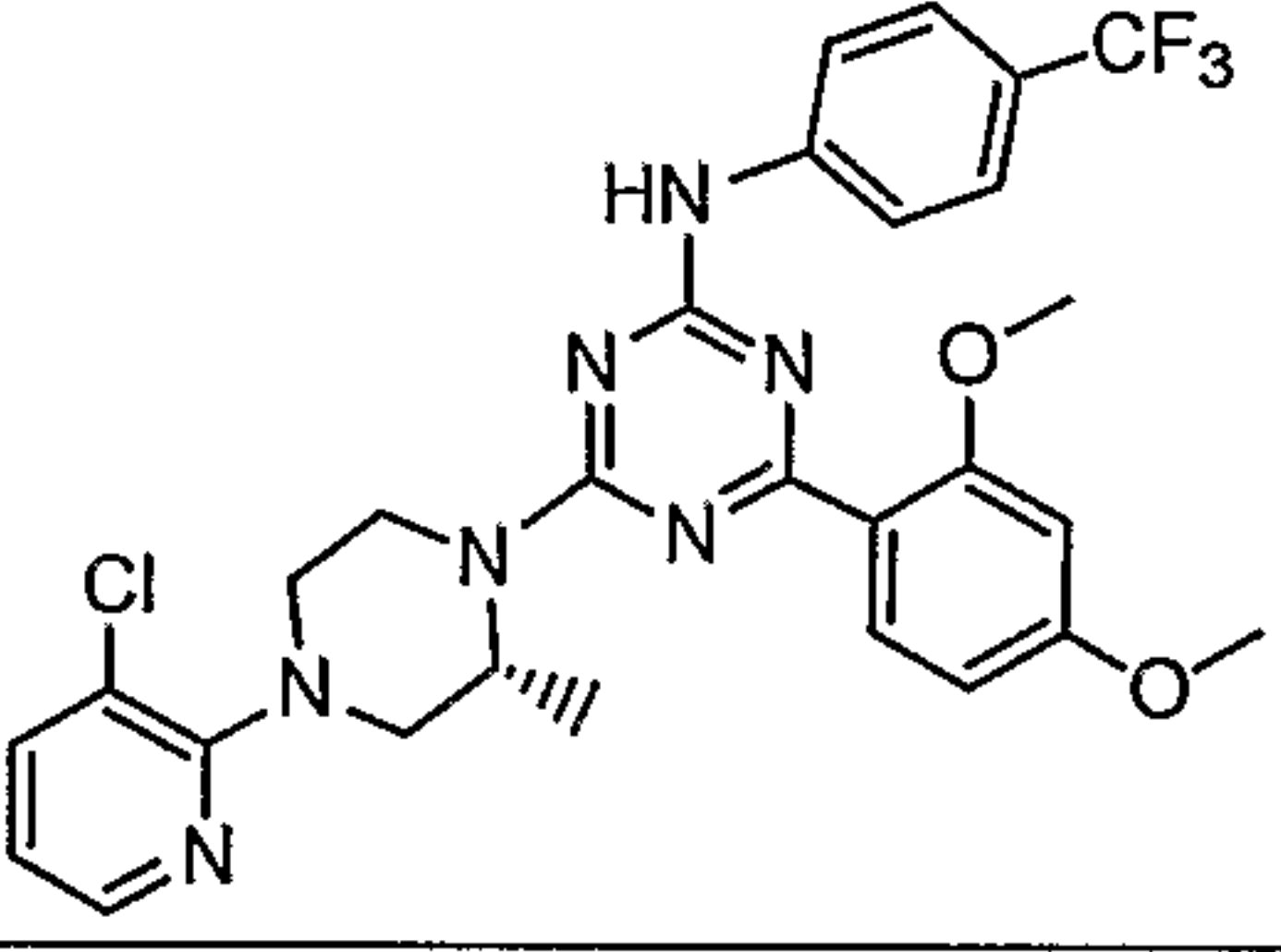
	Compound	Name	IC ₅₀	MS
84.		(3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine	*	520.33
85.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-o-tolyl-amine	*	500.36
86.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-m-tolyl-amine	*	500.36
87.		{4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-p-tolyl-amine	*	500.36
88.		(3-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine	*	516.36
89.		(4-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine	*	516.37

	Compound	Name	IC ₅₀	MS
90.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(4-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine	*	457.26
91.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3,4-difluoro-phenyl)-[1,3,5]triazine-2,4-diamine	*	475.27
92.		N-(3-Chloro-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N',N'-diethyl-[1,3,5]triazine-2,4-diamine	*	473.25
93.		6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-methoxy-phenyl)-[1,3,5]triazine-2,4-diamine	*	469.29
94.		N,N-Diethyl-N'-(4-fluoro-phenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	*	423.29
95.		N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	*	441.29

	Compound	Name	IC ₅₀	MS
96.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	521.31
97.		{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-phenyl-amine	*	453.28
98.		(4-Fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine	*	436.28
99.		N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R)	*	523.35
100.		6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3,4-difluoro-phenyl)-N',N'-diethyl-[1,3,5]triazine-2,4-diamine (R)	*	489.31
101.		{4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3,4-difluoro-phenyl)-amine (R)	*	503.28

Compound	Name	IC ₅₀	MS
102. 	N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R)	*	533.34
103. 	(3,4-Difluoro-phenyl)-{4-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine (R)	*	547.34
104. 	{4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine	*	485.29
105. 	(4-Fluoro-phenyl)-{6-morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine	*	504.31
106. 	{6-Morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-p-tolyl-amine	*	500.32
107. 	4-{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-diethylamino-[1,3,5]triazin-2-ylamino}-benzonitrile	*	449.26

	Compound	Name	IC ₅₀	MS
108.		N-(2,5-Dimethoxy-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine	*	450.31
109.		(3,4-Difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine	*	481.25
110.		{4-(3,4-Difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-methanol	*	467.13
111.		{2-Diethylaminomethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-(3,4-difluoro-phenyl)-amine	*	522.27
112.		(3,4-Difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine	*	536.25
113.		(3,4-Difluoro-phenyl)-{2-(2,6-dimethyl-morpholin-4-ylmethyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine	*	564.29

Compound	Name	IC ₅₀	MS
114. 	[4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(4-isopropyl-phenyl)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine	*	568
115. 	{4-(4-Butyl-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine	*	582
116. 	[4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2,4-dimethoxy-phenyl)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine	*	586

EXAMPLE 4

VR1-Transfected Cells and Membrane Preparations

This Example illustrates the preparation of VR1-transfected cells and VR1-containing
5 membrane preparations for use in capsaicin binding assays (Example 5).

A cDNA encoding full length human capsaicin receptor (SEQ ID NO:1, 2 or 3 of U.S. Patent No. 6,482,611) was subcloned in the plasmid pBK-CMV (Stratagene, La Jolla, CA) for recombinant expression in mammalian cells.

Human embryonic kidney (HEK293) cells were transfected with the pBK-CMV
10 expression construct encoding the full length human capsaicin receptor using standard methods. The transfected cells were selected for two weeks in media containing G418 (400 µg/ml) to obtain a pool of stably transfected cells. Independent clones were isolated from this pool by limiting dilution to obtain clonal stable cell lines for use in subsequent experiments.

15 For radioligand binding experiments, cells were seeded in T175 cell culture flasks in media without antibiotics and grown to approximately 90% confluency. The flasks were then

washed with PBS and harvested in PBS containing 5 mM EDTA. The cells were pelleted by gentle centrifugation and stored at -80°C until assayed.

Previously frozen cells were disrupted with the aid of a tissue homogenizer in ice-cold HEPES homogenization buffer (5mM KCl, 5.8mM NaCl, 0.75mM CaCl_2 , 2mM MgCl_2 , 320 mM sucrose, and 10 mM HEPES pH 7.4). Tissue homogenates were first centrifuged for 10 minutes at 1000 x g (4°C) to remove the nuclear fraction and debris, and then the supernatant from the first centrifugation is further centrifuged for 30 minutes at 35,000 x g (4°C) to obtain a partially purified membrane fraction. Membranes were resuspended in the HEPES homogenization buffer prior to the assay. An aliquot of this membrane homogenate was used to determine protein concentration via the Bradford method (BIO-RAD Protein Assay Kit, #500-0001, BIO-RAD, Hercules, CA).

EXAMPLE 5

Capsaicin Receptor Binding Assay

This Example illustrates a representative assay of capsaicin receptor binding that may be used to determine the binding affinity of compounds for the capsaicin (VR1) receptor.

Binding studies with [^3H] Resiniferatoxin (RTX) are carried out essentially as described by Szallasi and Blumberg (1992) *J. Pharmacol. Exp. Ther.* 262:883-888. In this protocol, non-specific RTX binding is reduced by adding bovine α_1 acid glycoprotein (100 μg per tube) after the binding reaction has been terminated.

[^3H] RTX (37 Ci/mmol) is synthesized by and obtained from the Chemical Synthesis and Analysis Laboratory, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD. [^3H] RTX may also be obtained from commercial vendors (e.g., Amersham Pharmacia Biotech, Inc.; Piscataway, NJ).

The membrane homogenate of Example 4 is centrifuged as before and resuspended to a protein concentration of 333 $\mu\text{g}/\text{ml}$ in homogenization buffer. Binding assay mixtures are set up on ice and contain [^3H]RTX (specific activity 2200 mCi/ml), 2 μl non-radioactive test compound, 0.25 mg/ml bovine serum albumin (Cohn fraction V), and 5×10^4 - 1×10^5 VR1-transfected cells. The final volume is adjusted to 500 μl (for competition binding assays) or 1,000 μl (for saturation binding assays) with the ice-cold HEPES homogenization buffer solution (pH 7.4) described above. Non-specific binding is defined as that occurring in the presence of 1 μM non-radioactive RTX (Alexis Corp.; San Diego, CA). For saturation

binding, [³H]RTX is added in the concentration range of 7-1,000 pM, using 1 to 2 dilutions. Typically 11 concentration points are collected per saturation binding curve.

Competition binding assays are performed in the presence of 60 pM [³H]RTX and various concentrations of test compound. The binding reactions are initiated by transferring
5 the assay mixtures into a 37°C water bath and are terminated following a 60 minute incubation period by cooling the tubes on ice. Membrane-bound RTX is separated from free, as well as any alpha₁-acid glycoprotein-bound RTX, by filtration onto WALLAC glass fiber filters (PERKIN-ELMER, Gaithersburg, MD) which were pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters are allowed to dry overnight then
10 counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT scintillation fluid.

Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values with the aid of the computer program FIT P (Biosoft, Ferguson, MO) as described by Szallasi, *et al.* (1993) *J. Pharmacol. Exp. Ther.* 266:678-683. Compounds
15 provided herein generally exhibit K_i values for capsaicin receptor of less than 1 μM, 100 nM, 50 nM, 25 nM, 10 nM, or 1nM in this assay.

EXAMPLE 6

Calcium Mobilization Assay

This Example illustrates representative calcium mobilization assays for use in
20 evaluating test compounds for agonist and antagonist activity.

Cells transfected with expression plasmids (as described in Example 4) and thereby expressing human capsaicin receptor are seeded and grown to 70-90% confluency in FALCON black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ). The culture medium is emptied from the 96 well plates and FLUO-3
25 AM calcium sensitive dye (Molecular Probes, Eugene, OR) is added to each well (dye solution: 1 mg FLUO-3 AM, 440 μL DMSO and 440 μl 20% pluronic acid in DMSO, diluted 1:250 in Krebs-Ringer HEPES (KRH) buffer (25 mM HEPES, 5 mM KCl, 0.96 mM NaH₂PO₄, 1 mM MgSO₄, 2 mM CaCl₂, 5 mM glucose, 1 mM probenecid, pH 7.4), 50 μl diluted solution per well). Plates are covered with aluminum foil and incubated at 37°C for
30 1-2 hours in an environment containing 5% CO₂. After the incubation, the dye is emptied from the plates, and the cells are washed once with KRH buffer, and resuspended in KRH buffer.

DETERMINATION CAPSAICIN EC₅₀

To measure the ability of a test compound to agonize or antagonize a calcium mobilization response in cells expressing capsaicin receptors to capsaicin or other vanilloid agonist, the EC₅₀ of the agonist capsaicin is first determined. An additional 20 µl of KRH buffer and 1 µl DMSO is added to each well of cells, prepared as described above. 100 µl capsaicin in KRH buffer is automatically transferred by the FLIPR instrument to each well. Capsaicin-induced calcium mobilization is monitored using either FLUOROSKAN ASCENT (Labsystems; Franklin, MA) or FLIPR (fluorometric imaging plate reader system; Molecular Devices, Sunnyvale, CA) instruments. Data obtained between 30 and 60 seconds after agonist application are used to generate an 8-point concentration response curve, with final capsaicin concentrations of 1 nM to 3 µM. KALEIDAGRAPH software (Synergy Software, Reading, PA) is used to fit the data to the equation:

$$y=a*(1/(1+(b/x)^c))$$

to determine the 50% excitatory concentration (EC₅₀) for the response. In this equation, y is the maximum fluorescence signal, x is the concentration of the agonist or antagonist (in this case, capsaicin), a is the E_{max}, b corresponds to the EC₅₀ value and c is the Hill coefficient.

DETERMINATION OF AGONIST ACTIVITY

Test compounds are dissolved in DMSO, diluted in KRH buffer, and immediately added to cells prepared as described above. 100 nM capsaicin (an approximate EC₉₀ concentration) is also added to cells in the same 96-well plate as a positive control. The final concentration of test compounds in the assay wells is between 0.1 nM and 5 µM.

The ability of a test compound to act as an agonist of the capsaicin receptor is determined by measuring the fluorescence response of cells expressing capsaicin receptors elicited by the compound as function of compound concentration. This data is fit as described above to obtain the EC₅₀, which is generally less than 1 micromolar, preferably less than 100 nM, and more preferably less than 10 nM. The extent of efficacy of each test compound is also determined by calculating the response elicited by a concentration of test compound (typically 1 µM) relative to the response elicited by 100 nM capsaicin. This value, called Percent of Signal (POS), is calculated by the following equation:

$$POS=100*\text{test compound response}/100\text{ nM capsaicin response}$$

This analysis provides quantitative assessment of both the potency and efficacy of test compounds as human capsaicin receptor agonists. Agonists of the human capsaicin receptor generally elicit detectable responses at concentrations less than 100 µM, or preferably at

concentrations less than 1 μM , or most preferably at concentrations less than 10 nM. Extent of efficacy at human capsaicin receptor is preferably greater than 30 POS, more preferably greater than 80 POS at a concentration of 1 μM . Certain agonists are essentially free of antagonist activity as demonstrated by the absence of detectable antagonist activity in the
5 assay described below at compound concentrations below 4 nM, more preferably at concentrations below 10 μM and most preferably at concentrations less than or equal to 100 μM .

DETERMINATION OF ANTAGONIST ACTIVITY

Test compounds are dissolved in DMSO, diluted in 20 μl KRH buffer so that the final
10 concentration of test compounds in the assay well is between 1 μM and 5 μM , and added to cells prepared as described above. The 96 well plates containing prepared cells and test compounds are incubated in the dark, at room temperature for 0.5 to 6 hours. It is important that the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response, 100 μl capsaicin in KRH buffer at twice the EC_{50} concentration determined as
15 described above is automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 μl and a final capsaicin concentration equal to the EC_{50} . The final concentration of test compounds in the assay wells is between 1 μM and 5 μM . Antagonists of the capsaicin receptor decrease this response by at least about 20%, preferably by at least about 50%, and most preferably by at least 80%, as compared to
20 matched control (*i.e.*, cells treated with capsaicin at twice the EC_{50} concentration in the absence of test compound), at a concentration of 10 micromolar or less, preferably 1 micromolar or less. The concentration of antagonist required to provide a 50% decrease, relative to the response observed in the presence of capsaicin and without antagonist, is the IC_{50} for the antagonist, and is preferably below 1 micromolar, 100 nanomolar, 10 nanomolar
25 or 1 nanomolar.

Certain preferred VR1 modulators are antagonists that are essentially free of agonist activity as demonstrated by the absence of detectable agonist activity in the assay described above at compound concentrations below 4 nM, more preferably at concentrations below 10 μM and most preferably at concentrations less than or equal to 100 μM .

EXAMPLE 7

Microsomal *in vitro* half-life

This Example illustrates the evaluation of compound half-life values ($t_{1/2}$ values) using a representative liver microsomal half-life assay.

5 Pooled human liver microsomes are obtained from XenoTech LLC (Kansas City, KS). Such liver microsomes may also be obtained from In Vitro Technologies (Baltimore, MD) or Tissue Transformation Technologies (Edison, NJ). Six test reactions are prepared, each containing 25 μ l microsomes, 5 μ l of a 100 μ M solution of test compound, and 399 μ l 0.1 M phosphate buffer (19 mL 0.1 M NaH_2PO_4 , 81 mL 0.1 M Na_2HPO_4 , adjusted to pH 7.4
10 with H_3PO_4). A seventh reaction is prepared as a positive control containing 25 μ l microsomes, 399 μ l 0.1 M phosphate buffer, and 5 μ l of a 100 μ M solution of a compound with known metabolic properties (*e.g.*, DIAZEPAM or CLOZAPINE). Reactions are preincubated at 39°C for 10 minutes.

CoFactor Mixture is prepared by diluting 16.2 mg NADP and 45.4 mg Glucose-6-phosphate in 4 mL 100 mM MgCl_2 . Glucose-6-phosphate dehydrogenase solution is prepared
15 by diluting 214.3 μ l glucose-6-phosphate dehydrogenase suspension (Roche Molecular Biochemicals; Indianapolis, IN) into 1285.7 μ l distilled water. 71 μ l Starting Reaction Mixture (3 mL CoFactor Mixture; 1.2 mL Glucose-6-phosphate dehydrogenase solution) is added to 5 of the 6 test reactions and to the positive control. 71 μ l 100 mM MgCl_2 is added
20 to the sixth test reaction, which is used as a negative control. At each time point (0, 1, 3, 5, and 10 minutes), 75 μ l of each reaction mix is pipetted into a well of a 96-well deep-well plate containing 75 μ l ice-cold acetonitrile. Samples are vortexed and centrifuged 10 minutes at 3500 rpm (Sorval T 6000D centrifuge, H1000B rotor). 75 μ l of supernatant from each reaction is transferred to a well of a 96-well plate containing 150 μ l of a 0.5 μ M solution of a
25 compound with a known LCMS profile (internal standard) per well. LCMS analysis of each sample is carried out and the amount of unmetabolized test compound is measured as AUC, compound concentration vs. time is plotted, and the $t_{1/2}$ value of the test compound is extrapolated.

Preferred compounds provided herein exhibit *in vitro* $t_{1/2}$ values of greater than 10
30 minutes and less than 4 hours, preferably between 30 minutes and 1 hour, in human liver microsomes.

EXAMPLE 8

MDCK Toxicity Assay

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 μ L of test compound is added to each well of a clear bottom 96-well plate (PACKARD, Meriden, CT) to give final concentration of compound in the assay of 10
5 micromolar, 100 micromolar or 200 micromolar. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a
10 concentration of 0.1×10^6 cells/ml with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μ L of diluted cells is added to each well, except for five standard curve control wells that contain 100 μ L of warm medium without cells. The plate is then incubated at 37°C under 95% O₂, 5% CO₂ for 2 hours with constant shaking. After incubation, 50 μ L of mammalian cell lysis solution (from the
15 PACKARD (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit) is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The ATP-LITE-M Luminescent ATP detection kit is generally used according to the
20 manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μ L of serially diluted PACKARD
25 standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM and 12.5 nM. PACKARD substrate solution (50 μ L) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil
30 and placing in the dark for 10 minutes. Luminescence is then measured at 22°C using a luminescence counter (e.g., PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μ M of a preferred test

compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μ M concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

5

EXAMPLE 9

Dorsal Root Ganglion Cell Assay

This Example illustrates a representative dorsal root ganglion cell assay for evaluating VR1 antagonist or agonist activity of a compound.

10 DRG are dissected from neonatal rats, dissociated and cultured using standard methods (Aguayo and White (1992) *Brain Research* 570:61-67). After 48 hour incubation, cells are washed once and incubated for 30-60 minutes with the calcium sensitive dye Fluo 4 AM (2.5-10 μ g/ml; TefLabs, Austin, TX). Cells are then washed once. Addition of capsaicin to the cells results in a VR1-dependent increase in intracellular calcium levels which is
15 monitored by a change in Fluo-4 fluorescence with a fluorometer. Data are collected for 60-180 seconds to determine the maximum fluorescent signal.

For antagonist assays, various concentrations of compound are added to the cells. Fluorescent signal is then plotted as a function of compound concentration to identify the concentration required to achieve a 50% inhibition of the capsaicin-activated response, or
20 IC_{50} . Antagonists of the capsaicin receptor preferably have an IC_{50} below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

For agonist assays, various concentrations of compound are added to the cells without the addition of capsaicin. Compounds that are capsaicin receptor agonists result in a VR1-dependent increase in intracellular calcium levels which is monitored by a change in Fluo-4
25 fluorescence with a fluorometer. The EC_{50} , or concentration required to achieve 50% of the maximum signal for a capsaicin-activated response, is preferably below 1 micromolar, below 100 nanomolar or below 10 nanomolar.

EXAMPLE 10

30 Animal Models for Determining Pain Relief

This Example illustrates representative methods for assessing the degree of pain relief provided by a compound.

A. Pain Relief Testing

The following methods may be used to assess pain relief.

MECHANICAL ALLODYNIA

Mechanical allodynia (an abnormal response to an innocuous stimulus) is assessed essentially as described by Chaplan *et al.* (1994) *J. Neurosci. Methods* 53:55-63 and Tal and Eliav (1998) *Pain* 64(3):511-518. A series of von Frey filaments of varying rigidity (typically 8-14 filaments in a series) are applied to the plantar surface of the hind paw with just enough force to bend the filament. The filaments are held in this position for no more than three seconds or until a positive allodynic response is displayed by the rat. A positive allodynic response consists of lifting the affected paw followed immediately by licking or shaking of the paw. The order and frequency with which the individual filaments are applied are determined by using Dixon up-down method. Testing is initiated with the middle hair of the series with subsequent filaments being applied in consecutive fashion, ascending or descending, depending on whether a negative or positive response, respectively, is obtained with the initial filament.

Compounds are effective in reversing or preventing mechanical allodynia-like symptoms if rats treated with such compounds require stimulation with a Von Frey filament of higher rigidity strength to provoke a positive allodynic response as compared to control untreated or vehicle treated rats. Alternatively, or in addition, testing of an animal in chronic pain may be done before and after compound administration. In such an assay, an effective compound results in an increase in the rigidity of the filament needed to induce a response after treatment, as compared to the filament that induces a response before treatment or in an animal that is also in chronic pain but is left untreated or is treated with vehicle. Test compounds are administered before or after onset of pain. When a test compound is administered after pain onset, testing is performed 10 minutes to three hours after administration.

MECHANICAL HYPERALGESIA

Mechanical hyperalgesia (an exaggerated response to painful stimulus) is tested essentially as described by Koch *et al.* (1996) *Analgesia* 2(3):157-164. Rats are placed in individual compartments of a cage with a warmed, perforated metal floor. Hind paw withdrawal duration (*i.e.*, the amount of time for which the animal holds its paw up before placing it back on the floor) is measured after a mild pinprick to the plantar surface of either hind paw.

Compounds produce a reduction in mechanical hyperalgesia if there is a statistically significant decrease in the duration of hindpaw withdrawal. Test compound may be administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

5 THERMAL HYPERALGESIA

Thermal hyperalgesia (an exaggerated response to noxious thermal stimulus) is measured essentially as described by Hargreaves *et al.* (1988) *Pain*. 32(1):77-88. Briefly, a constant radiant heat source is applied the animals' plantar surface of either hind paw. The time to withdrawal (*i.e.*, the amount of time that heat is applied before the animal moves its
10 paw), otherwise described as thermal threshold or latency, determines the animal's hind paw sensitivity to heat.

Compounds produce a reduction in thermal hyperalgesia if there is a statistically significant increase in the time to hindpaw withdrawal (*i.e.*, the thermal threshold to response or latency is increased). Test compound may be administered before or after onset of pain.
15 For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

B. Pain Models

Pain may be induced using any of the following methods, to allow testing of analgesic efficacy of a compound. In general, compounds provided herein result in a statistically
20 significant reduction in pain as determined by at least one of the previously described testing methods, using male SD rats and at least one of the following models.

ACUTE INFLAMMATORY PAIN MODEL

Acute inflammatory pain is induced using the carrageenan model essentially as described by Field *et al.* (1997) *Br. J. Pharmacol.* 121(8):1513-1522. 100-200 μ l of 1-2%
25 carrageenan solution is injected into the rats' hind paw. Three to four hours following injection, the animals' sensitivity to thermal and mechanical stimuli is tested using the methods described above. A test compound (0.01 to 50 mg/kg) is administered to the animal, prior to testing, or prior to injection of carrageenan. The compound can be administered orally or through any parenteral route, or topically on the paw. Compounds that relieve pain
30 in this model result in a statistically significant reduction in mechanical allodynia and/or thermal hyperalgesia.

CHRONIC INFLAMMATORY PAIN MODEL

Chronic inflammatory pain is induced using one of the following protocols:

1. Essentially as described by Bertorelli *et al.* (1999) *Br. J. Pharmacol.* 128(6):1252-1258, and Stein *et al.* (1998) *Pharmacol. Biochem. Behav.* 31(2):455-51, 200 μ l Complete Freund's Adjuvant (0.1 mg heat killed and dried *M. Tuberculosis*) is injected to the rats' hind paw: 100 μ l into the dorsal surface and 100 μ l into the plantar surface.
2. Essentially as described by Abbadie *et al.* (1994) *J Neurosci.* 14(10):5865-5871 rats are injected with 150 μ l of CFA (1.5 mg) in the tibio-tarsal joint.

Prior to injection with CFA in either protocol, an individual baseline sensitivity to mechanical and thermal stimulation of the animals' hind paws is obtained for each experimental animal.

Following injection of CFA, rats are tested for thermal hyperalgesia, mechanical allodynia and mechanical hyperalgesia as described above. To verify the development of symptoms, rats are tested on days 5, 6, and 7 following CFA injection. On day 7, animals are treated with a test compound, morphine or vehicle. An oral dose of morphine of 1-5 mg/kg is suitable as positive control. Typically, a dose of 0.01-50 mg/kg of test compound is used. Compounds can be administered as a single bolus prior to testing or once or twice or three times daily, for several days prior to testing. Drugs are administered orally or through any parenteral route, or applied topically to the animal.

Results are expressed as Percent Maximum Potential Efficacy (MPE). 0% MPE is defined as analgesic effect of vehicle, 100% MPE is defined as an animal's return to pre-CFA baseline sensitivity. Compounds that relieve pain in this model result in a MPE of at least 30%.

CHRONIC NEUROPATHIC PAIN MODEL

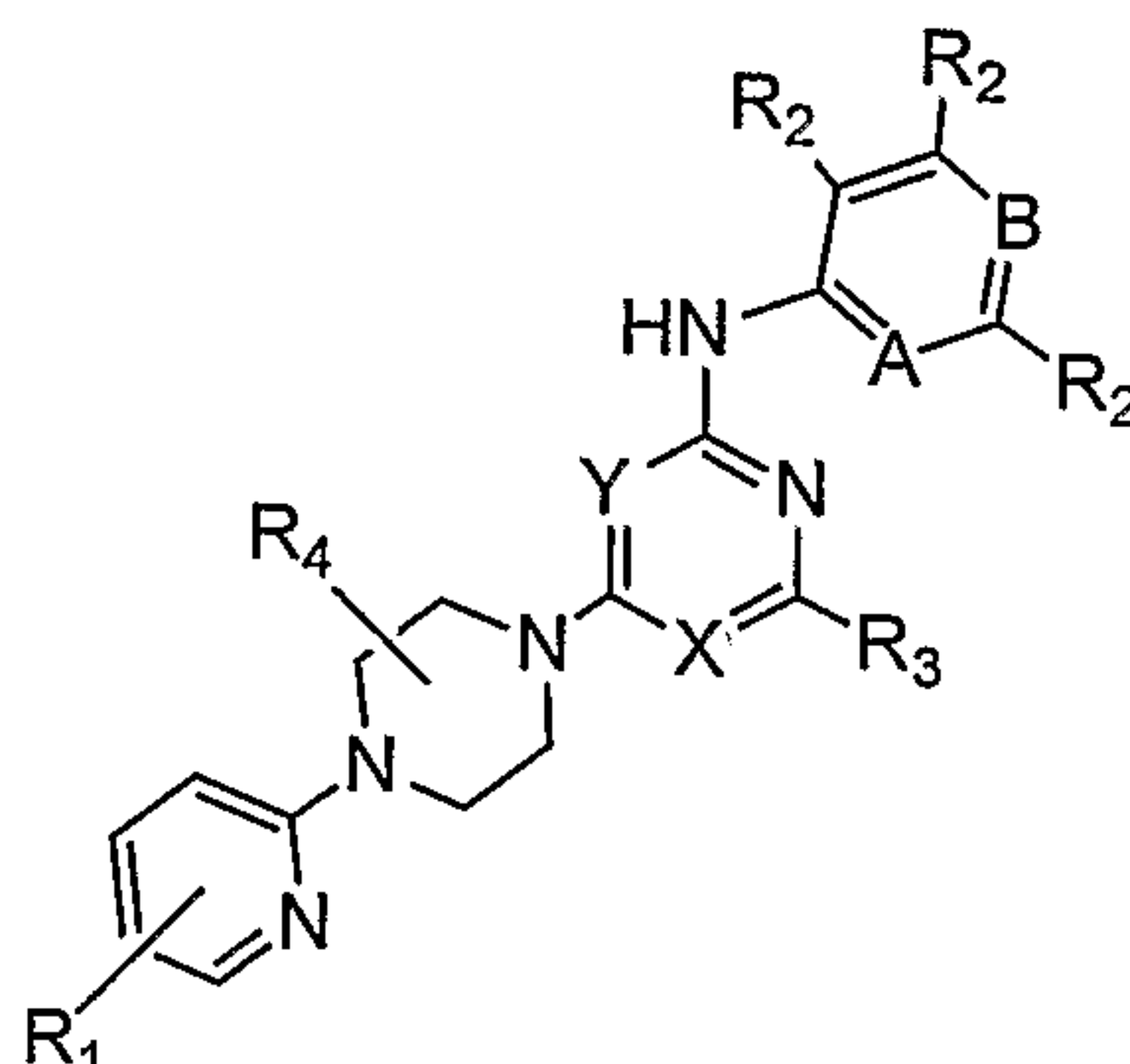
Chronic neuropathic pain is induced using the chronic constriction injury (CCI) to the rat's sciatic nerve essentially as described by Bennett and Xie (1988) *Pain* 33:87-107. Rats are anesthetized (*e.g.* with an intraperitoneal dose of 50-65 mg/kg pentobarbital with additional doses administered as needed). The lateral aspect of each hind limb is shaved and disinfected. Using aseptic technique, an incision is made on the lateral aspect of the hind limb at the mid thigh level. The biceps femoris is bluntly dissected and the sciatic nerve is exposed. On one hind limb of each animal, four loosely tied ligatures are made around the sciatic nerve approximately 1-2 mm apart. On the other side the sciatic nerve is not ligated

and is not manipulated. The muscle is closed with continuous pattern and the skin is closed with wound clips or sutures. Rats are assessed for mechanical allodynia, mechanical hyperalgesia and thermal hyperalgesia as described above.

5 Compounds that relieve pain in this model result in a statistically significant reduction in mechanical allodynia, mechanical hyperalgesia and/or thermal hyperalgesia when administered (0.01-50 mg/kg, orally, parenterally or topically) immediately prior to testing as a single bolus, or for several days: once or twice or three times daily prior to testing.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A and B are independently CR₂ or N;

X and Y are independently CR_x or N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

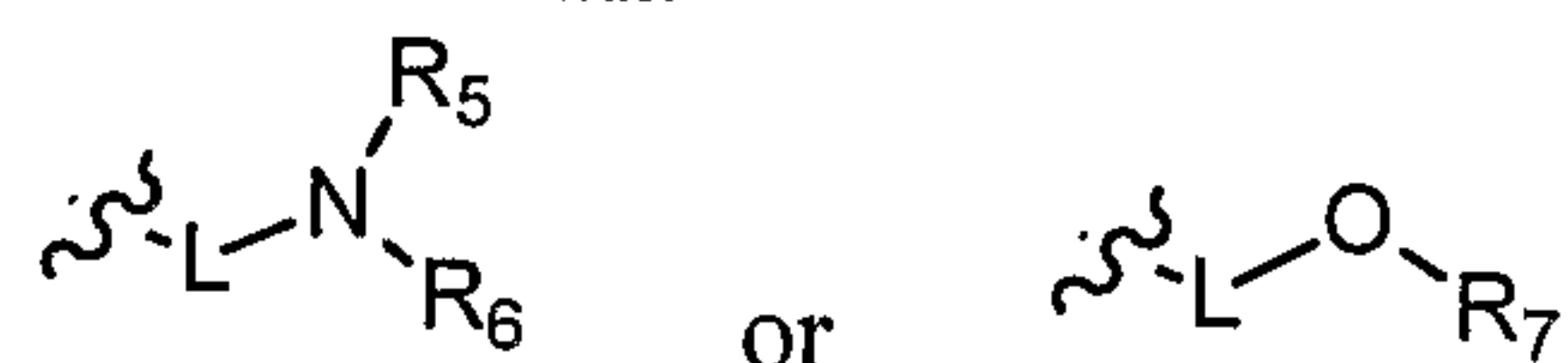
R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, -COOH, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is:

- (i) independently chosen from hydrogen, hydroxy, amino, cyano, halogen, C₁-C₆haloalkyl, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl; or
- (ii) taken together with an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen, oxo and C₁-C₆alkyl;

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl; and
- (iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl, such that neither R₅ nor R₆ is phenyl or pyridyl if L is a bond; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

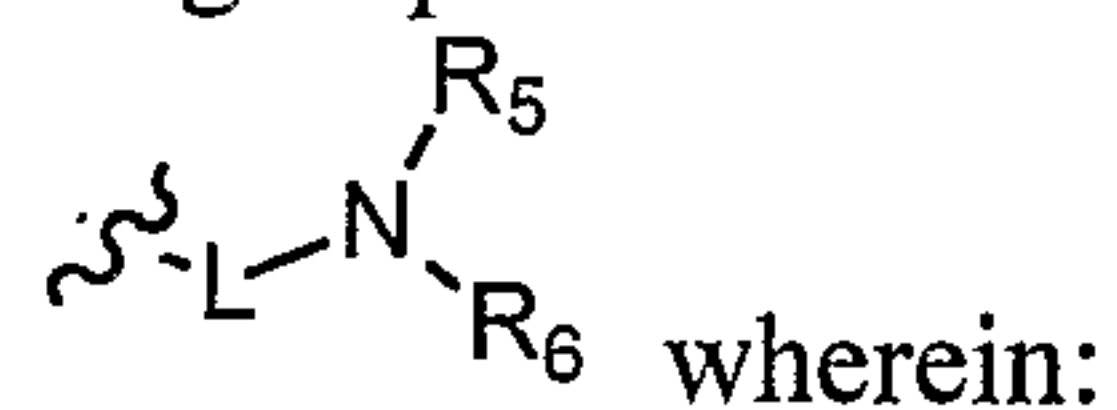
R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl.

2. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₁ represents from 0 to 2 substituents independently chosen from halogen, amino, cyano, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

3. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₁ represents one substituent located *ortho* to the point of attachment.

4. A compound or pharmaceutically acceptable form thereof according to claim 3, wherein R₁ is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl.

5. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₃ is a group of the formula:



L is a single covalent bond or C₁-C₄alkylene; and

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or

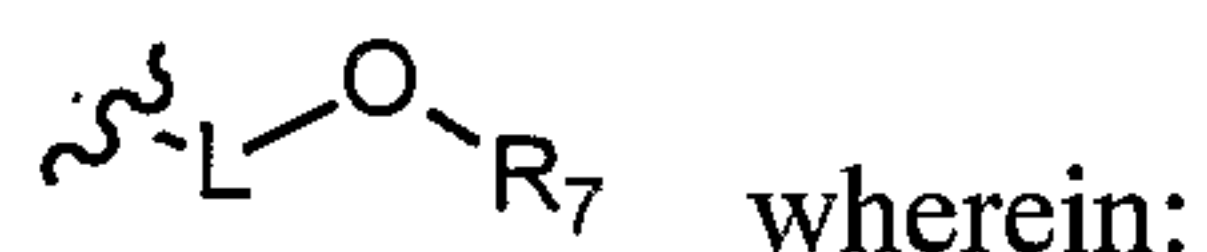
(b) taken together to form a 5- to 7-membered heterocycloalkyl;

wherein each of which alkyl, alkenyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, oxo, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₄alkyl)amino.

6. A compound or pharmaceutically acceptable form thereof according to claim 5, wherein R₃ is di(C₁-C₄alkyl)aminoC₀-C₂alkyl.

7. A compound or pharmaceutically acceptable form thereof according to claim 5, wherein R₃ is pyrrolidinylC₀-C₂alkyl, morpholinylC₀-C₂alkyl, piperidinylC₀-C₂alkyl, piperazinylC₀-C₂alkyl or azepanylC₀-C₂alkyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, amino, hydroxy and C₁-C₄alkyl.

8. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein R₃ is a group of the formula:



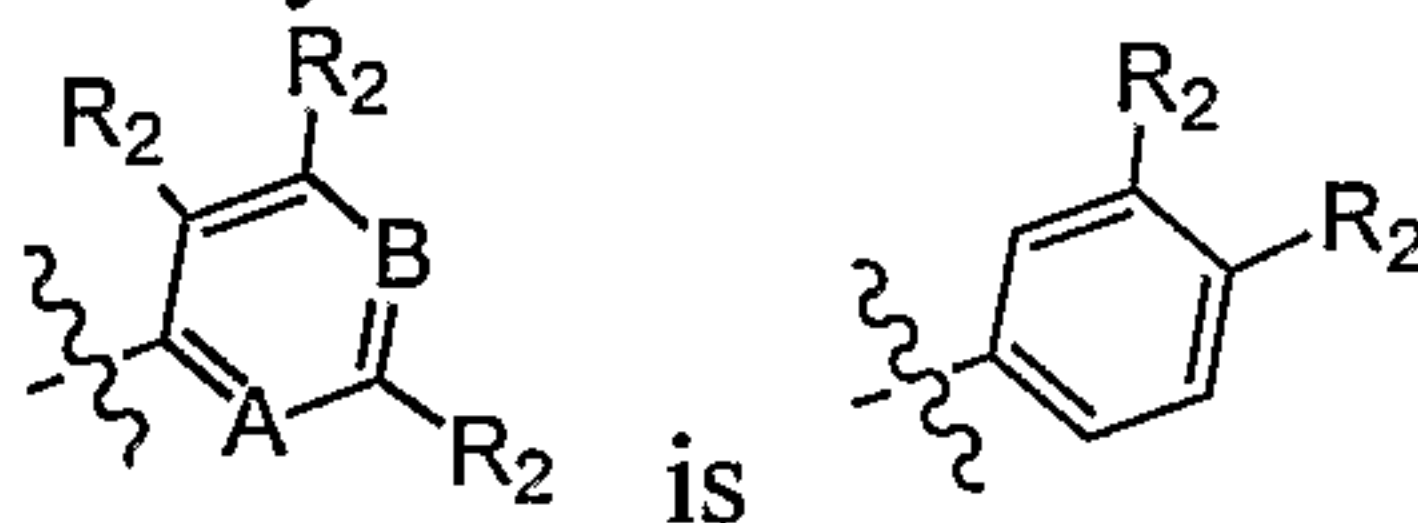
L is a single covalent bond or C₁-C₄alkylene; and

R₇ is hydrogen, C₁-C₆alkyl or phenylC₀-C₆alkyl, wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, cyano, amino, C₁-C₄alkyl, C₁-C₆haloalkyl and C₁-C₆alkoxy.

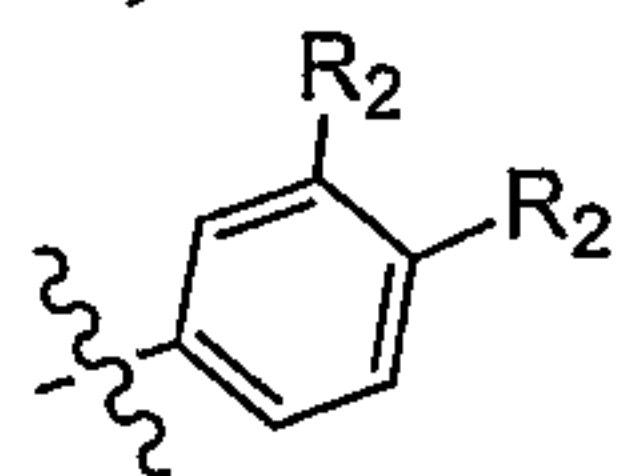
9. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein each R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

10. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein A and B are CR₂.

11. A compound or pharmaceutically acceptable form thereof according to claim 10, wherein the group represented by:



12. A compound or pharmaceutically acceptable form thereof according to claim 11, wherein:

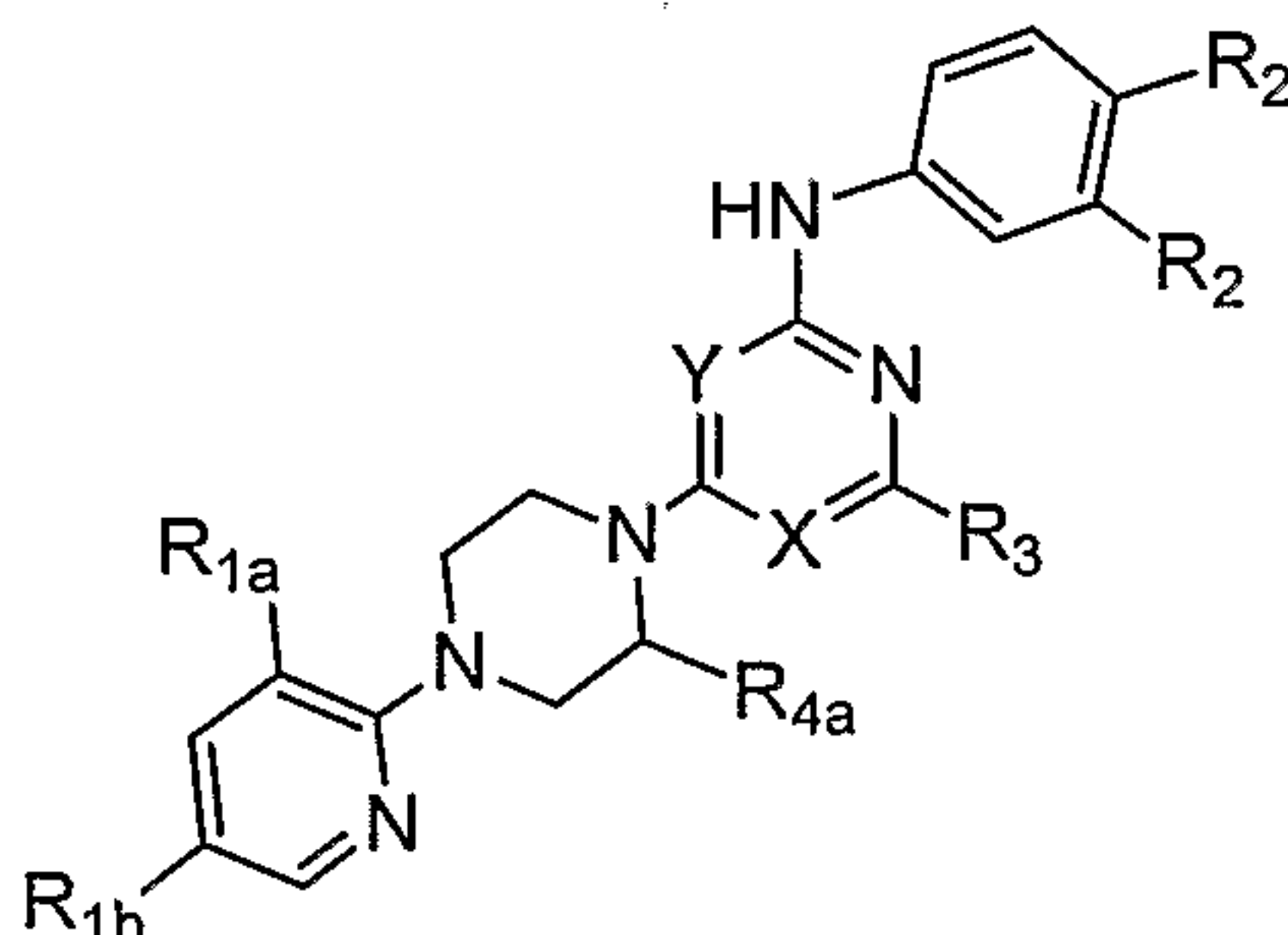


is selected from: phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, *para*-tolyl, *meta*-tolyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-*tert*-butylphenyl, 3-*tert*-butylphenyl, 4-cyanophenyl, 3-cyanophenyl, and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl.

13. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein X is N.

14. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein Y is N.

15. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein the compound has the formula:



wherein:

R_{1a} is halogen, amino, cyano, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)sulfonamido;

R_{1b} is hydrogen, halogen, amino, hydroxy, cyano, -COOH, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₆hydroxyalkyl or C₁-C₄haloalkyl; and

R_{4a} is hydrogen or methyl.

16. A compound or pharmaceutically acceptable form thereof according to claim 15, wherein:

R_{1a} is fluoro, chloro, cyano, methyl or trifluoromethyl;

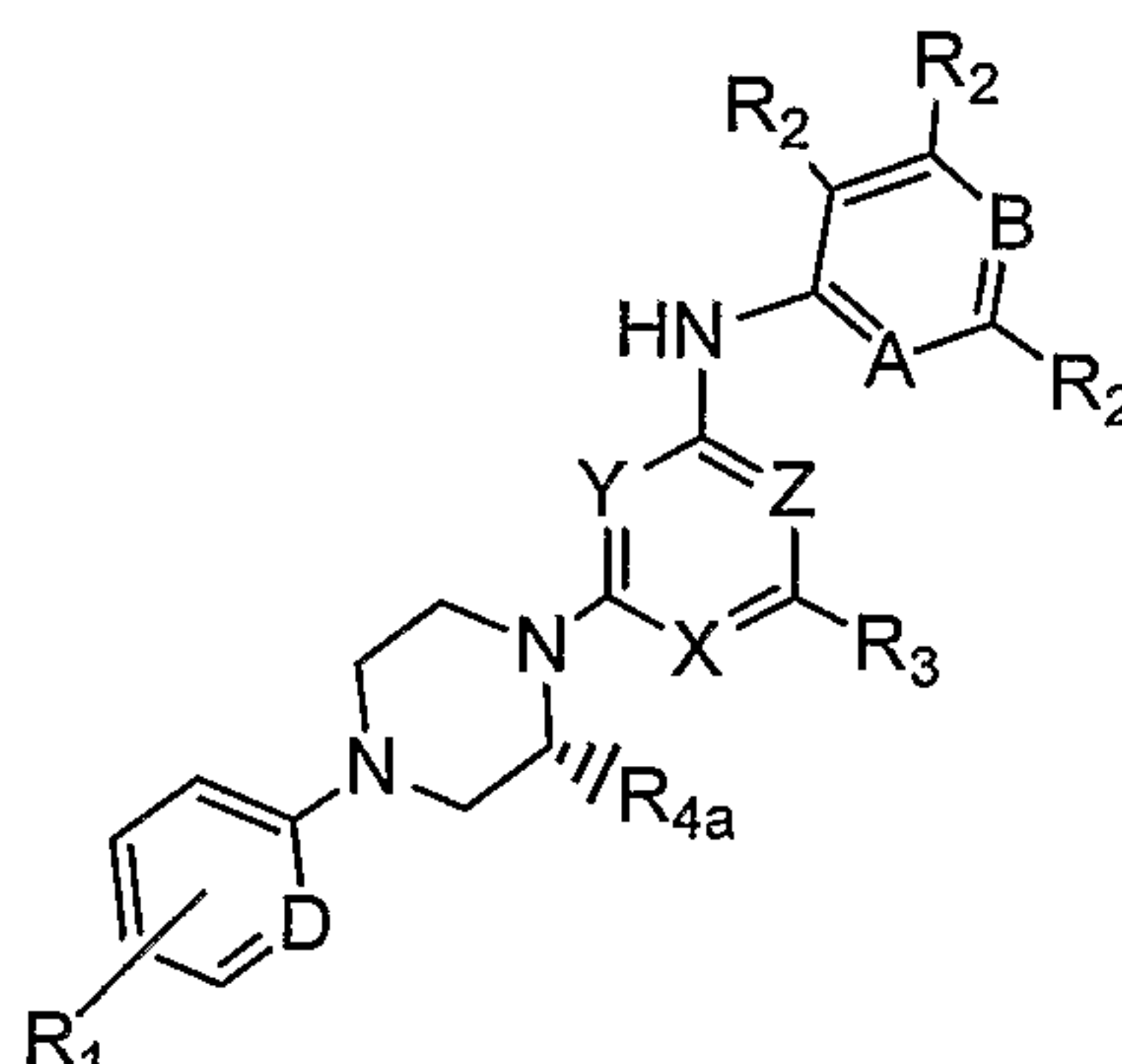
each R₂ is independently chosen from hydrogen, halogen, cyano and C₁-C₄haloalkyl; and

R₃ is mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, C₂-C₄alkyl ether, pyrrolidinylC₀-C₂alkyl, morpholinylC₀-C₂alkyl, piperidinylC₀-C₂alkyl, piperazinylC₀-C₂alkyl or benzyloxyC₀-

C₂alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, cyano, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₆alkyl)amino.

17. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein the compound exhibits no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism.

18. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A and B are independently CR₂ or N;

D is CH or N;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₁ represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, -COOH, aminocarbonyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

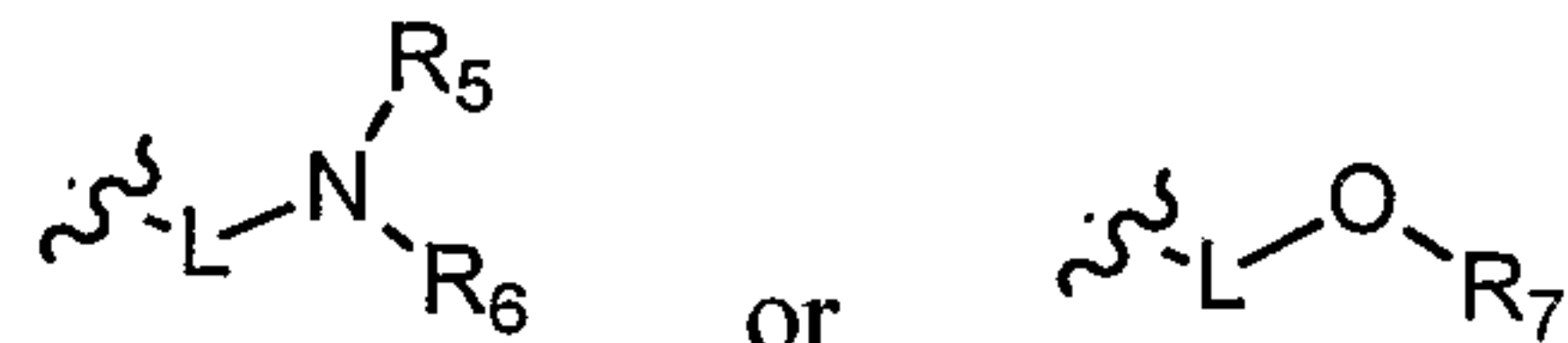
Each R₂ is:

(i) independently chosen from hydrogen, hydroxy, amino, cyano, nitro, halogen, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₆alkyl ether, C₁-C₆alkoxycarbonyl, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl; or

(ii) taken together with an adjacent R₂ to form a fused 5- to 10-membered carbocyclic or heterocyclic group that is substituted with from 0 to 3 substituents independently chosen from halogen, oxo and C₁-C₆alkyl;

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen, cyano and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;
- and
- (iii) groups of the formula:



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
- (b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted on from 0 to 3 carbon atoms with substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R_{4a} is methyl or C₁haloalkyl.

19. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein D is N.

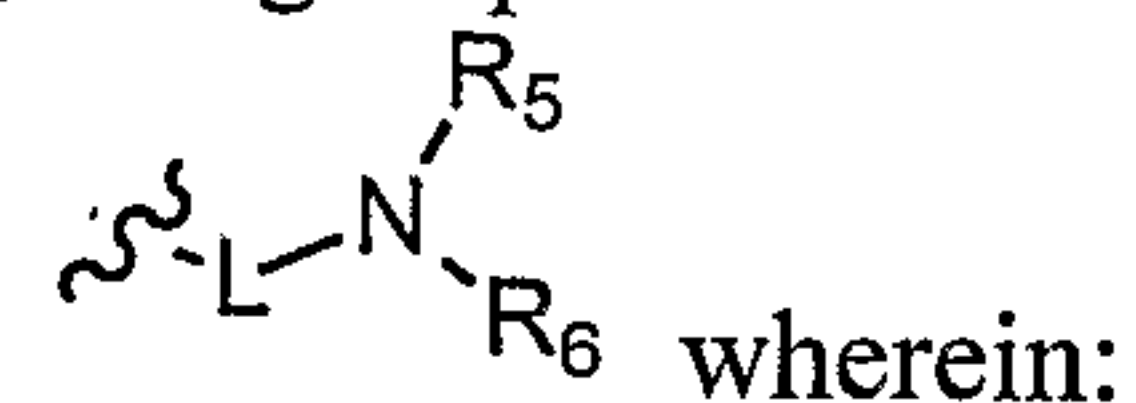
20. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein Z is N.

21. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₁ represents from 0 to 2 substituents independently chosen from halogen, amino, cyano, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

22. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₁ represents one substituent located *ortho* to the point of attachment.

23. A compound or pharmaceutically acceptable form thereof according to claim 22, wherein R₁ is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl.

24. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₃ is a group of the formula:



L is a single covalent bond or C₁-C₄alkylene; and

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₆alkyl and C₁-C₆alkenyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl;

wherein each of which alkyl, alkenyl and heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, amino, hydroxy, oxo, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₄alkyl)amino.

25. A compound or pharmaceutically acceptable form thereof according to claim 24, wherein R₃ is di(C₁-C₄alkyl)aminoC₀-C₂alkyl.

26. A compound or pharmaceutically acceptable form thereof according to claim 24, wherein R₃ is pyrrolidinylC₀-C₂alkyl, morpholinylC₀-C₂alkyl, piperidinylC₀-C₂alkyl, piperazinylC₀-C₂alkyl or azepanylC₀-C₂alkyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, amino, hydroxy and C₁-C₄alkyl.

27. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₃ is a group of the formula:



L is a single covalent bond or C₁-C₄alkylene; and

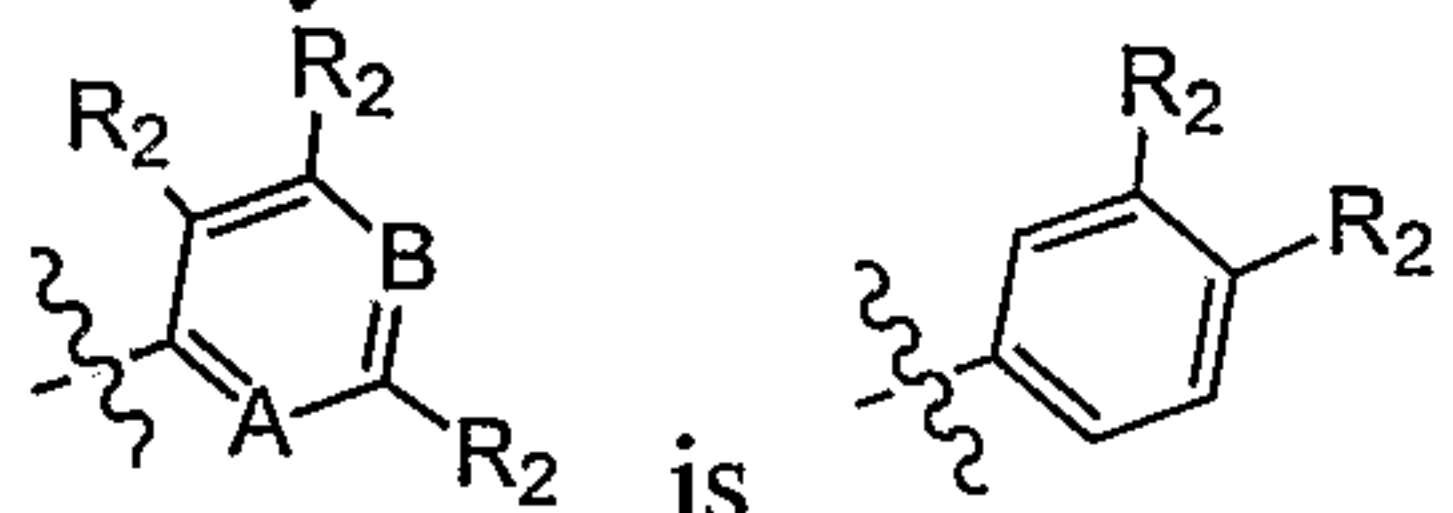
R₇ is hydrogen, C₁-C₆alkyl or phenylC₀-C₆alkyl, wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, cyano, amino, C₁-C₄alkyl, C₁-C₆haloalkyl and C₁-C₆alkoxy.

28. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein each R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆haloalkoxy,

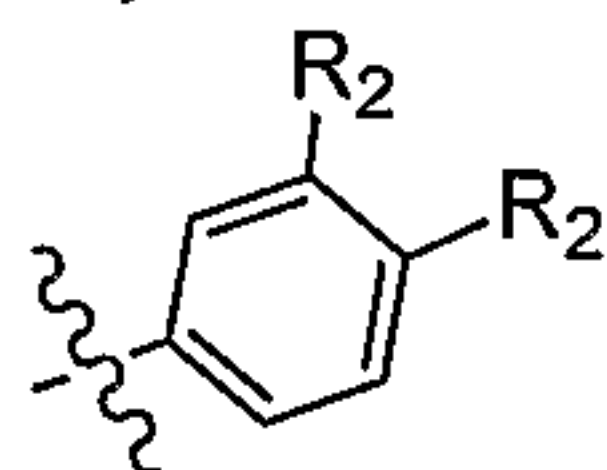
C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

29. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein A and B are CR₂.

30. A compound or pharmaceutically acceptable form thereof according to claim 29, wherein the group represented by:



31. A compound or pharmaceutically acceptable form thereof according to claim 30, wherein:



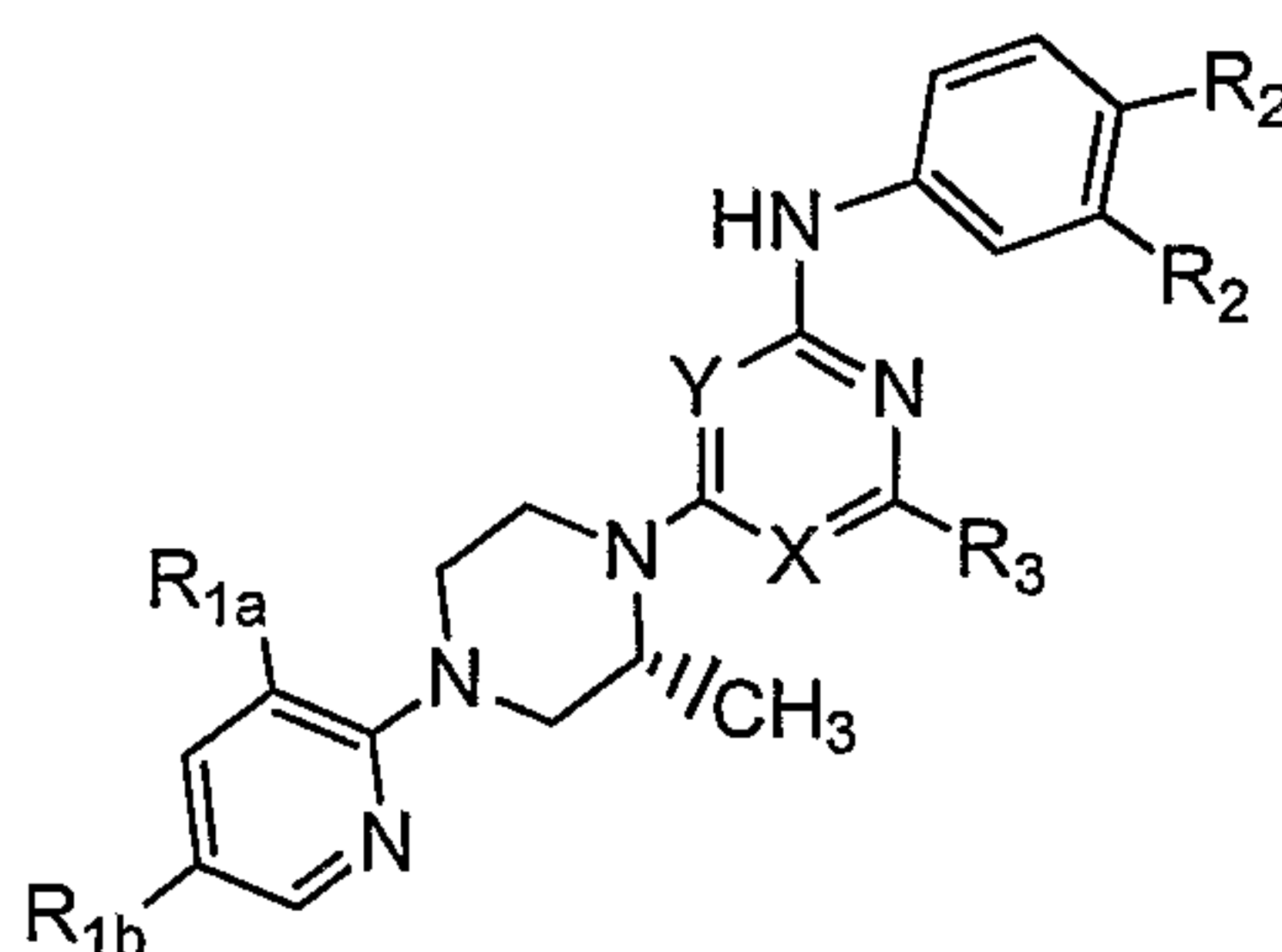
is selected from: phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, *para*-tolyl, *meta*-tolyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-*tert*-butylphenyl, 3-*tert*-butylphenyl, 4-cyanophenyl, 3-cyanophenyl, and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl.

32. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein X is N.

33. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein Y is N.

34. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein Z and X are N.

35. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein the compound has the formula:



wherein R_{1a} is halogen, amino, cyano, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)sulfonamido; and R_{1b} is hydrogen, halogen, amino, hydroxy, cyano, -COOH, aminocarbonyl, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₆hydroxyalkyl or C₁-C₄haloalkyl.

36. A compound or pharmaceutically acceptable form thereof according to claim 35, wherein:

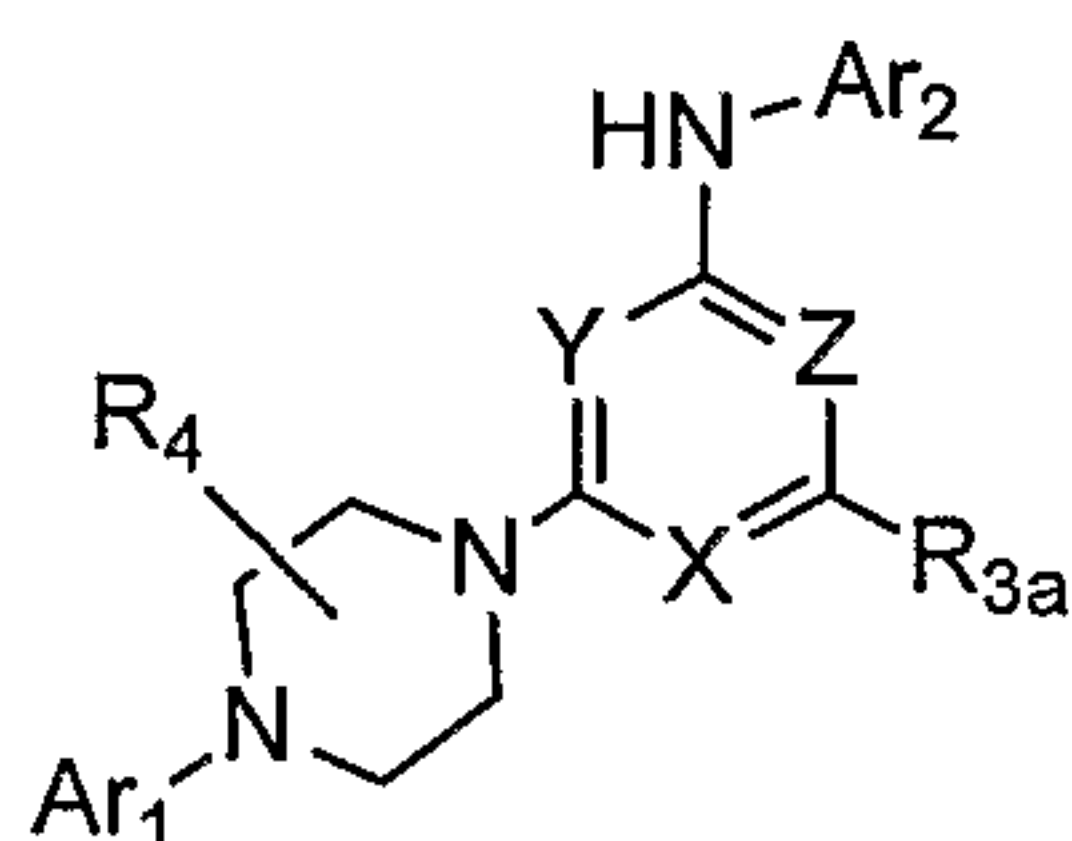
R_{1a} is fluoro, chloro, cyano, methyl or trifluoromethyl;

each R₂ is independently chosen from hydrogen, halogen, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₃ is mono- or di-(C₁-C₆alkyl)aminoC₀-C₂alkyl, C₂-C₄alkyl ether, pyrrolidinylC₀-C₂alkyl, morpholinylC₀-C₂alkyl, piperidinylC₀-C₂alkyl, piperazinylC₀-C₂alkyl or benzyloxyC₀-C₂alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, amino, hydroxy, C₁-C₄alkyl, cyano, C₁-C₄alkoxy, C₁-C₄haloalkyl and mono- and di-(C₁-C₆alkyl)amino.

37. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein the compound exhibits no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism.

38. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH,

aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

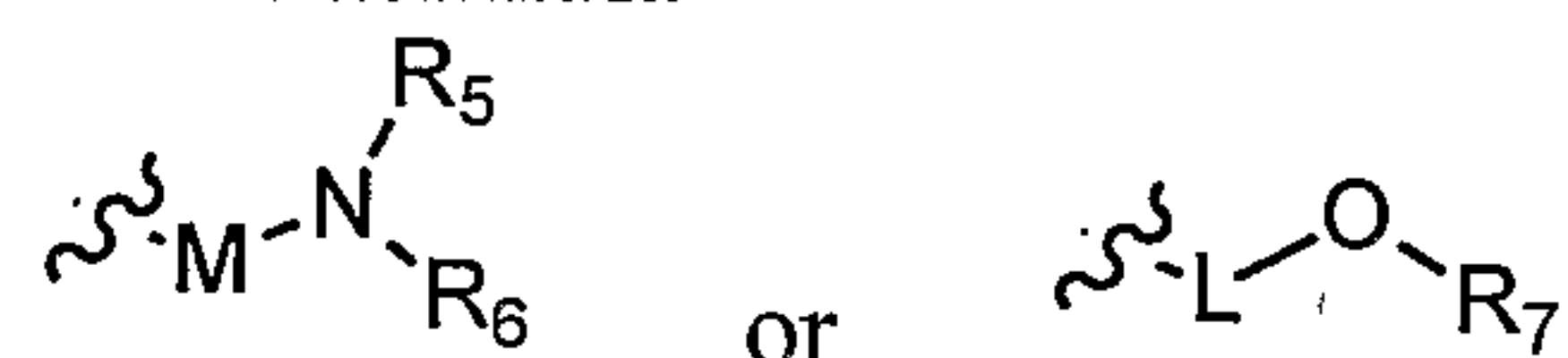
R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R_{3a} is selected from:

(i) hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl; and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkyl;

M is C₁-C₆alkyl;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to M to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

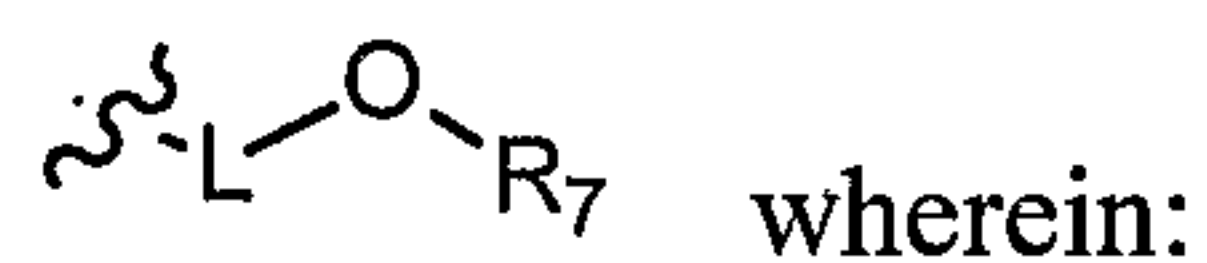
R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 C₁-C₆alkyl substituents.

39. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein R_{3a} is halogen, C₁-C₆alkyl or (C₃-C₈cycloalkyl)C₀-C₄alkyl.

40. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein R_{3a} is a group of the formula:



L is a single covalent bond or C_1 - C_4 alkylene; and

R_7 is hydrogen, C_1 - C_6 alkyl or phenyl C_0 - C_6 alkyl, wherein each alkyl and phenylalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, C_1 - C_4 alkyl, C_1 - C_6 haloalkyl and C_1 - C_6 alkoxy.

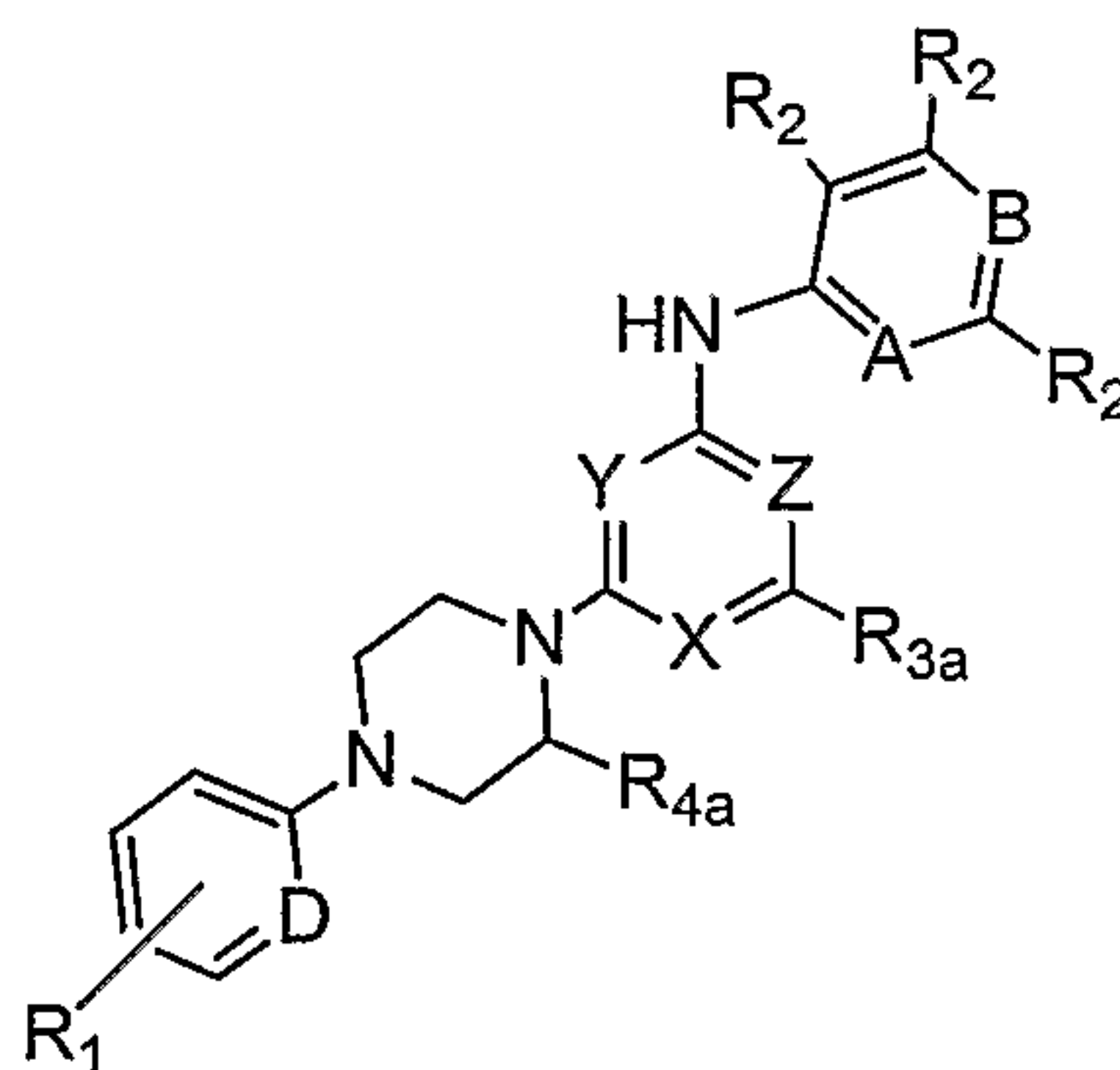
41. A compound or pharmaceutically acceptable form thereof according to claim 40, wherein R_{3a} is C_2 - C_6 alkyl ether or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, C_1 - C_4 alkyl, cyano and C_1 - C_4 haloalkyl.

42. A compound or pharmaceutically acceptable form thereof according to claim 40, wherein R_{3a} is C_2 - C_6 alkyl ether or benzyloxy, each of which is optionally substituted with Cl, F or trifluoromethyl.

43. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein X is N.

44. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein Y is N.

45. A compound or pharmaceutically acceptable form thereof according to claim 38, having the formula:



wherein:

A and B are independently CR_2 or N;

D is CH or N;

R_1 represents from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, cyano, $-\text{COOH}$, aminocarbonyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkyl ether, C_2 - C_6 alkanoyl, C_3 - C_6 alkanone, C_1 - C_6 hydroxyalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, mono-

and di-(C₁-C₆alkyl)amino, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, and mono- and di-(C₁-C₆alkyl)aminocarbonyl;

Each R₂ is independently hydrogen, halogen, cyano, amino, hydroxy, nitro, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)sulfonamido, mono- or di-(C₁-C₆alkyl)aminocarbonyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl or (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl; and

R_{4a} is hydrogen, oxo, methyl or C₁haloalkyl.

46. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein D is N.

47. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein R₁ represents from 0 to 2 substituents independently chosen from halogen, amino, cyano, -COOH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

48. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein R₁ represents one substituent located *ortho* to the point of attachment.

49. A compound or pharmaceutically acceptable form thereof according to claim 48, wherein R₁ is halogen, amino, cyano, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)sulfonamido.

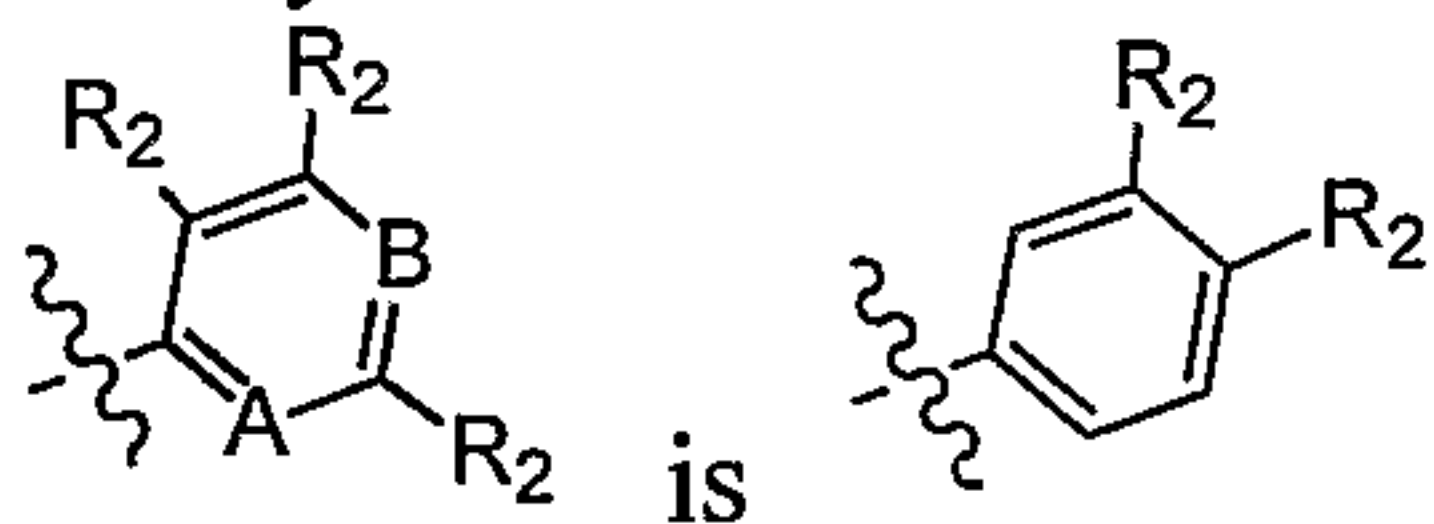
50. A compound or pharmaceutically acceptable form thereof according to claim 49, wherein R₁ is fluoro, chloro, cyano, methyl, trifluoromethyl or methylsulfonyl.

51. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein each R₂ is independently chosen from hydrogen, halogen, cyano, amino, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

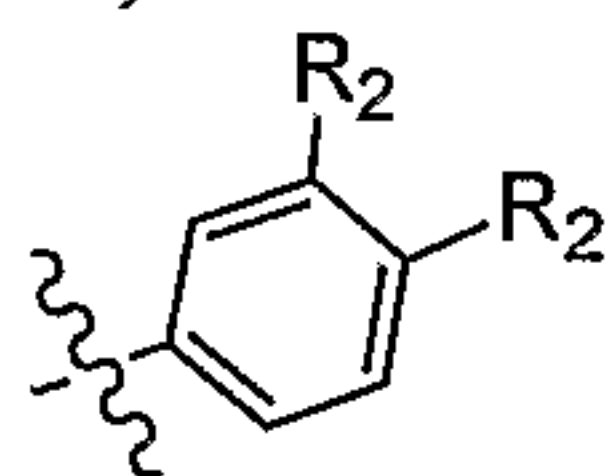
52. A compound or pharmaceutically acceptable form thereof according to claim 51, wherein each R₂ is independently chosen from hydrogen, amino, cyano, halogen, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl and mono- and di-(C₁-C₆alkyl)sulfonamido.

53. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein A is CH and B is CR₂.

54. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein the group represented by:



55. A compound or pharmaceutically acceptable form thereof according to claim 54, wherein:



is selected from: phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, *para*-tolyl, *meta*-tolyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-*tert*-butylphenyl, 3-*tert*-butylphenyl, 4-cyanophenyl, 3-cyanophenyl, and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl.

56. A compound or pharmaceutically acceptable form thereof according to claim 49, wherein:

R₁ is fluoro, chloro, cyano, methyl or trifluoromethyl;

each R₂ is independently chosen from hydrogen, halogen, cyano, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R_{3a} is C₂-C₆alkyl ether or benzyloxy, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, cyano and C₁-C₄haloalkyl.

57. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein the compound exhibits no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism.

58. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 1 micromolar or less in a capsaicin receptor calcium mobilization assay.

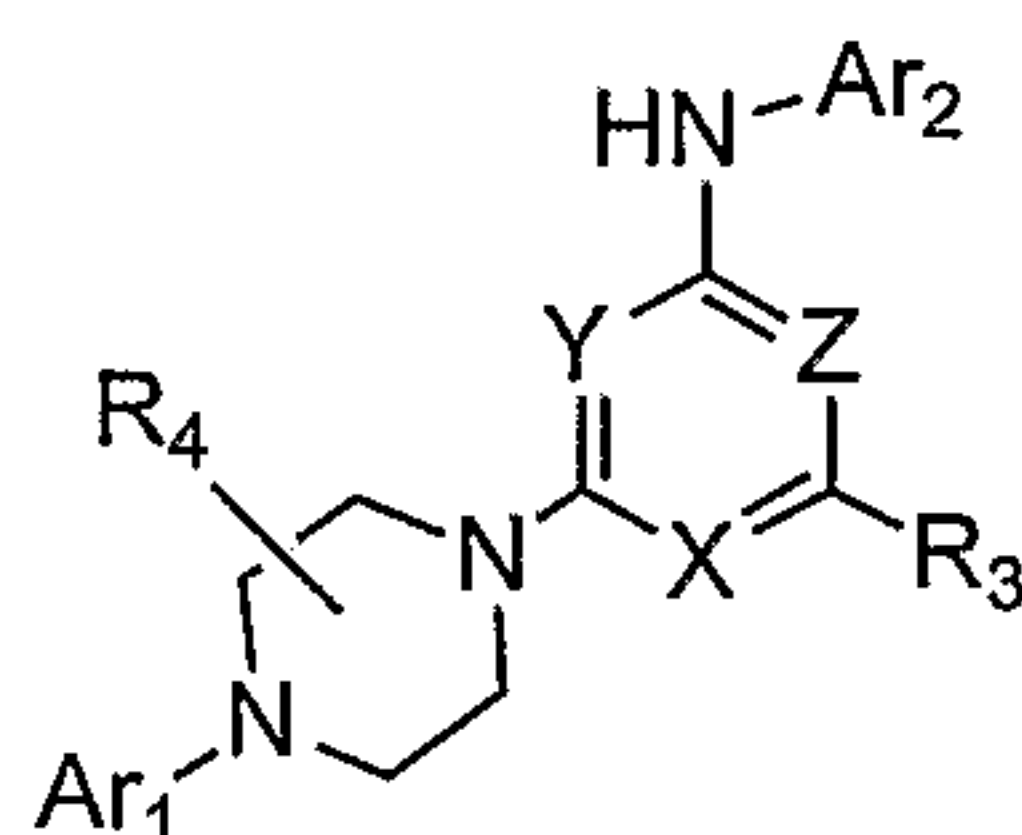
59. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 100 nanomolar or less in a capsaicin receptor calcium mobilization assay.

60. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38, wherein the compound has an IC₅₀ value of 10 nanomolar or less in a capsaicin receptor calcium mobilization assay.

61. A pharmaceutical composition, comprising at least one compound or pharmaceutically acceptable form thereof according to any one of claims 1, 18 or 38 in combination with a physiologically acceptable carrier or excipient.

62. A pharmaceutical composition according to claim 61 wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

63. A method for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell expressing a capsaicin receptor with at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

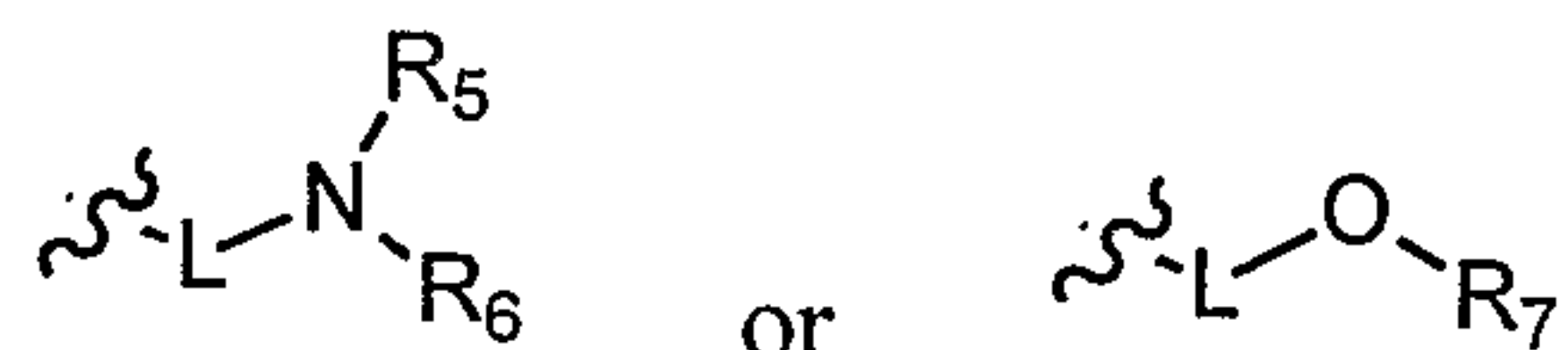
R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;

and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

and thereby reducing calcium conductance of the capsaicin receptor.

64. A method according to claim 63, wherein the cell is contacted *in vivo* in an animal.

65. A method according to claim 64, wherein the cell is a neuronal cell.

66. A method according to claim 64, wherein the cell is a urothelial cell.

67. A method according to claim 64, wherein during contact the compound is present within a body fluid of the animal.

68. A method according to claim 67, wherein the compound or pharmaceutically acceptable form thereof is present in the blood of the animal at a concentration of 1 micromolar or less.

69. A method according to claim 68, wherein the compound is present in the blood of the animal at a concentration of 500 nanomolar or less.

70. A method according to claim 69, wherein the compound is present in the blood of the animal at a concentration of 100 nanomolar or less.

71. A method according to claim 64, wherein the animal is a human.

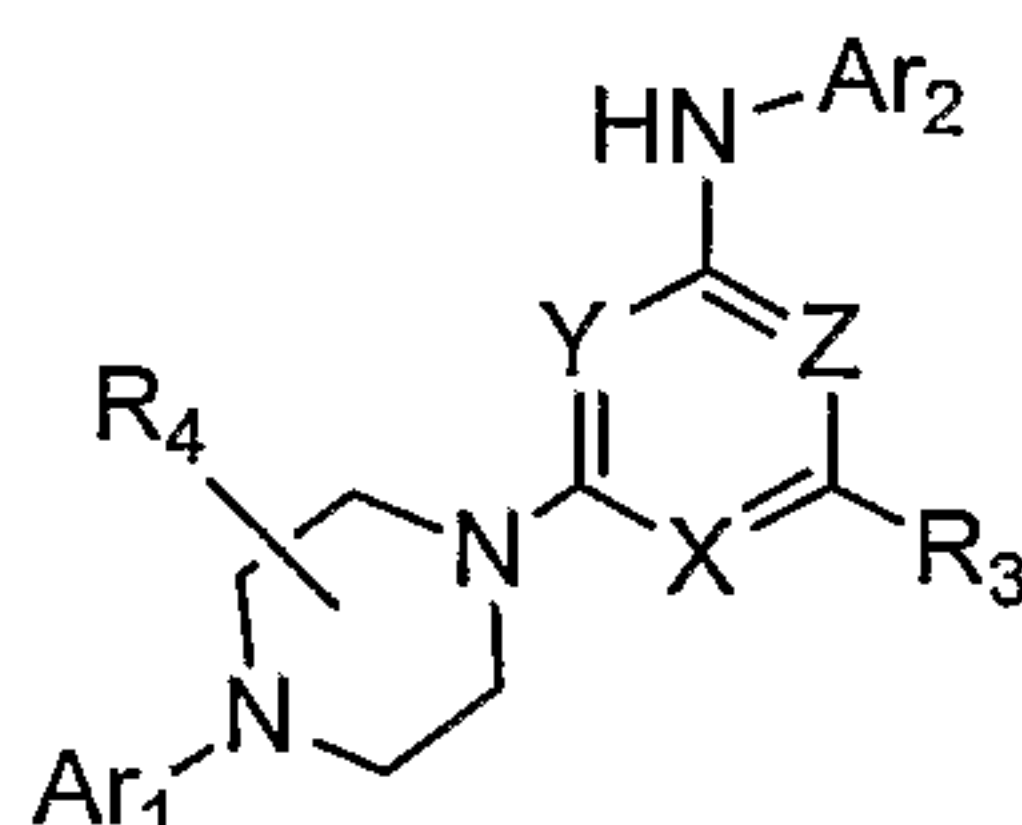
72. A method according to claim 64, wherein the compound or pharmaceutically acceptable form thereof is administered orally.

73. A method according to claim 63, wherein the compound is a compound according to claim 1.

74. A method according to claim 63, wherein the compound is a compound according to claim 18.

75. A method according to claim 63, wherein the compound is a compound according to claim 38.

76. A method for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro*, the method comprising contacting capsaicin receptor with at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

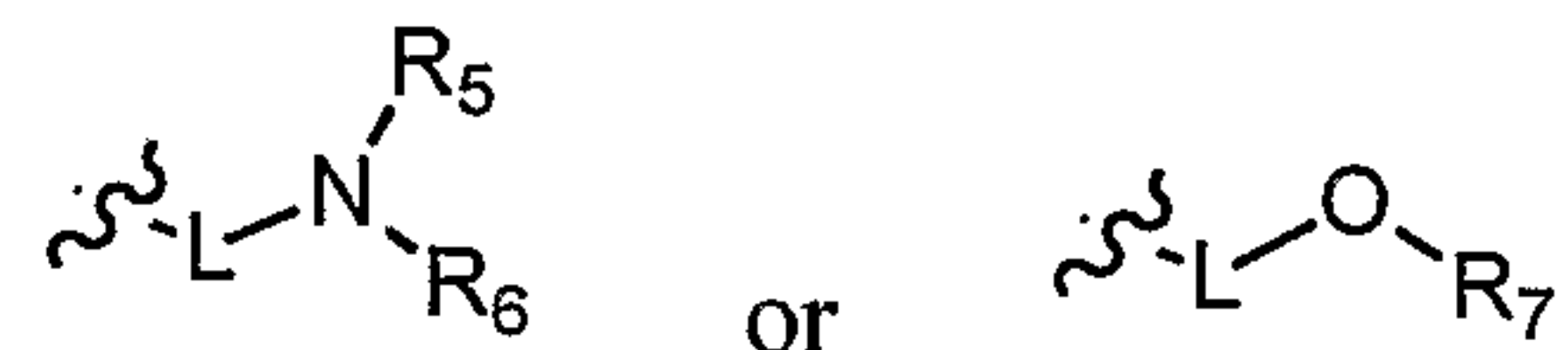
R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl; and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

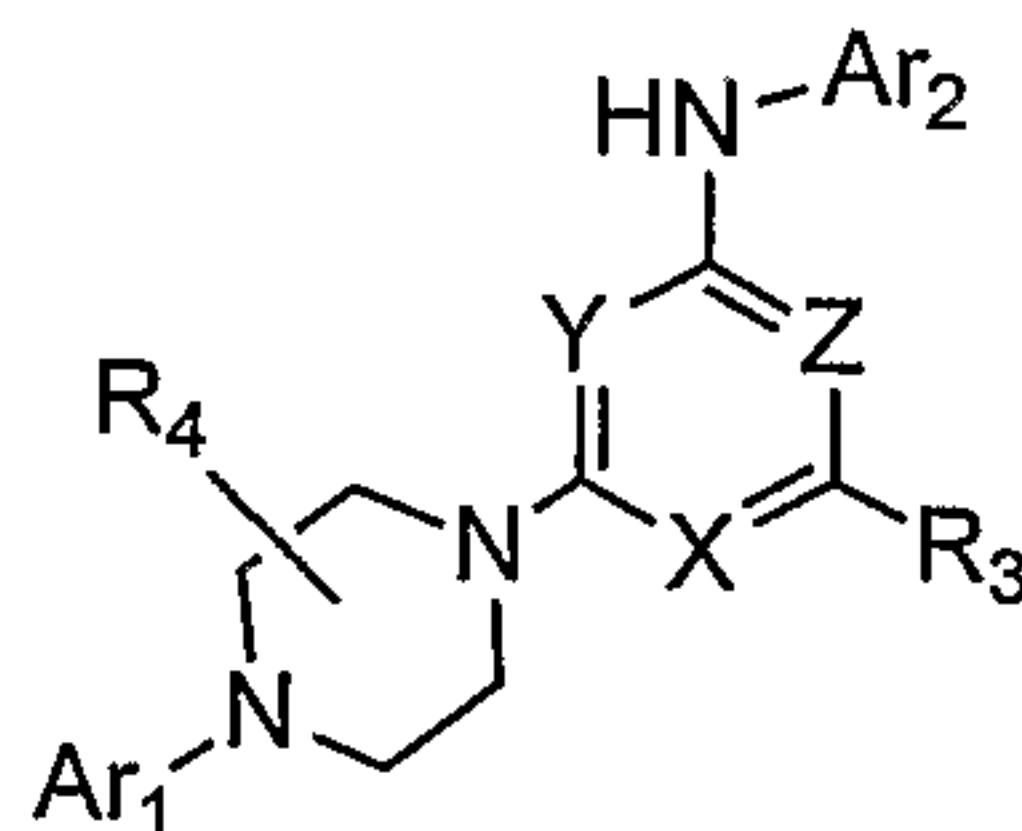
under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to capsaicin receptor.

77. A method according to claim 76, wherein the compound is a compound according to claim 1.

78. A method according to claim 76, wherein the compound is a compound according to claim 18.

79. A method according to claim 76, wherein the compound is a compound according to claim 38.

80. A method for inhibiting binding of vanilloid ligand to a capsaicin receptor in a patient, the method comprising contacting cells expressing capsaicin receptor with at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

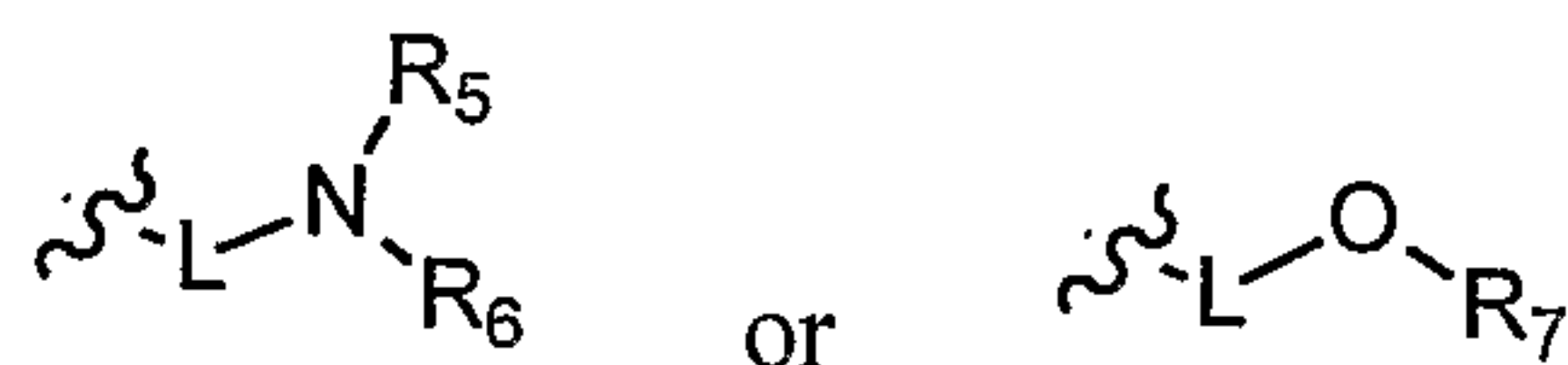
Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;
- and
- (iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

- (b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

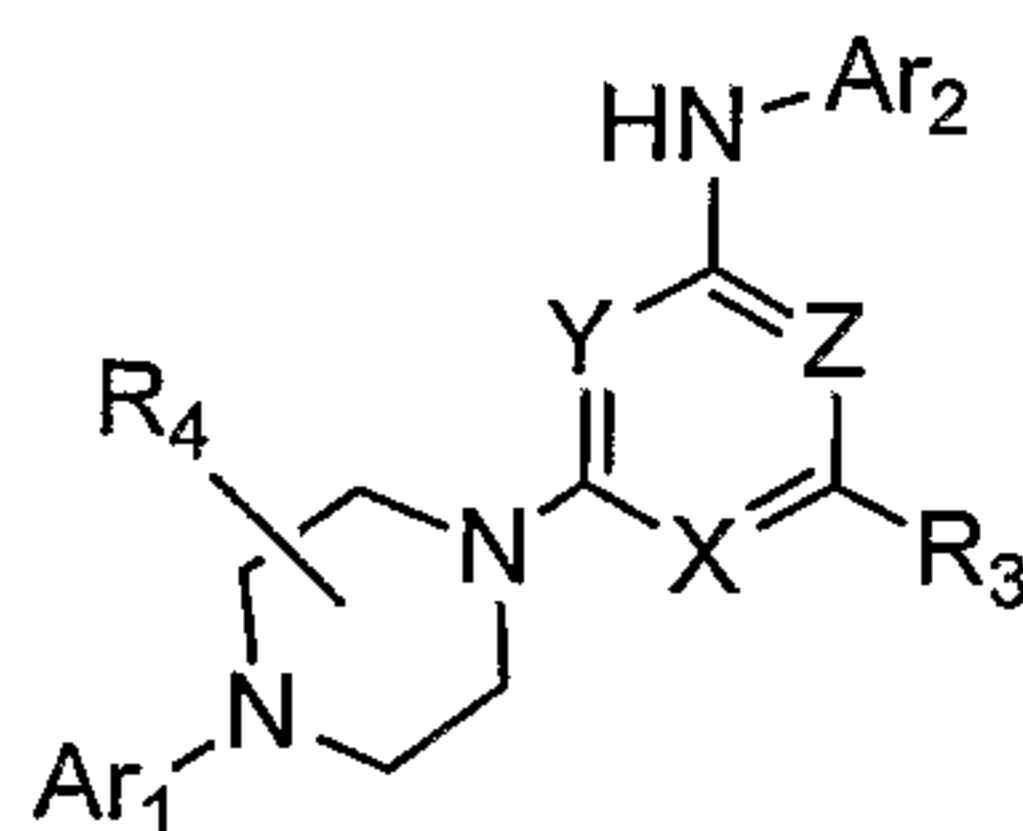
in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

81. A method according to claim 80, wherein the compound is a compound according to claim 1.

82. A method according to claim 80, wherein the compound is a compound according to claim 18.

83. A method according to claim 80, wherein the compound is a compound according to claim 38.

84. A method for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a capsaicin receptor modulatory amount of a compound having the formula:

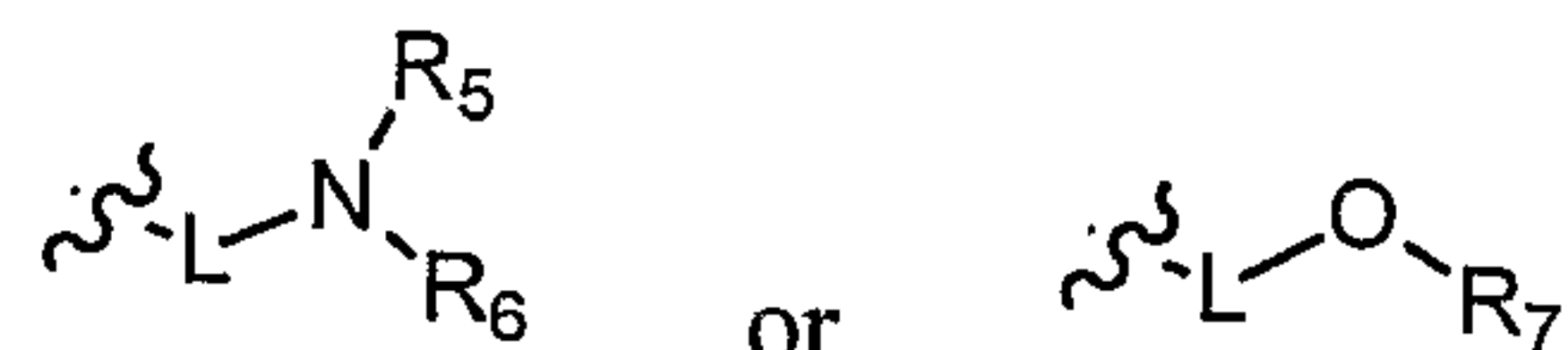


or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;
 R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;
 R₃ is selected from:

- (i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;
- (ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;
 and
- (iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

- (a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or
 - (b) taken together to form a 5- to 7-membered heterocycloalkyl; and
- R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

and thereby alleviating the condition in the patient.

85. A method according to claim 84, wherein the patient is suffering from (i) exposure to capsaicin, (ii) burn or irritation due to exposure to heat, (iii) burns or irritation due to exposure to light, (iv) burn, bronchoconstriction or irritation due to exposure to tear gas, air pollutants or pepper spray, or (v) burn or irritation due to exposure to acid.

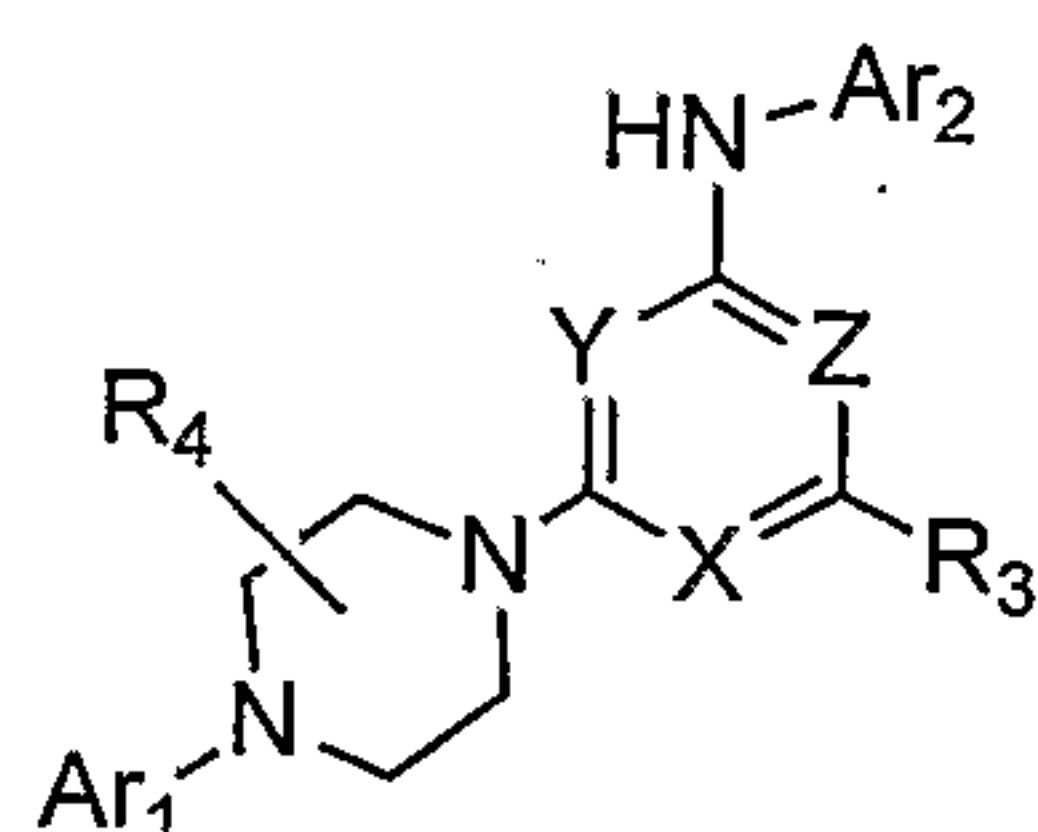
86. A method according to claim 84, wherein the condition is asthma or chronic obstructive pulmonary disease.

87. A method according to claim 84, wherein the compound is a compound according to claim 1.

88. A method according to claim 84, wherein the compound is a compound according to claim 18.

89. A method according to claim 84, wherein the compound is a compound according to claim 38.

90. A method for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

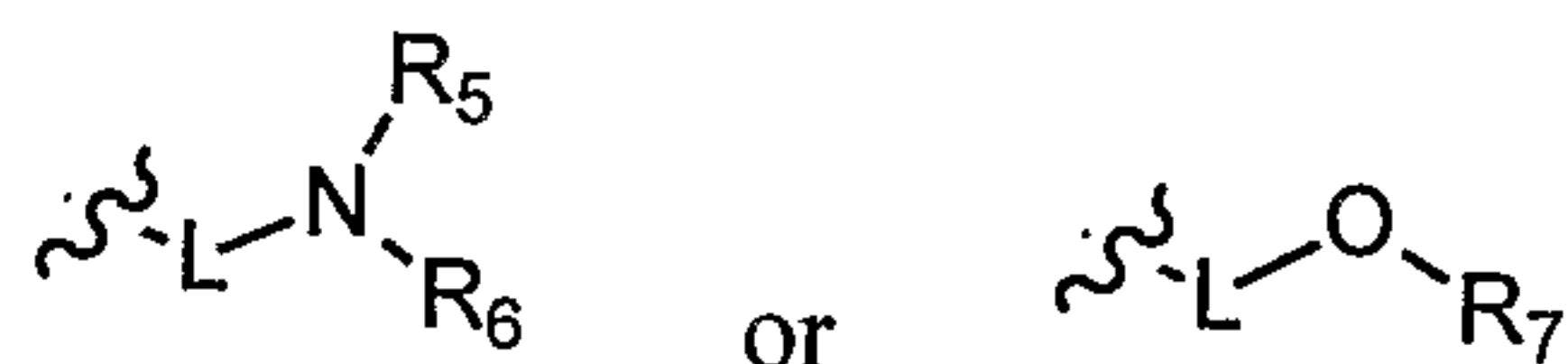
R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;
and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

and thereby alleviating pain in the patient.

91. A method according to claim 90, wherein the compound is present in the blood of the animal at a concentration of 1 micromolar or less.

92. A method according to claim 90, wherein the patient is suffering from neuropathic pain.

93. A method according to claim 90, wherein the pain is associated with a condition selected from: postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, neuritis, neuronitis, neuralgia, AIDS-related neuropathy, MS-related neuropathy, spinal cord injury-related pain, surgery-related pain, musculoskeletal pain, back pain, headache, migraine, angina, labor, hemorrhoids, dyspepsia, Charcot's pains, intestinal gas, menstruation, cancer, venom exposure, irritable bowel syndrome, inflammatory bowel disease, and/or trauma.

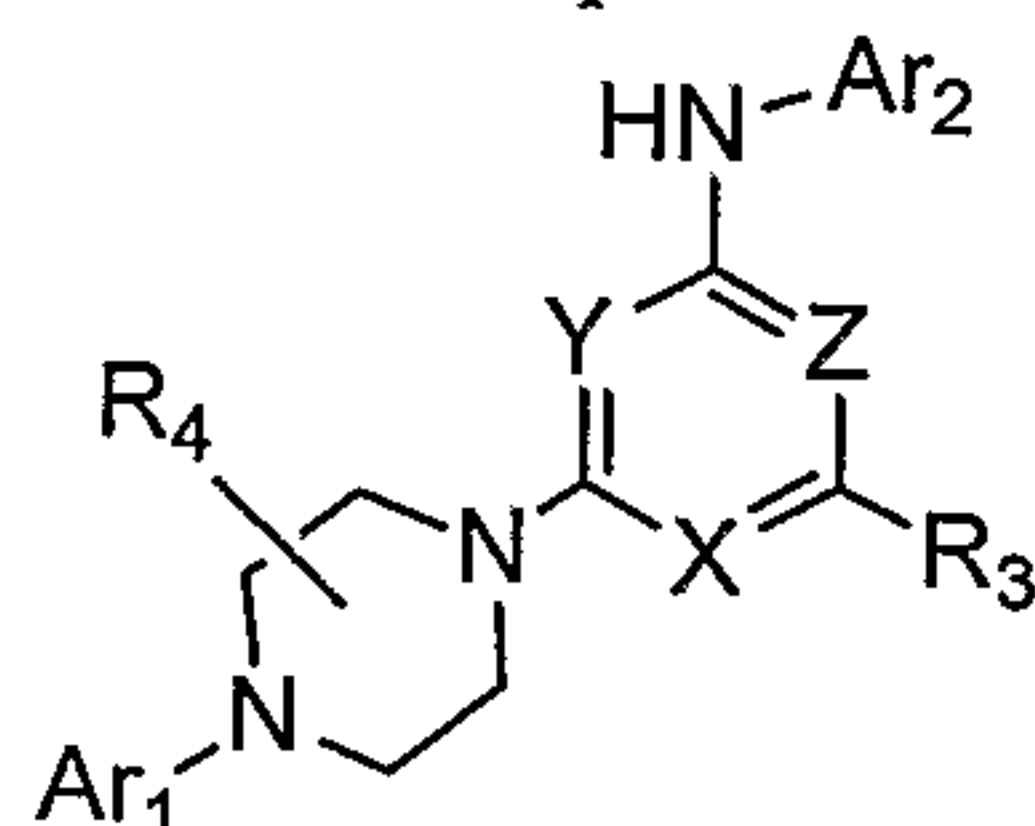
94. A method according to claim 90, wherein the patient is a human.

95. A method according to claim 90, wherein the compound is a compound according to claim 1.

96. A method according to claim 90, wherein the compound is a compound according to claim 18.

97. A method according to claim 90, wherein the compound is a compound according to claim 38.

98. A method for treating itch in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

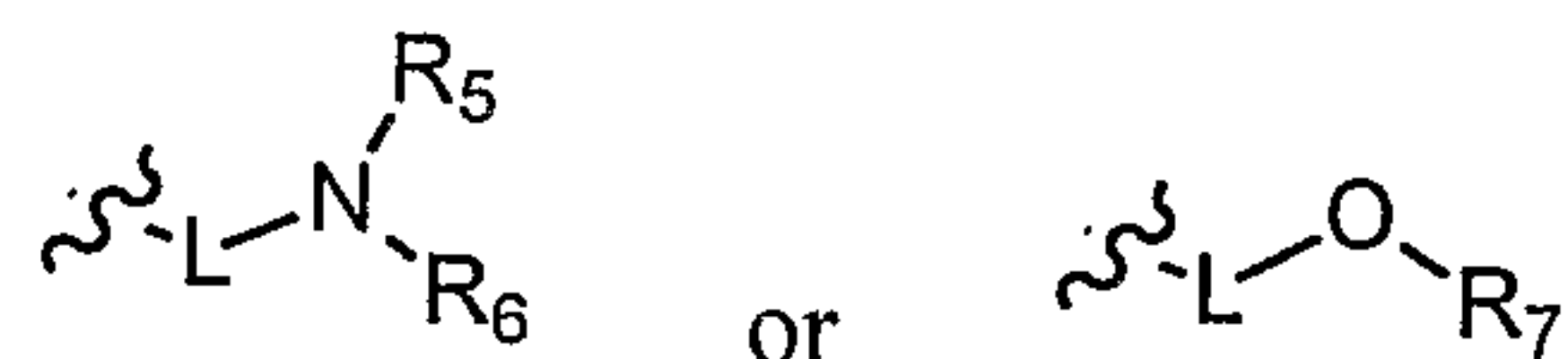
R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl; and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

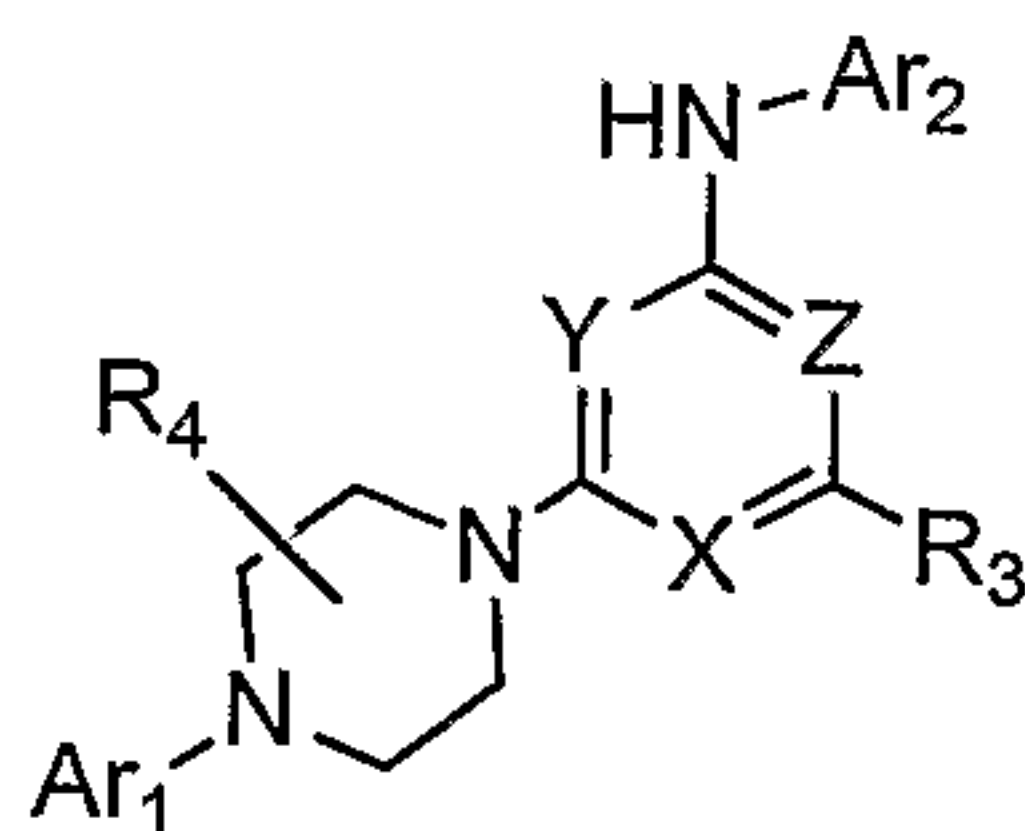
R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

and thereby alleviating itch in the patient.

99. A method for treating urinary incontinence or overactive bladder in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

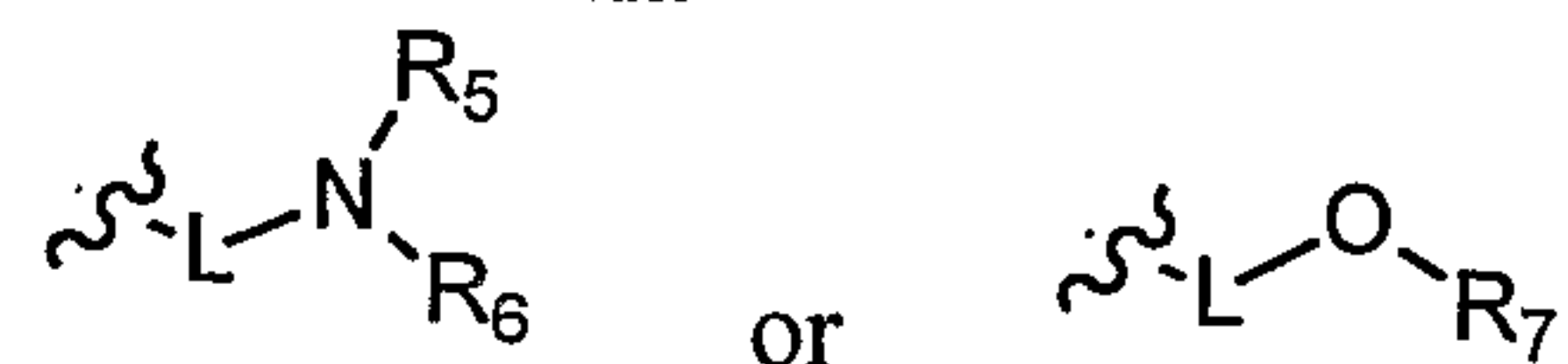
R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;

and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

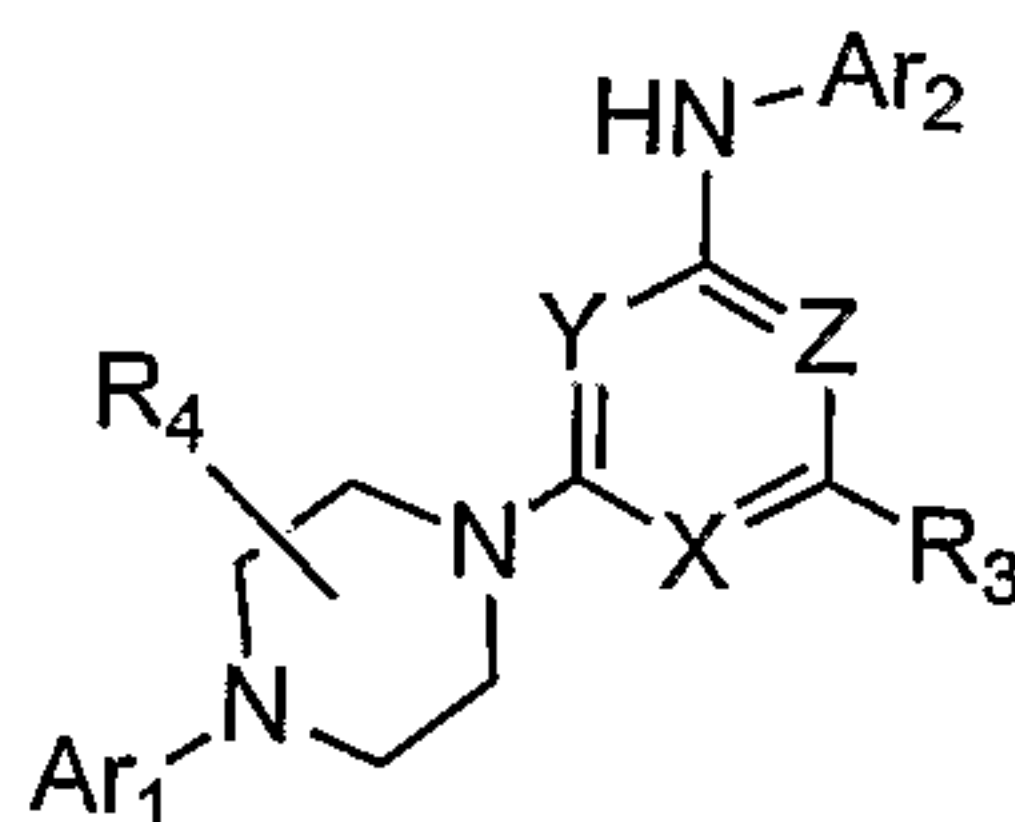
R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

and thereby alleviating urinary incontinence or overactive bladder in the patient.

100. A method for treating cough or hiccup in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-

(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

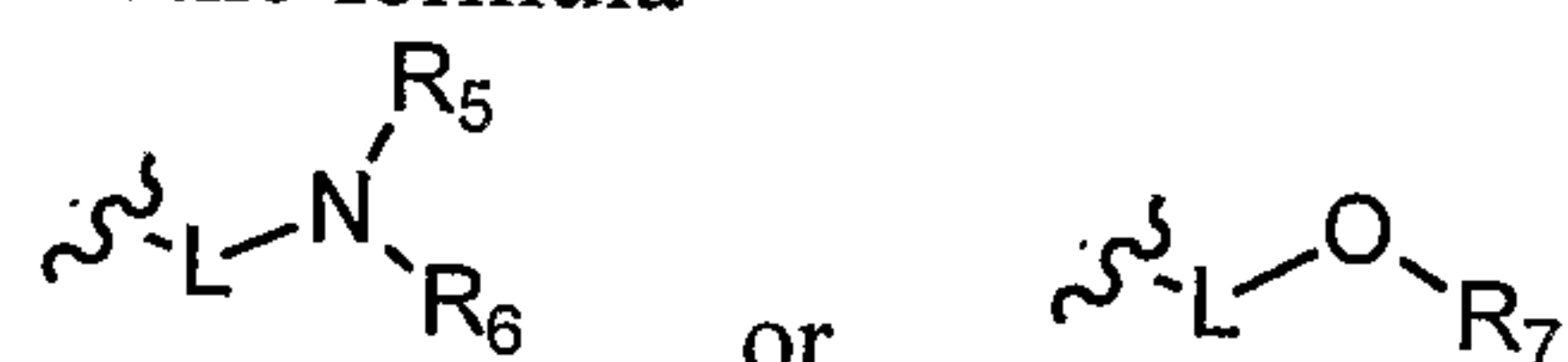
R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl;
and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

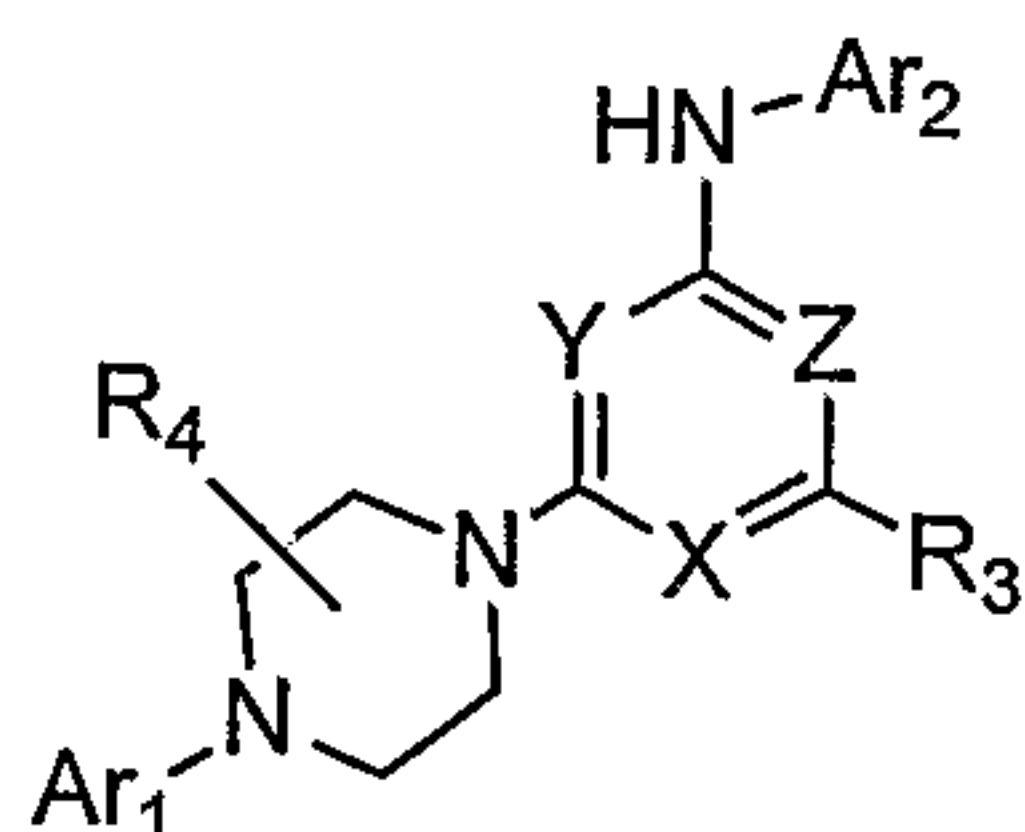
R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and

R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;

and thereby alleviating cough or hiccup in the patient.

101. A method for promoting weight loss in an obese patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound having the formula:



or a pharmaceutically acceptable form thereof, wherein

Ar₁ and Ar₂ are independently chosen from phenyl, naphthyl and 5- to 10-membered aromatic heterocycles, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, nitro, -COOH, aminocarbonyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆haloalkoxy, C₂-C₆alkanoyl, C₃-C₆alkanone, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆cyanoalkyl, C₁-C₆aminoalkyl, C₁-C₆alkylsulfonyl, mono- and di-(C₁-C₆alkyl)sulfonamido, mono- and di-(C₁-C₆alkyl)aminocarbonyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl and (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl;

X, Y and Z are independently CR_x or N, such that at least one of X, Y and Z is N;

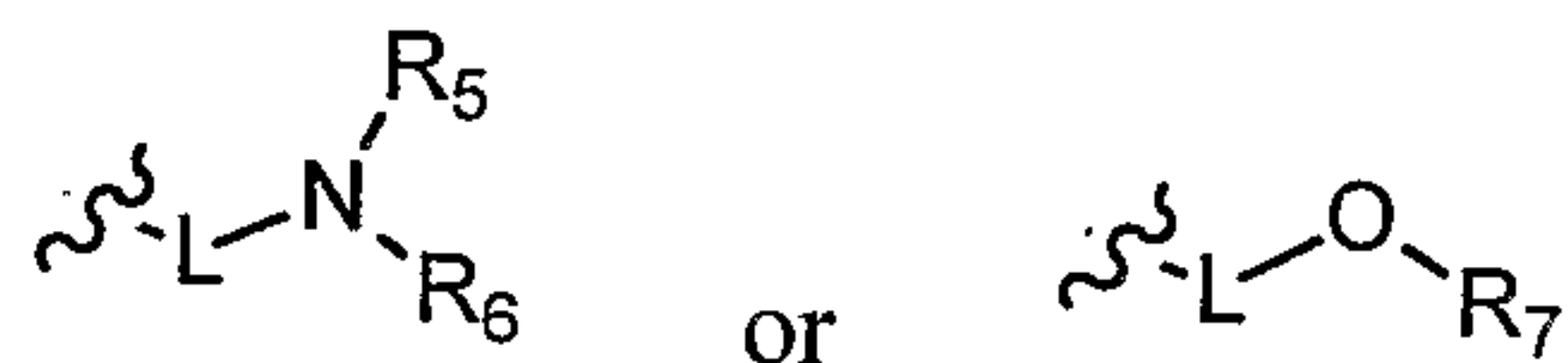
R_x is independently chosen at each occurrence from hydrogen, C₁-C₆alkyl, amino and cyano;

R₃ is selected from:

(i) hydrogen, hydroxy, halogen and C₁-C₆haloalkyl;

(ii) C₁-C₆alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, phenylC₀-C₄alkyl and pyridylC₀-C₄alkyl; and

(iii) groups of the formula



wherein

L is a single covalent bond or C₁-C₆alkylene;

R₅ and R₆ are:

(a) independently chosen from hydrogen, C₁-C₈alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, (3- to 7-membered heterocycloalkyl)C₀-C₄alkyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl and groups that are joined to L to form a 5- to 7-membered heterocycloalkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl; and

R₇ is C₁-C₈alkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkenyl, C₂-C₈alkanoyl, phenylC₀-C₆alkyl, pyridylC₀-C₆alkyl or a group that is joined to L to form a 5- to 7-membered heterocycloalkyl;

wherein each of (ii) and (iii) is substituted with from 0 to 4 substituents independently chosen from halogen, cyano, amino, hydroxy, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₂-C₆alkanoyl, C₁-C₆haloalkyl, mono- and di-(C₁-C₆alkyl)amino, phenyl, 5- to 6-membered heteroaryl and 4- to 8-membered heterocycloalkyl, wherein each phenyl, heteroaryl and heterocycloalkyl is substituted

with from 0 to 2 secondary substituents independently chosen from halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy and C₁-C₄haloalkyl; and
R₄ represents from 0 to 2 substituents independently chosen from oxo, C₁-C₄alkyl, C₁-C₄haloalkyl;
and thereby promoting weight loss in the patient.

102. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

103. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

104. A compound or pharmaceutically acceptable form thereof according to claim 38, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

105. A method for determining the presence or absence of capsaicin receptor in a sample, comprising the steps of:

- (a) contacting a sample with a compound or pharmaceutically acceptable form thereof according to claim 1, 18 or 38, under conditions that permit binding of the compound to capsaicin receptor; and
- (b) detecting a level of the compound bound to capsaicin receptor, and therefrom determining the presence or absence of capsaicin receptor in the sample.

106. A method according to claim 101, wherein the compound radiolabeled, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound compound in the sample.

107. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 59 in a container; and
- (b) instructions for using the composition to treat pain.

108. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 59 in a container; and
- (b) instructions for using the composition to treat itch.

109. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 59 in a container; and
- (b) instructions for using the composition to treat urinary incontinence or overactive bladder.

110. A packaged pharmaceutical preparation, comprising:
(a) a pharmaceutical composition according to claim 59 in a container; and
(b) instructions for using the composition to treat cough or hiccup.
111. A packaged pharmaceutical preparation, comprising:
(a) a pharmaceutical composition according to claim 59 in a container; and
(b) instructions for using the composition to treat obesity.
112. (3,4-Difluoro-phenyl)-{2-(2,6-dimethyl-morpholin-4-ylmethyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine or a pharmaceutically acceptable form thereof.
113. (3,4-Difluoro-phenyl)-{2-methoxymethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine or a pharmaceutically acceptable form thereof.
114. (3,4-Difluorophenyl)-(5-methyl-2-morpholin-4-yl-6-{4-[3-(trifluoromethyl)(2-pyridyl)]piperazinyl}pyrimidin-4-yl)amine or a pharmaceutically acceptable form thereof.
115. (3,4-Difluoro-phenyl)-{2-morpholin-4-ylmethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine or a pharmaceutically acceptable form thereof.
116. (3,4-Difluoro-phenyl)-{4-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine (R) or a pharmaceutically acceptable form thereof.
117. (3,4-Difluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.
118. (3-Chloro-phenyl)-{4-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.
119. (3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.
120. (3-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine or a pharmaceutically acceptable form thereof.
121. (3-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.

122. (3-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine or a pharmaceutically acceptable form thereof.
123. (4-Chloro-phenyl)-{4-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.
124. (4-Chloro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.
125. (4-Fluoro-phenyl)-[2-morpholin-4-yl-6-(4-pyridin-2-yl-piperazin-1-yl)-pyrimidin-4-yl]-amine or a pharmaceutically acceptable form thereof.
126. (4-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine or a pharmaceutically acceptable form thereof.
127. (4-Fluoro-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine or a pharmaceutically acceptable form thereof.
128. (4-Fluoro-phenyl)-{6-morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine or a pharmaceutically acceptable form thereof.
129. (4-Methoxy-phenyl)-{4-morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-amine or a pharmaceutically acceptable form thereof.
130. (4-*tert*-Butyl-phenyl)-[4-(4-pyridin-2-yl-piperazin-1-yl)-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine or a pharmaceutically acceptable form thereof.
131. (4-*tert*-Butyl-phenyl)-[4-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine (R) or a pharmaceutically acceptable form thereof.
132. (4-*tert*-Butyl-phenyl)-[4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine or a pharmaceutically acceptable form thereof.
133. (4-*tert*-Butyl-phenyl)-[4-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine (R) or a pharmaceutically acceptable form thereof.
134. (4-*tert*-Butyl-phenyl)-[4-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-amine (R) or a pharmaceutically acceptable form thereof.

135. (4-*tert*-Butyl-phenyl)-{4-chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R) or a pharmaceutically acceptable form thereof.
136. (4-*tert*-Butyl-phenyl)-{4-chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R) or a pharmaceutically acceptable form thereof.
137. (4-*tert*-Butyl-phenyl)-{4-chloro-6-[4-(3-fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-amine (R) or a pharmaceutically acceptable form thereof.
138. (4-*tert*-Butyl-phenyl)-{6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-amine (R) or a pharmaceutically acceptable form thereof.
139. [4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine (R) or a pharmaceutically acceptable form thereof.
140. [4-[2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-6-(4-trifluoromethyl-phenyl)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine (S) or a pharmaceutically acceptable form thereof.
141. [4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2,4-dimethoxy-phenyl)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
142. [4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine (R) or a pharmaceutically acceptable form thereof.
143. [4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(4-isopropyl-phenyl)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
144. [4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-(2-methyl-pyrrolidin-1-yl)-[1,3,5]triazin-2-yl]-(3-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
145. [4-[4-(3-Fluoro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-(2-trifluoromethyl-benzyloxy)-[1,3,5]triazin-2-yl]-(4-trifluoromethyl-phenyl)-amine (R) or a pharmaceutically acceptable form thereof.
146. {2-Diethylaminomethyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-(3,4-difluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.

147. {4-(2-Chloro-phenyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine (S) or a pharmaceutically acceptable form thereof.
148. {4-(3,4-Difluoro-phenylamino)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-methanol or a pharmaceutically acceptable form thereof.
149. {4-(4-Butyl-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
150. {4,6-Bis-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
151. {4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3,4-difluoro-phenyl)-amine (R) or a pharmaceutically acceptable form thereof.
152. {4-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
153. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-methyl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
154. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
155. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(4-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
156. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-p-tolyl-amine or a pharmaceutically acceptable form thereof.
157. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(3,4-difluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
158. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
159. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazin-2-yl}-phenyl-amine or a pharmaceutically acceptable form thereof.

160. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
161. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-piperidin-1-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
162. {4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-pyrrolidin-1-yl-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
163. {4-Azepan-1-yl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(3-fluoro-phenyl)-amine or a pharmaceutically acceptable form thereof.
164. {4-Chloro-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine (S) or a pharmaceutically acceptable form thereof.
165. {4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazin-2-yl}-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-amine (R) or a pharmaceutically acceptable form thereof.
166. {4-Chloro-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
167. {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-(4-trifluoromethyl-phenyl)-amine or a pharmaceutically acceptable form thereof.
168. {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazin-2-yl}-p-tolyl-amine or a pharmaceutically acceptable form thereof.
169. {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-o-tolyl-amine or a pharmaceutically acceptable form thereof.
170. {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-m-tolyl-amine or a pharmaceutically acceptable form thereof.
171. {4-Morpholin-4-yl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-p-tolyl-amine or a pharmaceutically acceptable form thereof.
172. {6-Chloro-2-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-pyrimidin-4-yl}-(4-trifluoromethyl-phenyl)-amine (R) or a pharmaceutically acceptable form thereof.

173. {6-Morpholin-4-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-p-tolyl-amine or a pharmaceutically acceptable form thereof.
174. 4-{4-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-6-diethylamino-[1,3,5]triazin-2-ylamino}-benzonitrile or a pharmaceutically acceptable form thereof.
175. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3,4-difluoro-phenyl)-N',N'-diethyl-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
176. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
177. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-phenyl-propyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
178. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-(3-trifluoromethyl-benzyl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
179. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
180. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S) or a pharmaceutically acceptable form thereof.
181. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N,N-dipropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
182. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
183. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isobutyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

184. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
185. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
186. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
187. 6-[4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-propyl-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
188. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3,4-difluoro-phenyl)-N',N'-diethyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
189. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-methyl-N'-propyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
190. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N',N'-dimethyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
191. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-isopropyl-N'-methyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
192. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-(3-fluoro-phenyl)-N'-propyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
193. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
194. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(3-methoxy-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
195. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-diethyl-N'-(4-fluoro-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.

196. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N,N-dimethyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
197. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
198. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N'-(3-fluoro-phenyl)-N-isopropyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
199. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-ethyl-N-isopropyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
200. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
201. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-isopropyl-N-methyl-N'-phenyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
202. 6-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
203. N-(2,5-Dimethoxy-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
204. N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
205. N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
206. N-(3,4-Difluoro-phenyl)-N',N'-diethyl-6-[4-(3-methanesulfonyl-pyridin-2-yl)-2-methyl-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
207. N-(3-Chloro-phenyl)-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N',N'-diethyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.

208. N-(3-Methyl-butyl)-6-[2-methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (S) or a pharmaceutically acceptable form thereof.
209. N-(3-Methyl-butyl)-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
210. N,N-Diallyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
211. N,N-Dibutyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
212. N,N-Diethyl-N'-(4-fluoro-phenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
213. N,N-Dimethyl-6-(4-phenyl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
214. N,N-Dimethyl-6-(4-pyridin-2-yl-piperazin-1-yl)-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
215. N,N-Dimethyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
216. N,N-Dimethyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.
217. N-Benzyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.
218. N-Butyl-6-[4-(2-chloro-phenyl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

219. N-Butyl-6-[4-(2-chloro-phenyl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

220. N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

221. N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

222. N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N-methyl-N'-(4-trifluoromethyl-phenyl)-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

223. N-Butyl-6-[4-(3-chloro-pyridin-2-yl)-piperazin-1-yl]-N'-(3-fluoro-phenyl)-N-methyl-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.

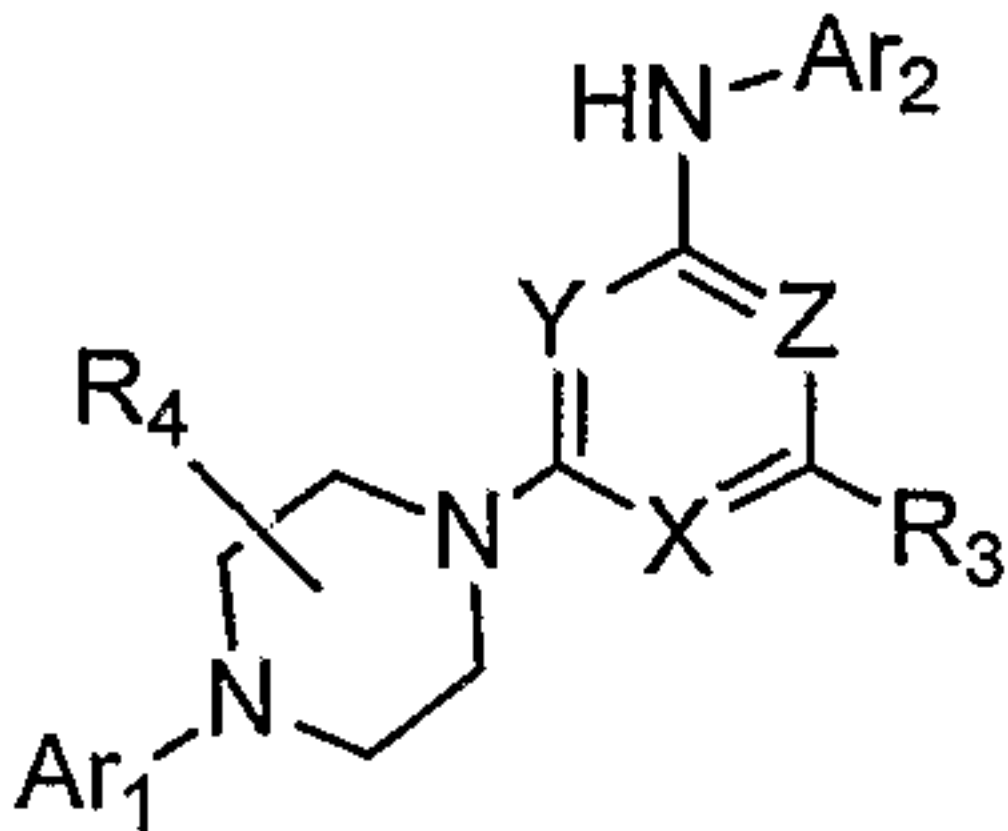
224. N-Isopropyl-N-methyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.

225. N-Isopropyl-N-methyl-N'-phenyl-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.

226. N-Methyl-N-propyl-N'-(4-trifluoromethyl-phenyl)-6-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[1,3,5]triazine-2,4-diamine or a pharmaceutically acceptable form thereof.

227. N-sec-Butyl-6-[4-(3-chloro-pyridin-2-yl)-2-methyl-piperazin-1-yl]-N'-[4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-[1,3,5]triazine-2,4-diamine (R) or a pharmaceutically acceptable form thereof.

228. Phenyl-{6-piperidin-1-yl-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-pyrimidin-4-yl}-amine or a pharmaceutically acceptable form thereof.



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