# [1,2,4]-TRIAZOLE BICYCLIC ADENOSINE $A_{2a}$ RECEPTOR ANTAGONISTS

## BACKGROUND

The present invention relates to substituted [1,2,4]-triazole bicyclic adenosine $A_{2a}$ receptor antagonists, the use of said compounds in the treatment of central nervous system diseases, in particular Parkinson's disease, and to pharmaceutical compositions comprising said compounds.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On the central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets.

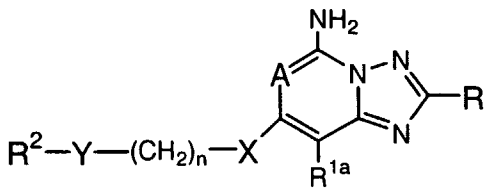
Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins. Biochemical and pharmacological studies, together with advances in molecular biology, have allowed the identification of at least four subtypes of adenosine receptors: $A_1$, $A_{2a}$, $A_{2b}$ and $A_3$. $A_1$ and $A_3$ are high-affinity, inhibiting the activity of the enzyme adenylate cyclase, and $A_{2a}$ and $A_{2b}$ are low-affinity, stimulating the activity of the same enzyme. Analogs of adenosine able to interact as antagonists with the $A_1$, $A_{2a}$, $A_{2b}$ and $A_3$ receptors have also been identified.

Selective antagonists for the $A_{2a}$ receptor are of pharmacological interest because of their reduced level of side affects. In the central nervous system, $A_{2a}$ antagonists can have antidepressant properties and stimulate cognitive functions. Moreover, data has shown that $A_{2a}$ receptors are present in high density in the basal ganglia, known to be important in the control of movement. Hence, $A_{2a}$ antagonists can improve motor impairment due to neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin.

Some xanthine-related compounds have been found to be $A_1$ receptor selective antagonists, and xanthine and non-xanthine compounds have been found to have high $A_{2a}$ affinity with varying degrees of $A_{2a}$ vs. $A_1$ selectivity. Certain imidazolo- and pyrazolo-substituted triazolo-pyrimidine adenosine $A_{2a}$ receptor antagonists have been disclosed previously, for example in WO 95/01356; WO 97/05138; and WO 98/52568. Certain pyrazolo-substituted triazolo-pyrimidine adenosine $A_{2a}$ receptor antagonists are disclosed in US 09/207,143, filed May 24, 2001. Certain imidazolo-substituted triazolo-pyrimidine adenosine $A_{2a}$ receptor antagonists are disclosed in US Provisional Application 60/329,567, filed October 15, 2001. US 5,565,460 discloses certain triazolo-triazines as antidepressants; EP 0976753 and WO 99/43678 disclose certain triazolo-pyrimidines as adenosine $A_{2a}$ receptor antagonists; and WO 01/17999 discloses certain triazolo pyridines as adenosine $A_{2a}$ receptor antagonists.

## SUMMARY OF THE INVENTION

The present invention relates to a compound represented by the structural formula I



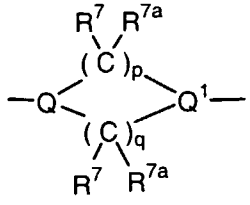
I

or a pharmaceutically acceptable salt thereof, wherein:

A is $C(R^1)$ or N;

$R^1$ and $R^{1a}$ are independently selected from the group consisting of H, $(C_1\text{-}C_6)$-alkyl, halo, CN and $-CF_3$;

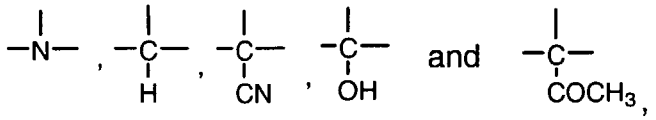
Y is –O-, -S-, -SO-, $-SO_2$-, $R^5$-heteroaryldiyl, $R^5$-arylene or



;

p and q are independently 2-3;

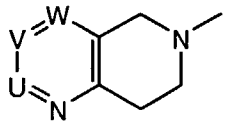
Q and Q$^1$ are independently selected from the group consisting of



provided that at least one of Q and Q$^1$ is ;

R is R$^5$-aryl, R$^5$-heteroaryl, R$^6$-($C_2$-$C_6$)alkenyl or R$^6$-($C_2$-$C_6$)alkynyl;

R$^2$ is R$^5$-aryl, R$^5$-heteroaryl, R$^5$-aryl($C_1$-$C_6$)alkyl or R$^5$-heteroaryl($C_1$-$C_6$)alkyl; or R$^2$-Y is



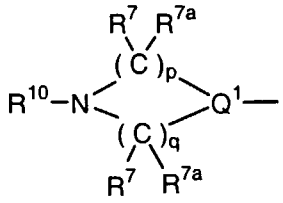
;

U, V, and W are independently selected from the group consisting of N and CR$^1$, provided that at least one of U, V and W is CR$^1$;

n is 1, 2 or 3; and

(a) A is C(R$^1$) and X is –C(R$^3$)(R$^{3a}$)-, -C(O)-, -O-, -S-, -SO-, -$SO_2$-, R$^4$-arylene, R$^4$-heteroaryldiyl, or -N(R$^9$)-; or A is C(R$^1$), Y is a bond, and X is –C(R$^3$)(R$^{3a}$)-, -C(O)-, -O-, -S-, -SO-, -$SO_2$-, R$^4$-arylene, -N(R$^9$)- or R$^4$-heteroaryldiyl, provided that when X is -N(R$^9$)- or R$^4$-heteroaryldiyl, R$^2$ is not phenyl or phenyl-($C_1$-$C_6$)alkyl; or

(b) A is N, X is -N(R$^9$)-, Y is R$^5$-arylene and R$^2$ is

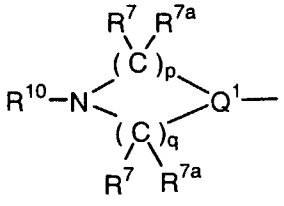


;

or n is 2 or 3; and

(c) A is N and X is –C(R$^3$)(R$^{3a}$)-, -C(O)-, -O-, -S-, -SO-, -$SO_2$-, -N(R$^9$)-, R$^4$-arylene or R$^4$-heteroaryldiyl; or A is N, Y is a bond and X is -C(O)-, -N(R$^9$)-, R$^4$-arylene or R$^4$-heteroaryldiyl; or A is N, Y is –N(R$^{9a}$)-, -C(O)N(R$^{9a}$)- or

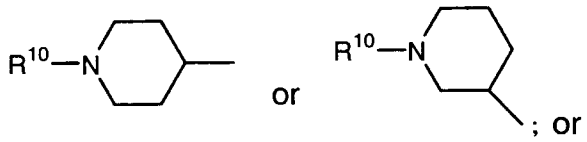
–O-$(CH_2)_2$-N($R^{9a}$)-, and X is -N($R^9$)-; or A is N, X is -N($R^9$)-, and Y and $R^2$ together are



;

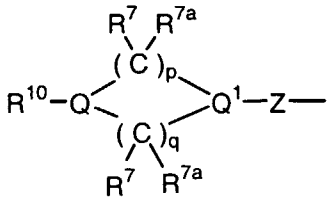
or n is 0; and

(d) A is N, Y is a bond, X is -N($R^9$)-, and $R^2$ is



; or

(e) A is N, X is -N($R^9$)- and Y and $R^2$ together are



,

wherein Z is –C(O)-$CH_2$-, -C(O)-CH($C_1$-$C_6$ alkyl)-, -$CH_2$-CH($C_1$-$C_6$ alkyl)-, or -CH($C_1$-$C_6$ alkyl)-$CH_2$-;

$R^3$ and $R^{3a}$ are independently selected from the group consisting of H, -OH, $C_1$-$C_6$ alkyl, hydroxy($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl, amino($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl and di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl;

$R^4$ is 1-3 substituents selected from the group consisting of H, ($C_1$-$C_6$)alkyl, -OH, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkoxy, halo, -$CF_3$, and –CN;

$R^5$ is 1-3 substituents independently selected from the group consisting of H, ($C_1$-$C_6$)alkyl, -OH, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)-alkoxy, halo, -$CF_3$, -CN, -$NH_2$, ($C_1$-$C_6$)alkylamino, di($C_1$-$C_6$)alkylamino, amino($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl, di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkanoyl-amino, ($C_1$-$C_6$)alkanesulfonylamino, ($C_1$-$C_6$)alkylthio, ($C_1$-$C_6$)alkylthio($C_1$-$C_6$)alkyl, $R^6$-($C_2$-$C_6$)alkenyl, $R^6$-($C_2$-$C_6$)alkynyl, hydroxy($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy-C(O)-amino, or heterocycloalkyl($C_1$-$C_6$)alkyl;

$R^6$ is 1 to 3 substituents independently selected from the group consisting of H, -OH, ($C_1$-$C_6$)alkoxy and halo;

$R^7$ and $R^{7a}$ are independently selected from the group consisting of H, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl, $R^8$-aryl and $R^8$-heteroaryl, or an $R^7$ and an $R^{7a}$ substituent on the same carbon can form =O;

$R^8$ is 1 to 3 substituents independently selected from H, ($C_1$-$C_6$)alkyl, -OH, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkoxy, halo, -$CF_3$, and –CN;

$R^9$ and $R^{9a}$ are independently selected from the group consisting of H, ($C_1$-$C_6$)alkyl, hydroxy($C_2$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy($C_2$-$C_6$)alkyl, amino($C_2$-$C_6$)alkyl, ($C_1$-$C_6$)alkylamino($C_2$-$C_6$)alkyl, di($C_1$-$C_6$)alkylamino($C_2$-$C_6$)alkyl, halo-($C_3$-$C_6$)alkenyl, $CF_3$-($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)alkenyl, ($C_3$-$C_6$)cycloalkyl and ($C_3$-$C_6$)cycloalkyl-($C_1$-$C_6$)alkyl; and

$R^{10}$ is H, -C(O)-O-($C_1$-$C_6$)alkyl, $R^5$-aryl, -C(O)-($C_1$-$C_6$)alkyl, -C(O)-($R^5$-aryl) or $R^5$-aryl-($C_1$-$C_6$)alkyl.

Another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula I in a pharmaceutically acceptable carrier.

Yet another aspect of the invention is a method of treating central nervous system diseases such as depression, cognitive diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia or psychoses of organic origin, or stroke, comprising administering at least one compound of formula I to a mammal in need of such treatment. In particular, the invention is drawn to the method of treating Parkinson's disease comprising administering at least one compound of formula I to a mammal in need of such treatment.

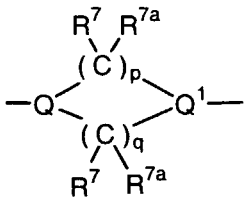
Still another aspect of the invention is a method of treating Parkinson's disease with a combination of at least one compound of formula I and one or more agents useful in the treatment of Parkinson's disease, for example dopamine; a dopaminergic agonist; an inhibitor of monoamine oxidase, type B (MAO-B); a DOPA decarboxylase inhibitor (DCI); or a catechol-O-methyltransferase (COMT) inhibitor. Also claimed is a pharmaceutical composition comprising at least one compound of formula I and one or more agents known to be useful in the treatment of Parkinson's in a pharmaceutically acceptable carrier. In the method comprising the administration of the combination of the invention, one or more compounds of formula I and one or more other anti-Parkinson's agents can be administered simultaneously or

sequentially in separate dosage forms. Therefore, also claimed is a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Parkinson's disease wherein one container comprises a pharmaceutical composition comprising an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and wherein, in separate containers, one or more pharmaceutical compositions each comprise an effective amount of an agent useful in the treatment of Parkinson's disease in a pharmaceutically acceptable carrier.

## DETAILED DESCRIPTION

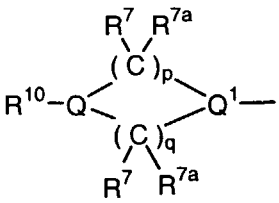
Referring to compounds of formula I above, preferred compounds of formula I are those wherein A is N. R is preferably furyl. $R^{1a}$ is preferably hydrogen. Another group of preferred compounds is that wherein X is –O-, -S-, -N($R^9$)- or $R^4$-arylene, with compounds wherein X is -N($R^9$)- being more preferred. $R^9$ is preferably $C_1$-$C_6$ alkyl, with methyl and ethyl being most preferred.

Preferred definitions for Y are a bond or piperazinyl (i.e., a group of the formula

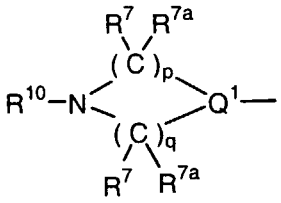


wherein Q and $Q^1$ are each nitrogen, p and q are each 2, and each $R^7$ and each $R^{7a}$ is H). $R^2$ is preferably $R^5$-aryl, more preferably $R^5$-phenyl.

When Y and/or $R^2$ is



or



,

Q is preferably N, $Q^1$ is preferably N, p and q are each preferably 2, each $R^7$ and $R^{7a}$ is preferably hydrogen, and $R^{10}$ is preferably -C(O)-O-($C_1$-$C_6$)alkyl, -C(O)-($C_1$-$C_6$)alkyl or -C(O)-($R^5$-aryl).

$R^5$ is preferably 1 or 2 substituents selected from the group consisting of H, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)-alkoxy, halo and -$CF_3$. More preferred are H, methoxy, methoxyethoxy, fluoro and chloro.

$R^4$ is preferably H, halo or $(C_1$-$C_6)$alkyl. $R^3$ and $R^{3a}$ are preferably independently selected from H and $(C_1$-$C_6)$alkyl. $R^{9a}$ is preferably H or $(C_1$-$C_6)$alkyl. $R^6$ is preferably hydrogen.

As used herein, the term alkyl includes saturated straight or branched carbon chains.

Halo means fluoro, chloro, bromo or iodo.

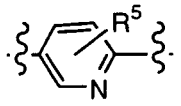
Alkenyl means a straight or branched hydrocarbon chain having at least one double bond. Similarly, alkynyl means a straight or branched hydrobcarbon chain having at least one triple bond.

Aryl means a single aromatic carbocylic ring or a bicyclic fused carbocyclic ring of 6 to 10 carbon atoms, for example phenyl or naphthyl.

Heteroaryl means a single ring heteroaromatic group of 5 to 6 atoms comprised of 2 to 5 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, or a bicyclic heteroaromatic group of 5 to 10 atoms comprised of 1 to 9 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, provided that the rings do not include adjacent oxygen and/or sulfur atoms. Examples of single-ring heteroaryl groups are pyridyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazinyl, pyrimidyl, pyridazinyl and triazolyl. Examples of bicyclic heteroaryl groups are naphthyridyl (e.g., 1,5 or 1,7), imidazopyridyl, pyridopyrimidinyl and 7-azaindolyl. Also included in the definition of heteroaryl are benzofused heteroaryl groups comprising a heteroaryl ring as defined above fused at adjacent carbon atoms to a phenyl ring. Examples of benzofused heteroaryl groups are indolyl, quinolyl, isoquinolyl, phthalazinyl, benzothienyl (i.e., thionaphthenyl), benzimidazolyl, benzofuranyl, benzoxazolyl and benzofurazanyl. All positional isomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. N-oxides of the ring nitrogens for all heteroaryl groups are also included. $R^4$- and $R^5$-substituted heteroaryl refers to such groups wherein substitutable ring carbon atoms have a substituent as defined above.

Heteroaryldiyl means a heteroaryl ring bonded to two different groups. For example, in the context of this invention, when Y is $R^5$-heteroaryldiyl, one ring member is attached to the group $-(CH_2)_n$-, and another ring member is attached to

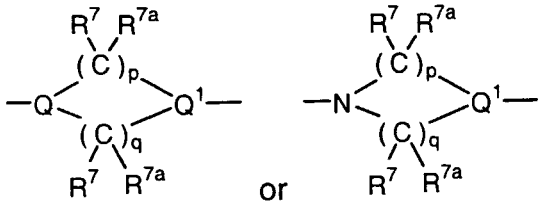
variable $R^2$; the $R^5$ substituents are attached to one or more of the remaining ring carbons. As an example, a pyridinediyl ring is shown:



Similarly, arylene means a divalent aryl ring, that is, an aryl ring bonded to two different groups, e.g., phenylene.

Heterocycloalkyl means a 3 to 6-membered saturated ring comprised of 2 to 5 carbon atoms and 1 or 2 heteroatoms selected from the group consisting of N, S and O, provided that two heteroatoms are not adjacent to each other. Typical heterocycloalkyl rings are piperidinyl, piperazinyl, morpholinyl, azetidinyl, pyrrolidinyl, tetrahydrothienyl, tetrahydrofuranyl, tetrahydropyranyl and thiomorpholinyl.

When Y and/or $R^2$ comprise



each $R^7$ and $R^{7a}$ substituent is independently selected from the groups included in the definition above; preferably no more than two of the substituents are other than hydrogen.

Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers). The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures.

Certain compounds will be acidic in nature, e.g. those compounds which possess a phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts.

Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic functionality such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic

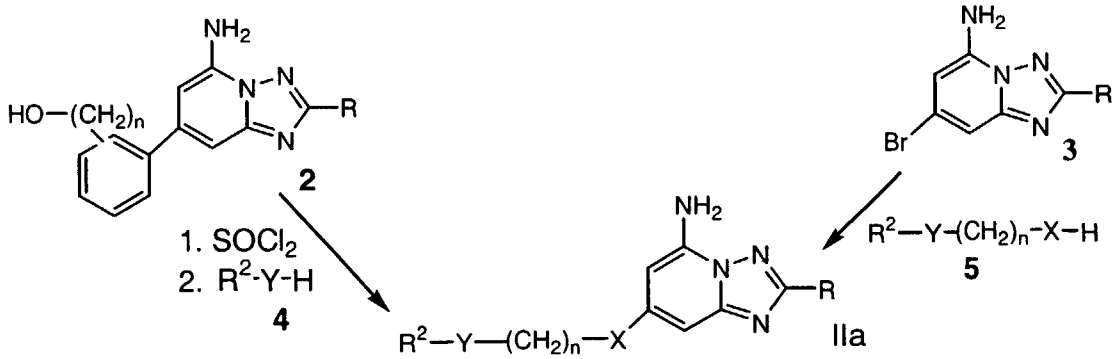
acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula I are prepared by general methods known in the art. Preferably, the compounds of formula I are prepared by the methods shown in the following reaction schemes. In the Schemes and examples that follow, the following abbreviations are used : Ph is phenyl, Me is methyl, Et is ethyl, TFA is trifluoroacetic acid, BSA is N,O-bis(trimethylsilyl)acetamide, DMF is dimethylformamide, EtOAc is ethyl acetate, THF is tetrahydrofuran, and DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

Compounds of formula IIa where A is $C(R^1)$ can be prepared by methods described in application WO 01/11799. In addition, compounds wherein Y is not a bond can be prepared by methods illustrated in Scheme 1.

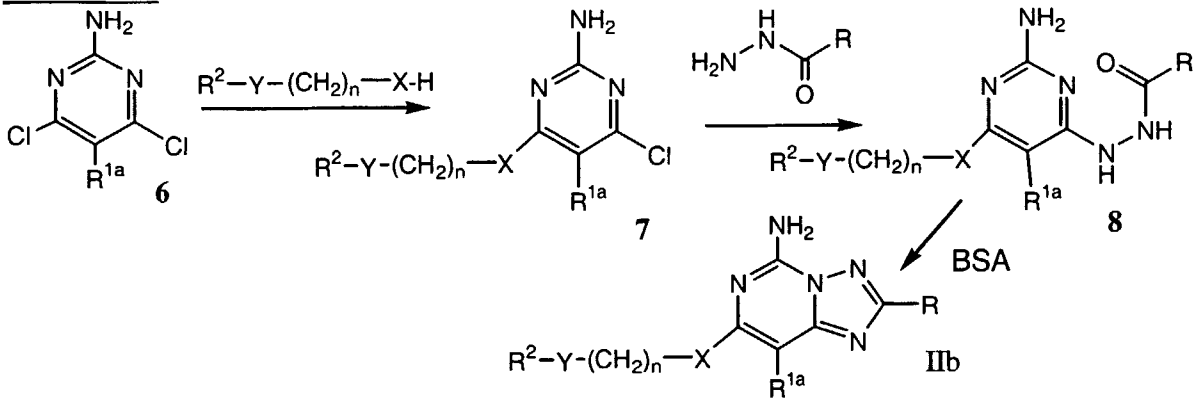
Scheme 1:




Where X is arylene, an intermediate of type **2** may be activated, e.g. to a chloride, which may then be reacted with a nucleophile **4** (e.g., Y=piperazinyl) to provide IIa. Alternatively, bromide **3** may be reacted with a nucleophile of type **5** provide IIa.

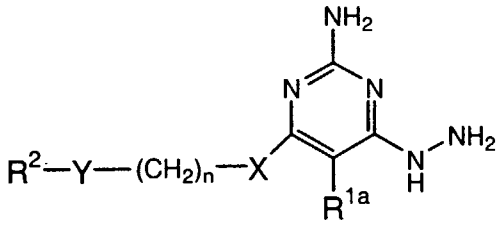
Compounds of formula IIb where A is N, and X is –O-, -S-, or –N($R^9$)-can be prepared by methods described in Schemes 2 and 3.

Scheme 2:




Chloride **6** is treated with an amine, alcohol or thiol in the presence of base to yield **7**. Reaction with the appropriate hydrazide yields **8**. Dehydrative cyclization with an agent such as BSA then yields the desired compound of formula IIb.

In a variant of this scheme, R in the hydrazide $RCONHNH_2$ may be a removable protective group such a *t*-butoxy or benzyloxy. In such a case, deprotection of **8** leads to **8a**,

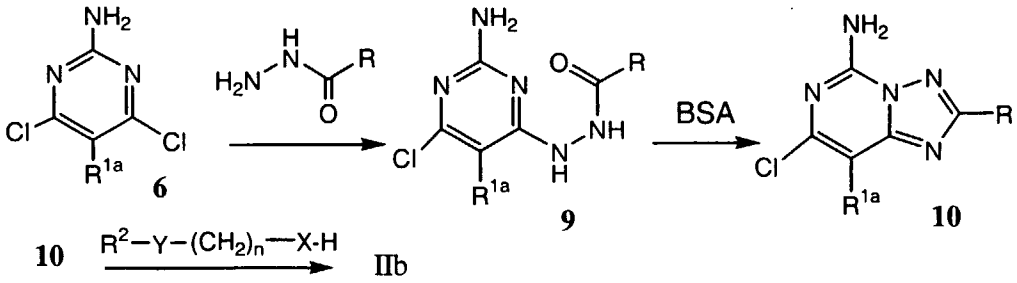



**8a**

which may be acylated with RCOOH or the corresponding acid chloride, anhydride, or mixed anhydride. This produces a new **8**, which may be converted to the desired compound of formula IIb.

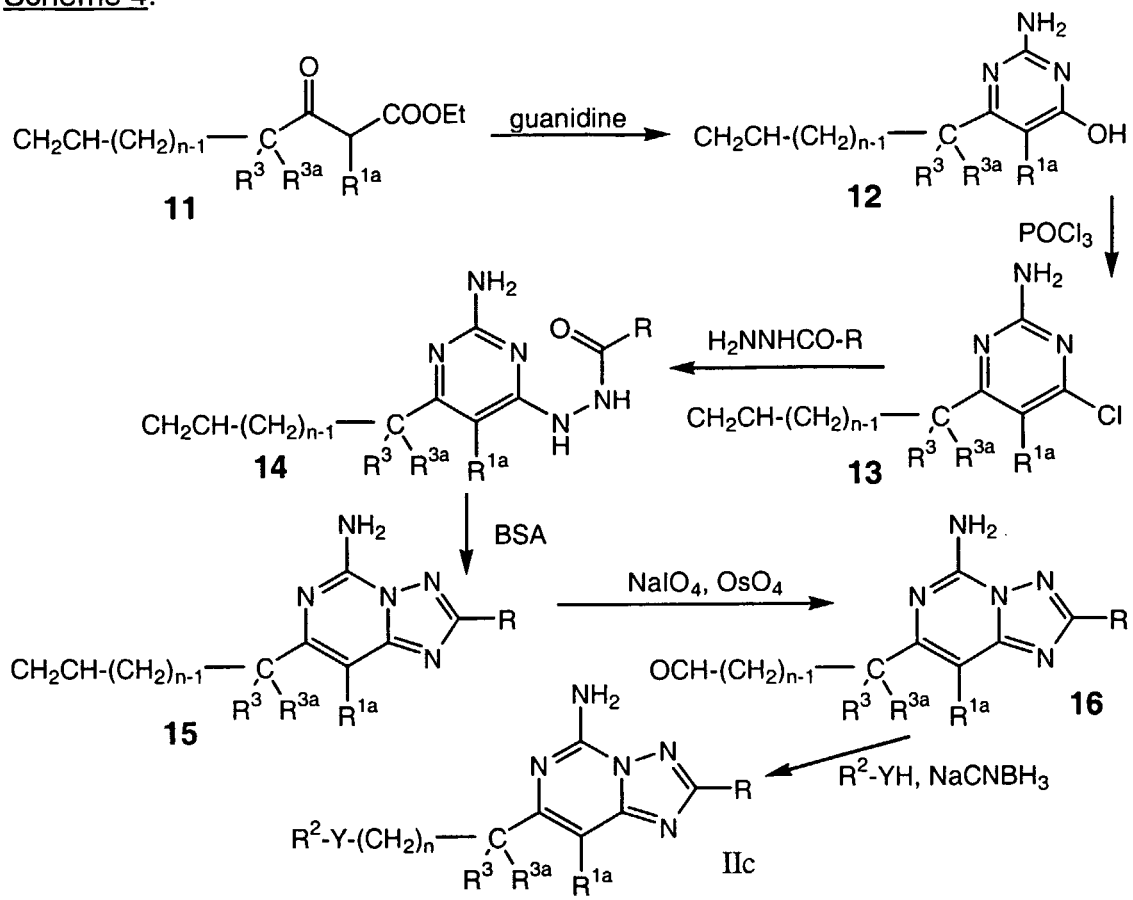
In Scheme 3, the order of the steps is reversed in order to prepare compounds of formula IIb.

Scheme 3:



In Scheme 4, compounds of formula IIc, wherein A is N and X is $-C(R^3)(R^{3a})-$ are prepared.

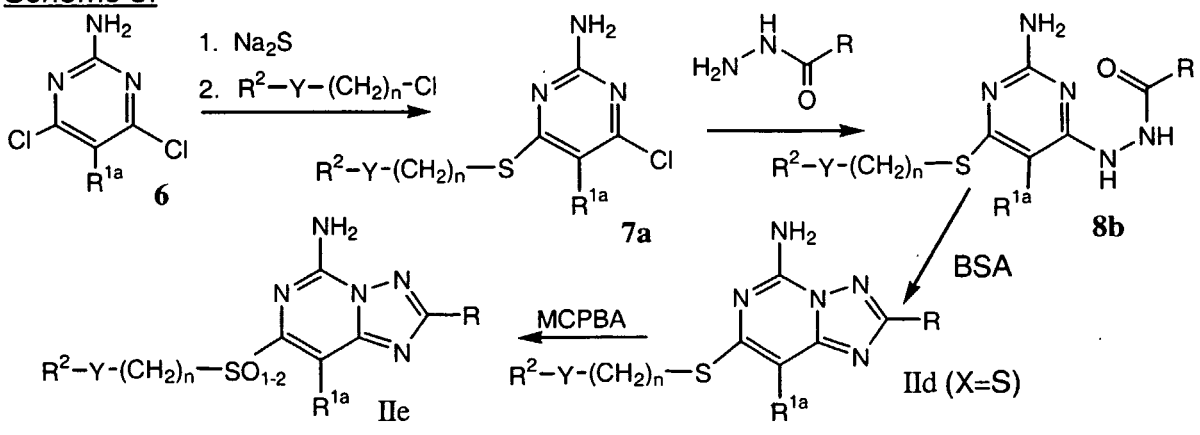
Scheme 4:




Keto-ester **11** is converted to pyrimidine **12**, then to chloride **13**. Reaction with a hydrazide provides **14**, and BSA cyclization yields **15**. The olefinic bond is cleaved to give aldehyde **16**. When Y in IIc is linked to the alkylene chain through a nitrogen atom, reductive amination of **16** yields the desired compounds IIc.

A method of preparing compounds of formula IId or IIe where A is N and X is $-S-$, $-SO-$ or $-SO_2-$ is described in Scheme 5.

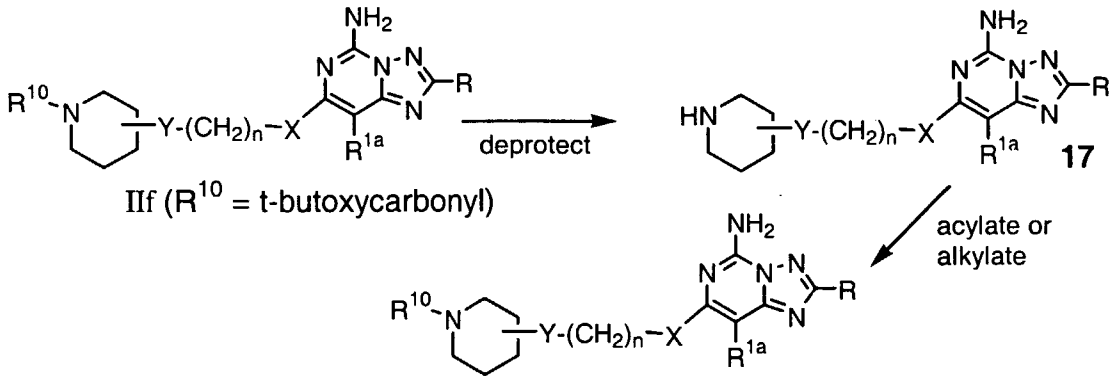
Scheme 5:



Chloride **6** is reacted with $Na_2S$ and the intermediate then alkylated with a chloride or equivalent to give **7a**. This is then converted to IId as in Scheme 2. Subsequent oxidation is employed to prepare the sulfoxide or sulfone of formula IIe.

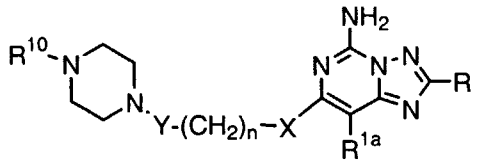
For compounds IIf where $R^2$ contains an $R^{10}$ moiety, such moieties may be modified, as shown in Scheme 6. When $R^{10}$ is *t*-butoxycarbonyl or benzyloxycarbonyl or the like, the group may be converted to H, e.g. by treatment respectively with acid such as TFA or by hydrogenolysis. The resulting **17** may then be converted to a different compound IIf. For $R^{10}$ = alkoxycarbonyl or aroyl, acylation may be achieved with an alkyl chloroformate or aroyl chloride or similar acylating agent. For $R^{10}$ = aralkyl, reductive alkylation of **17** may be achieved with an aryl aldehyde and $NaBH(OAc)_3$.

Scheme 6:



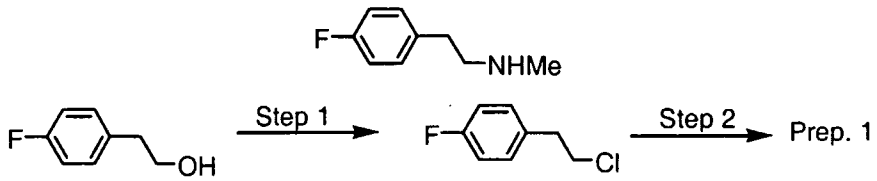

IIf

Similar methodology can be employed to prepare compounds of formula IIg:




IIg

Preparation 1

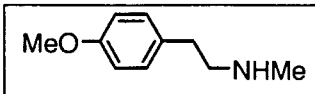
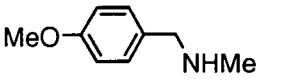
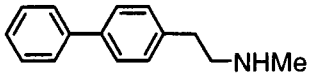
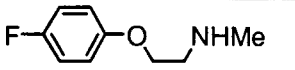
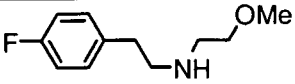
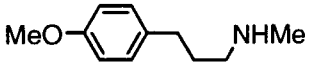
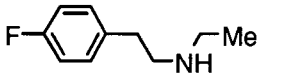
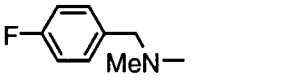
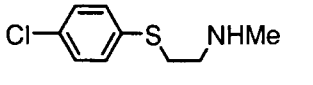
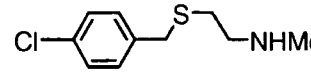
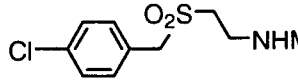
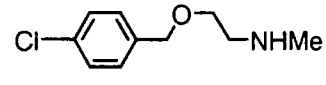
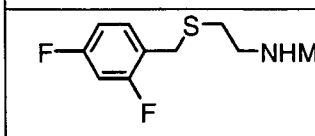
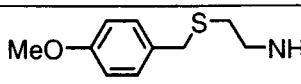



Step 1: To 2-(4-fluorophenyl)ethanol (2.80 g, 20.0 mmol) add $SOCl_2$ (7.14 g, 60 mmol). Add two drops DMF and heat at 70 ºC for 3 h. Concentrate, partition

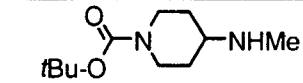
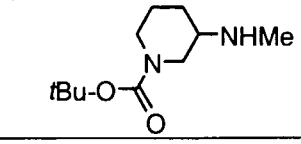
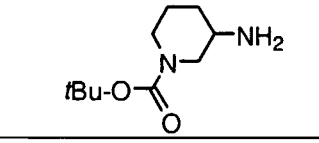
between hexane and ice-water, dry ($MgSO_4$), and concentrate to obtain the chloride as an almost colorless oil.

Step 2: Combine the chloride of Step 1 (1.00 g, 6.3 mmol) with 40% aqueous $CH_3NH_2$ (20 g, 260 mmol). Heat in a sealed tube at 65 ºC for 2.5 h. Allow to cool, dilute with water, and extract with EtOAc. Extract the EtOAc with 0.5M HCl, basify with 20% NaOH, and extract with $CH_2Cl_2$. Dry ($MgSO_4$) and concentrate to obtain the title amine as a yellow oil.

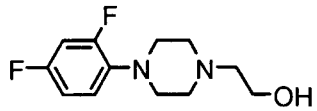
Similarly, convert the corresponding alcohols to the following amines:

| | | |
|---|---|---|
|  |  |  |
|  (from the analogous bromide) |  |  |
|  |  |  |
|  |  |  |
|  |  | |

Similarly, convert the corresponding alcohols via the mesylates into the following amines:

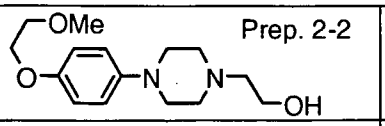
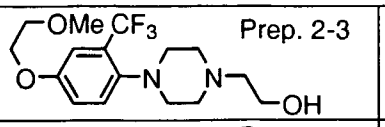
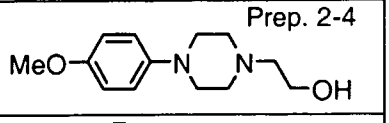
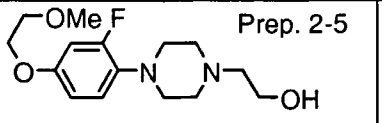
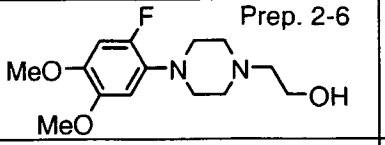
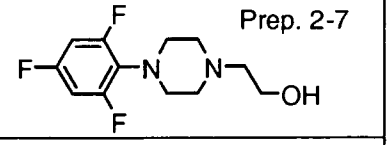
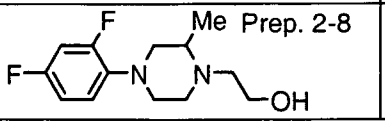
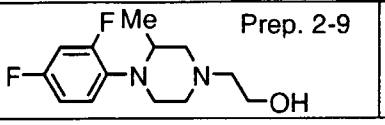
| | | |
|---|---|---|
|  |  |  |

Preparation 2

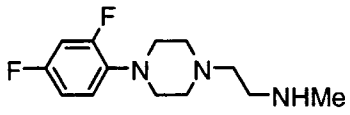


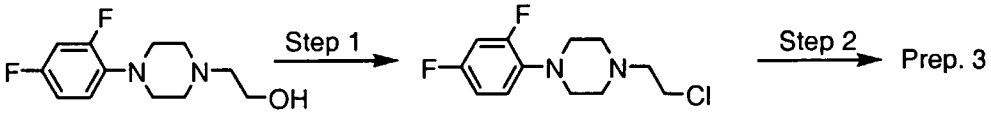
Combine 1-(2,4-difluorophenyl)piperazine (0.50 g, 2.5 mmol), 2-bromoethanol (0.37 g, 3.0 mmol), and $Et_3N$ (0.30 g, 3.0 mmol) in THF (5 ml). Heat at reflux 4 h, allow to cool, and partition between water and $CH_2Cl_2$. Wash the $CH_2Cl_2$ with brine, dry ($MgSO_4$), and concentrate to obtain the title alcohol as a yellow oil.

Similarly prepare:

| | | |
|---|---|---|
|  Prep. 2-2 |  Prep. 2-3 |  Prep. 2-4 |
|  Prep. 2-5 |  Prep. 2-6 |  Prep. 2-7 |
|  Prep. 2-8 |  Prep. 2-9 | |

Preparation 3

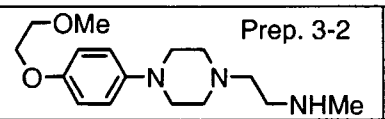
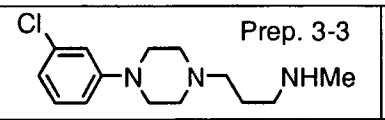
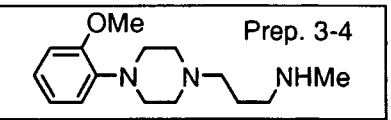
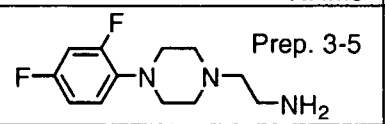
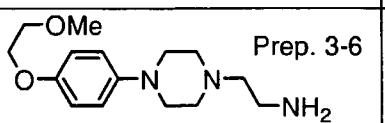
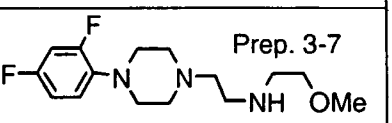
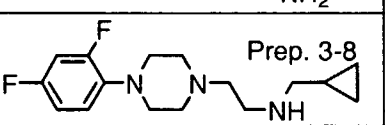
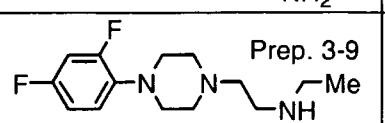
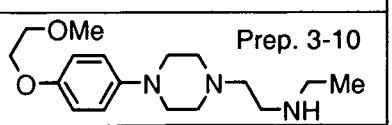
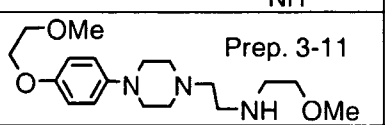
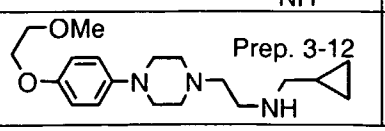
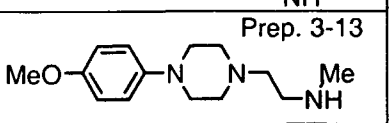


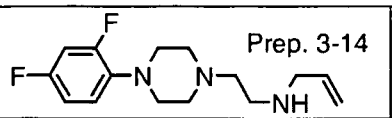
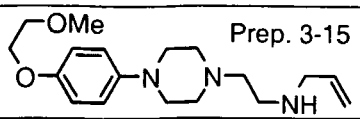
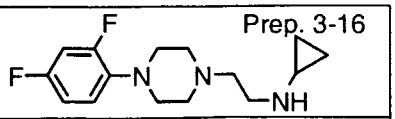
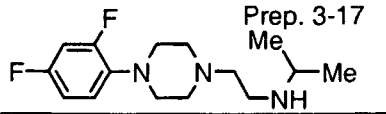
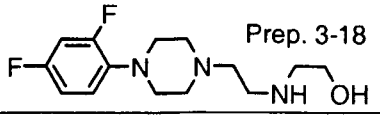
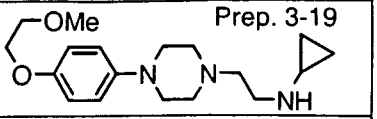
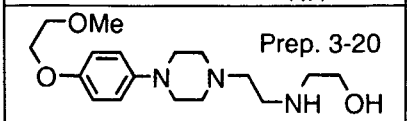
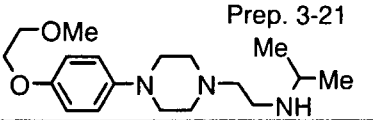
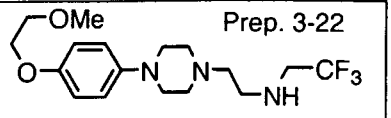
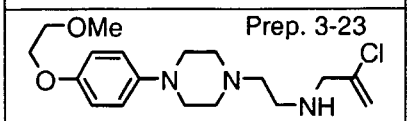
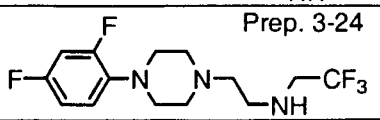
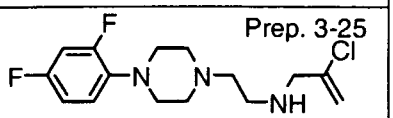
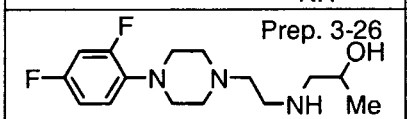
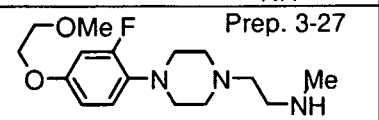
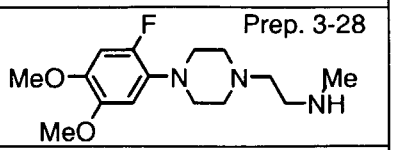
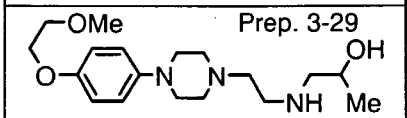
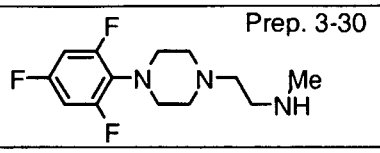
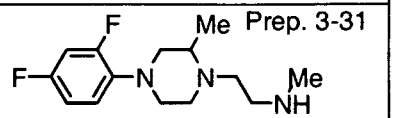
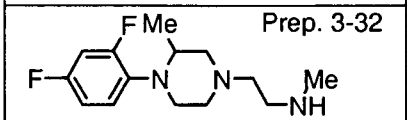
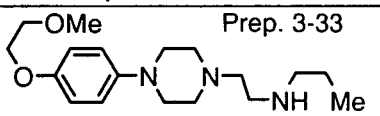
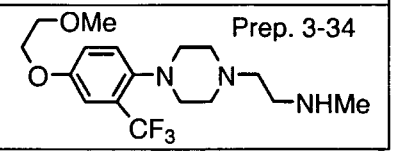



Step 1: To the product of Preparation 2 (0.50 g, 2.1 mmol) in $CH_2Cl_2$ (10 ml) add $SOCl_2$ (0.49 g, 4.2 mmol). Add two drops DMF and stir 4 h. Concentrate, partition between EtOAc and water, dry ($MgSO_4$), and concentrate to obtain the chloride as an almost colorless oil.

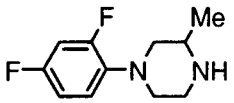
Step 2: Combine the product of Step 1 (0.51 g, 2.0 mmol) with 40% aqueous $CH_3NH_2$ (10 ml, 130 mmol) in EtOH (10 ml). Heat in a sealed tube at 80 ºC for 2 h, allow to cool, concentrate, and partition between EtOAc and water. Dry ($MgSO_4$) and concentrate to obtain the title amine as a yellow oil.

Similarly prepare:

| | | |
|---|---|---|
|  Prep. 3-2 |  Prep. 3-3 |  Prep. 3-4 |
|  Prep. 3-5 |  Prep. 3-6 |  Prep. 3-7 |
|  Prep. 3-8 |  Prep. 3-9 |  Prep. 3-10 |
|  Prep. 3-11 |  Prep. 3-12 |  Prep. 3-13 |

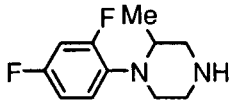
| | | |
|---|---|---|
|  Prep. 3-14 |  Prep. 3-15 |  Prep. 3-16 |
|  Prep. 3-17 |  Prep. 3-18 |  Prep. 3-19 |
|  Prep. 3-20 |  Prep. 3-21 |  Prep. 3-22 |
|  Prep. 3-23 |  Prep. 3-24 |  Prep. 3-25 |
|  Prep. 3-26 |  Prep. 3-27 |  Prep. 3-28 |
|  Prep. 3-29 |  Prep. 3-30 |  Prep. 3-31 |
|  Prep. 3-32 |  Prep. 3-33 |  Prep. 3-34 |

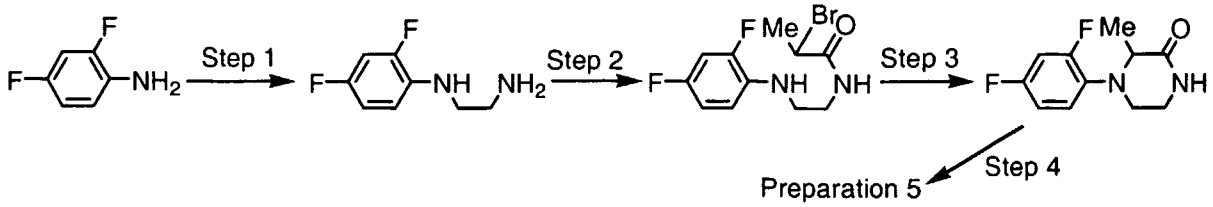
## Preparation 4



Combine 2, 4-difluorobromobenzene (4.0g, 20.7mmol), 2-methylpiperazine (24.9g, 249mmol), NaO-*t*Bu (2.79g, 29.0mmol), ±-BINAP (0.77g, 1.2mmol), and $Pd_2(dba)_3$ (0.24g, 0.41mmol) in toluene (40ml). Heat at reflux 16h, allow to cool, and extract with 1N HCl (4x50ml). Basify with NaOH to pH 13 and extract with $CH_2Cl_2$. Dry ($MgSO_4$) and concentrate to give the product as a brown oil.

## Preparation 5





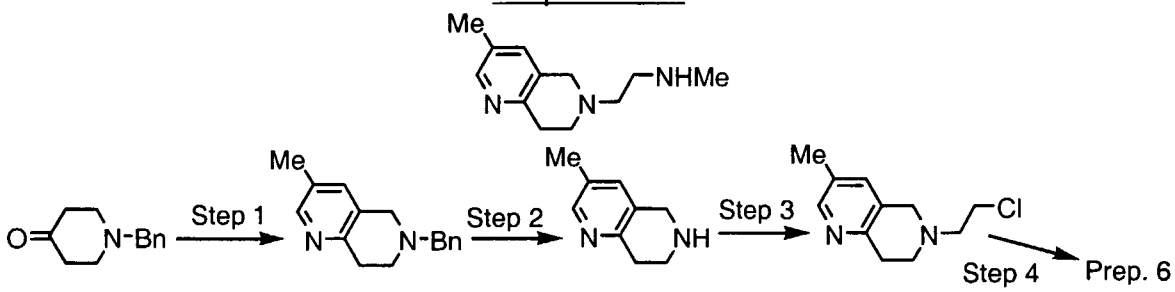
Step 1: Combine 2,4-difluoroaniline (10.0g, 77.4mmol) and 2-bromoethylamine•HBr (15.9g, 77.4mmol) in toluene (100ml). Heat at reflux 16h, allow to cool, and remove the toluene layer. Dissolve the oily layer in water, basify with NaOH to pH 11, and extract with $CH_2Cl_2$. Dry ($MgSO_4$), concentrate, and distill at 120-30 °C (1mm). Chromatograph on silica to obtain the product as a brown oil.

Step 2: Dissolve the product of Step 1 (3.0g, 17mmol) in $CH_2Cl_2$ (25ml). Cool in ice and add $Et_3N$ (5.3ml, 38mmol), followed by 2-bromopropionyl bromide (2.1ml, 19mmol). Allow to warm to RT, stir 16h, cool in ice, and add more bromide (1.1g) and $Et_3N$ (1.0g). Allow to warm to RT, stir 2h, wash with water, dry ($MgSO_4$) and concentrate to obtain crude brown oil.

Step 3: Treat the product of Step 2 (5.86g, 19mmol) with DIPEA (2.97g, 23mmol) and KI (1.58g, 9.5mmol) in DMF (15ml). Heat at 80 ºC 18h, allow to cool, concentrate and chromatograph on silica to obtain the product as a brown solid.

Step 4: Dissolve the product of Step 3 (1.33g, 5.86mmol) in THF (20ml) and cool in ice. Add slowly 1.0M $BH_3$· THF solution (15ml, 15mmol). Allow to warm to RT, stir 1h, add additional $BH_3$· THF solution (7ml), and stir 2h. Cool in ice and quench slowly with MeOH. Concentrate and partition with $CH_2Cl_2$ and 0.5N NaOH. Dry ($MgSO_4$), concentrate and purify by PLC to obtain the title compound as a yellow oil.

Preparation 6




Step 1: Combine N-benzyl-4-piperidone (3.57ml, 20mmol), 3-ethoxymethacrolein (3.76ml, 30mmol), $NH_4OAc$ (0.82g, 11mmol), and 28% aqueous ammonia (4.17ml, 62mmol). Heat in a sealed tube at 90 ºC 48h, allow to cool, and partition between $Et_2O$ and 1N $NaHCO_3$. Extract the $Et_2O$ with 1N HCl and basify the extract with NaOH to pH 13. Extract with $Et_2O$, dry ($MgSO_4$) and concentrate. Subject the oil to Kugelrohr distillation at 0.5mm, collecting 90-160 ºC to obtain the product as an orange oil.

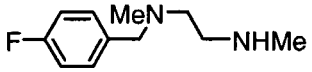
Step 2: Dissolve the product of Step 1 (1.73g, 7.3mmol) in 10:1 MeOH/conc. HCl (44ml). Add 10% Pd/C (0.40g) and hydrogenate at 60psi for 18h. Filter through Celite and concentrate to solid. Dissolve in 95% EtOH and add NaO-*t*Bu (0.70g).

Concentrate, treat with EtOH, filter, and concentrate to leave the crude product as a yellow solid.

Step 3: Combine the product of Step 2 (0.200g, 1.35mmol), 1-bromo-2-chloroethane (0.45ml, 5.4mmol), and DIPEA (0.28ml, 1.6mmol) in DMF (10ml). Stir 48h, add 1N NaOH (5ml), and extract with $Et_2O$. Dry ($MgSO_4$), concentrate and purify by PLC to obtain the product as a yellow oil.

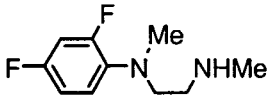
Step 4: Combine the product of Step 3 (0.22g, 1.0mmol), with 40% aqueous $MeNH_2$ (5.0ml) and EtOH (5ml). Heat in a sealed tube at 100 ºC 3h, allow to cool, add 1N NaOH (3ml), concentrate and partition between $CH_2Cl_2$ and water. Dry ($MgSO_4$), and concentrate to obtain the title compound as a light brown oil.

Preparation 7



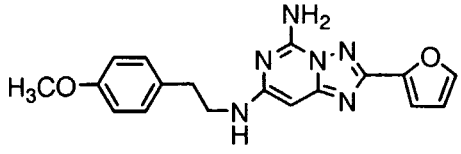

Combine 4-fluorobenzyl chloride (1.74g, 12.0mmol), N,N'-dimethylethylene-diamine (3.17g,36mmol), KI (0.20g, 1.2mmol), and $NaHCO_3$ (1.51g, 18mmol) in EtOH (20ml). Heat at reflux 4h, filter, and concentrate. Partition with 1N HCl and EtOAc and basify the aqueous layer with NaOH. Extract with $CH_2Cl_2$, dry ($MgSO_4$), and concentrate. Distill at 0.5mm up to 100 ºC to obtain the title compound as a colorless liquid.

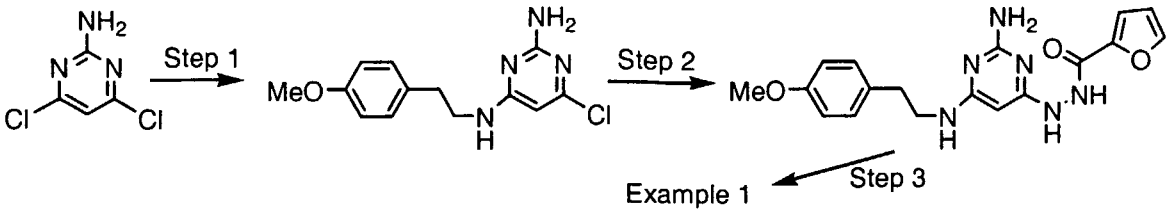
Preparation 8




Combine 2,4-difluorfluoro-N-methylaniline (1.00g, 6.98mmol) and 4M HCl/ dioxane (10ml) in MeOH (10ml). Concentrate to a white solid. Add 3-methyl-2-oxazolidinone (0.60g, 6.98mmol). Heat at 160 ºC 18h. Allow to cool, basify with NaOH, and extract with $CH_2Cl_2$. Dry ($MgSO_4$), concentrate, and chromatograph on silica to obtain the title compound as a yellow oil. This contains some of the product with aniline methyl removed.

Example 1



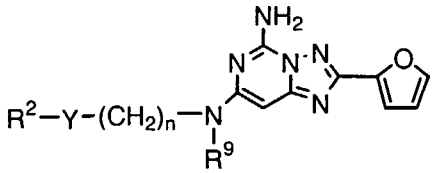



Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.50 g, 3.0 mmol), 2-(4-methoxy-phenyl)ethylamine (0.51 g, 3.4 mmol) and $K_2CO_3$ (0.46 g, 3.4 mmole) in EtOH (8 ml). Heat in a sealed tube at 90 ºC 1 h. Stir another 16 h, dilute with water (15 ml), filter, and purify on PLC to obtain the chloropyrimidine as a white solid.

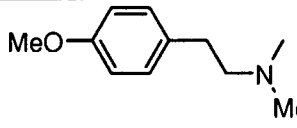
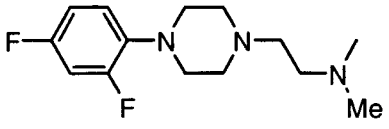
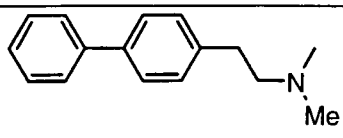
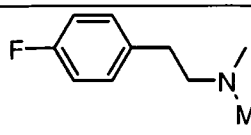
Step 2: Combine the product of Step 1 (0.30 g, 1.08 mmol), 2-furoic hydrazide (0.16 g, 1.3 mmol),and 1.0N HCl (0.4 ml) in EtOH (3 ml). Heat in a sealed tube at 90 ºC for 16 h. Basify with $NH_3$, extract with EtOAc, and purify on PLC to obtain the hydrazide as a yellow solid.

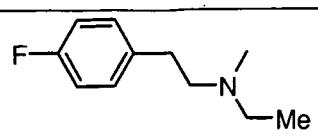
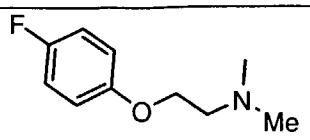
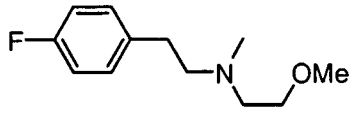
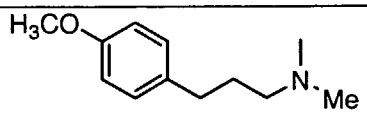
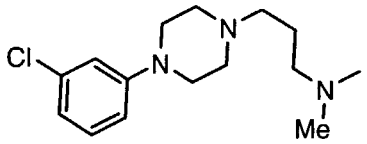
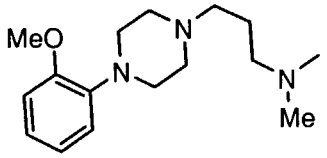
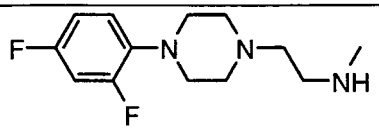
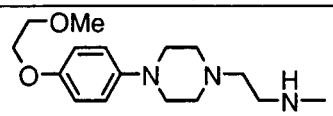
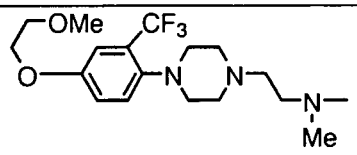
Step 3: Add the product of Step 2 to BSA (4.0 ml). Heat at 120 ºC 18 h. Pour into $CH_3OH$, concentrate, and purify on PLC to obtain the title compound as a white solid, MS: m/e 351 (M+1).

In a similar manner, prepare the following compounds ($Et_3N$ employed as base in Step 1):

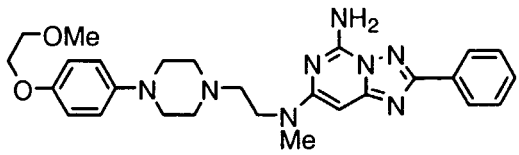



wherein $R^2$-Y-$(CH_2)_n$-N($R^9$)- is as defined in the table:

| Example | $R^2$-Y-$(CH_2)_n$-N($R^9$)- | MS m/e |
|---|---|---|
| 1-2 |  | 365 |
| 1-3 |  | 455 |
| 1-4 |  | 411 |
| 1-5 |  | 353 |

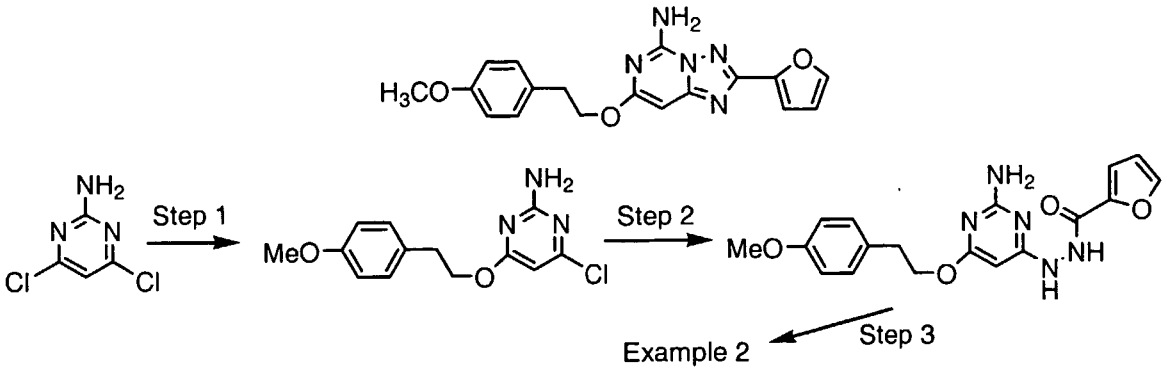
| | | |
|---|---|---|
| 1-6 |  | 367 |
| 1-7 |  | 369 |
| 1-8 |  | 397 |
| 1-9 |  | 379 |
| 1-10 |  | 467, 469 |
| 1-11 |  | 463 |
| 1-12 |  | 441 |
| 1-13 |  | 479 |
| 1-14 |  | 561 |

Similarly, by employing benzoic hydrazide in place of furoic hydrazide, prepare Example 1-15 as a yellow solid.



1-15: MS: m/e 503 (M+1)

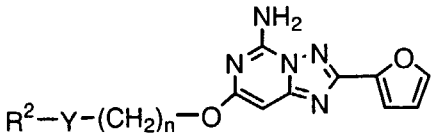
Example 2



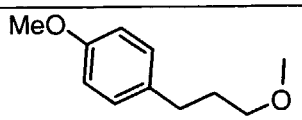
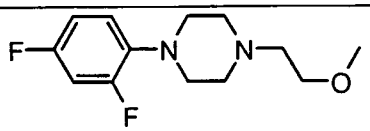
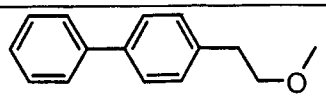
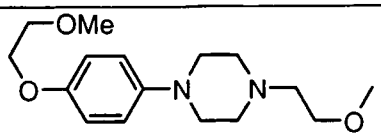
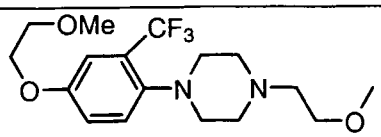

Step 1: To NaH (60% in oil, 0.16 g, 4.0 mmol) in THF (6 ml) add 2-(4-methoxy-phenyl)ethanol (0.46 g, 3.0 mmol). Stir 0.5 h and add 2-amino-4,6-dichloro-pyrimidine (0.50 g, 3.0 mmol). Heat at reflux 24 h. Filter, wash with $CH_2Cl_2$, concentrate, and purify on PLC to obtain the chloropyrimidine as a white solid.

Conduct Steps 2 and 3 as in Example 1 to obtain the title compound as a white solid, MS: m/e 352 (M+1).

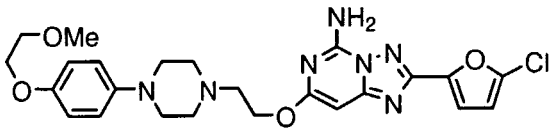
In a similar manner prepare the following:




wherein $R^2$-Y-$(CH_2)_n$-O- is as defined in the table:

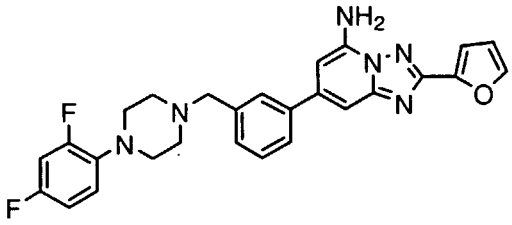
| Example | $R^2$-Y-$(CH_2)_n$-O- | MS m/e |
|---|---|---|
| 2-2 |  | 366 |
| 2-3 |  | 442 |
| 2-4 |  | 398 |
| 2-5 |  | 480 |
| 2-6 |  | 548 |

Similarly, by employing 5-chloro-2-furoic hydrazide in place of furoic hydrazide, prepare Example 2-7 as a yellow solid:

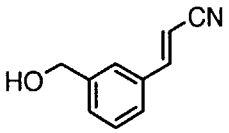


2-7: MS m/e 514, 516 (M+1)

Example 3

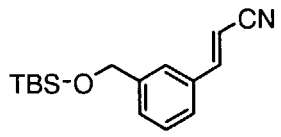


Step 1:



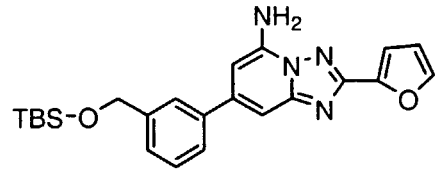
Combine 3-iodobenzyl alcohol (2.00 g, 8.5 mmol), acrylonitrile (0.67 ml, 10.2 mmol), and $Et_3N$ (4.3 ml, 26 mmol) in DMF (30 ml). Purge with $N_2$ and add $(Ph_3P)_2PdCl_2$ (0.12 g, 0.17 mmol). Heat in a sealed vessel 3 days at 120º, allow to cool, and partition between $CH_2Cl_2$ and sat. $NaHCO_3$. Dry ($MgSO_4$) and concentrate. Chromatograph on silica to obtain the nitrile as a yellow oil.

Step 2:



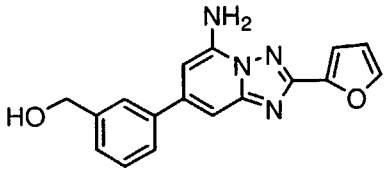
Combine the product of Step 1 (1.25 g, 7.9 mmol), *t*-butyldimethylsilyl chloride (1.42 g, 9.4 mmol), and imidazole (0.69 g, 10.2 mmol) in DMF (15 ml). Stir 7h, partition between $Et_2O$ and water, dry the $Et_2O$ ($MgSO_4$) and concentrate to obtain the silyl ether as a colorless oil.

Step 3:



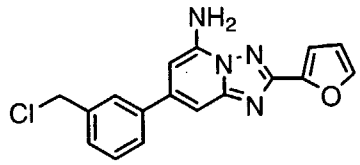
To a boiling suspension of potassium t-butoxide (2.34 g, 24.4 mmol) in THF (20 ml) add dropwise over 5h a solution of the product of Step 2 (2.15 g, 7.9 mmol) and 3-(2-furyl)-5-phenylsulfonylmethyl[1,2,4]triazole (2.27g, 7.9mmol) in THF (20 ml). Heat 18h, allow to cool, add water (30 ml), and extract 3x with 5% $CH_3OH/CH_2Cl_2$. Dry ($MgSO_4$), concentrate, and chromatograph on silica to obtain the bicyclic as a yellow solid.

Step 4:



To the product of Step 3 (0.75 g, 1.8 mmol) in THF (5 ml) add tetrabutylammonium fluoride (1.0M in THF, 2.14 ml). Stir 2h, concentrate, and purify on PLC to obtain the alcohol as a yellow solid.

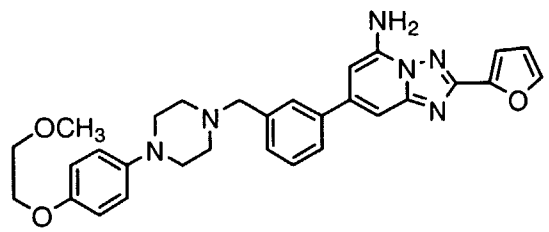
Step 5:



To the product of Step 4 (0.200 g, 0.65 mmol) in $CH_2Cl_2$ (10 ml) add $SOCl_2$ (0.19 ml, 2.6 mmol) and two drops pyridine. Heat at reflux 1h, allow to cool, wash with 1N NaOH, concentrate, dry ($MgSO_4$), and concentrate to obtain the crude chloride as a yellow solid.

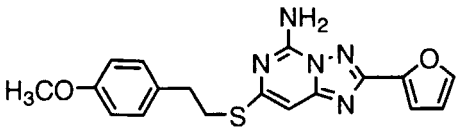
Step 6: Combine the product of Step 5 (0.090 g, 0.28 mmol) with 1-(2,4-difluorophenyl)piperazine (0.065 g, 0.33 mmol) and diisopropylethylamine (0.058 ml) in DMF (4 ml). Stir 3 days, heat to 60º for 3h, allow to cool, concentrate, and purify on PLC to obtain the title compound as a white solid: MS m/e = 487 (M+1).

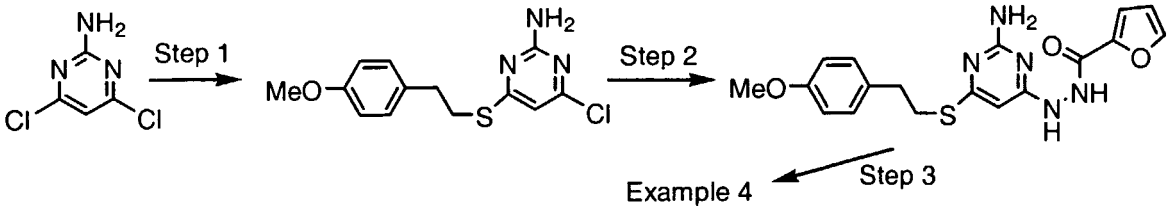
In similar fashion, employ 1-(4-(2-methoxyethoxy)phenyl)piperazine to obtain Example 3-2 as a white solid.



3-2: MS m/e 525

Example 4

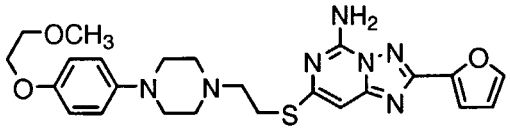




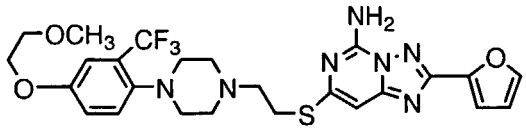

Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.50 g, 3.0 mmol) and $Na_2S$ (0.29 g, 3.7 mmole) in DMF (6 ml). Stir for 1 h. Add 4-methoxyphenethyl chloride (0.64 g, 3.77 mmol) and heat at 80 ºC 18 h. Add water and extract with EtOAc. Purify on PLC to obtain the chloropyrimidine as a white solid.

Steps 2 and 3: Conduct as for Example 1, Steps 2 and 3, to obtain the title compound as a white solid, MS: m/e 368 (M+1).

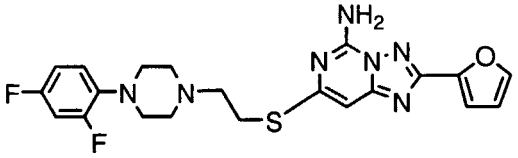
In a similar manner, from the products of Preparation 3-2, Step 1, and Preparation 3-6, Step 1, prepare the following:



4-2: MS: m/e 496

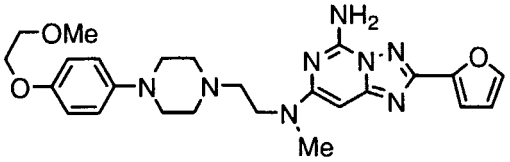


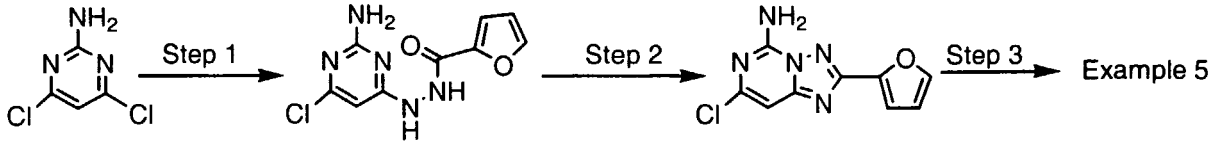
4-3: MS: m/e 564



4-4: MS m/e 458

Example 5



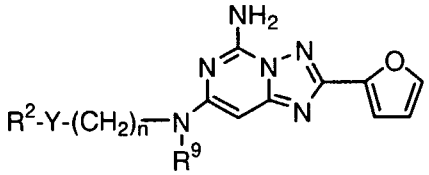


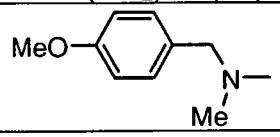
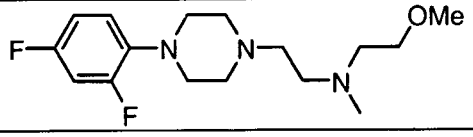
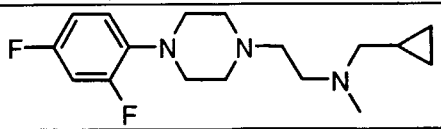
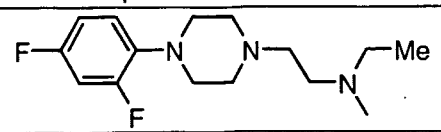
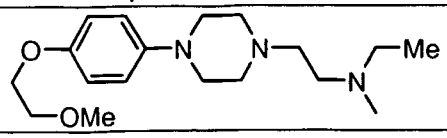
Step 1: Combine 2-amino-4,6-dichloropyrimidine (1.00 g, 6.10 mmol), 2-furoic hydrazide (0.97 g, 7.7 mmol) and $K_2CO_3$ (1.13 g, 8.2 mmole) in EtOH (6 ml). Heat in a sealed tube at 100 ºC 18 h. Allow to cool, filter, wash with water to obtain product. Extract the filtrate with EtOAc, concentrate and recrystallize from EtOAc to obtain additional product as a yellow solid.

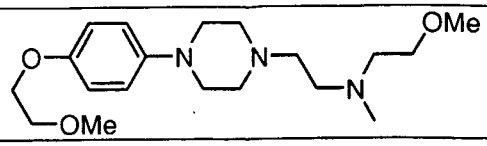
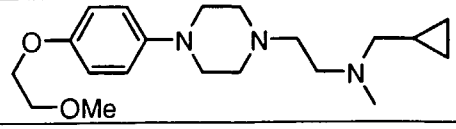
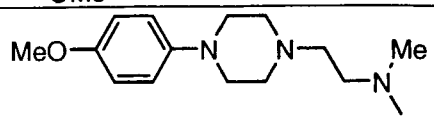
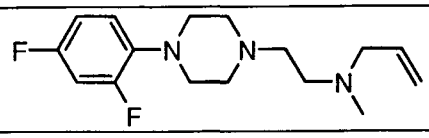
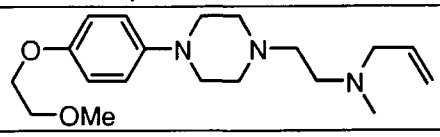
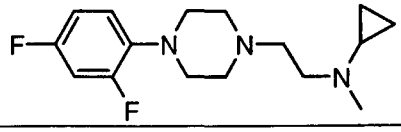
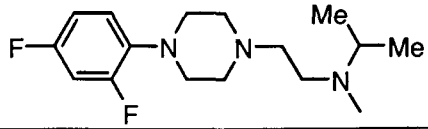
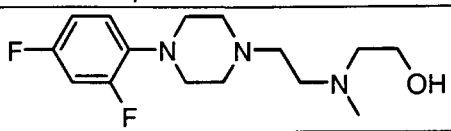
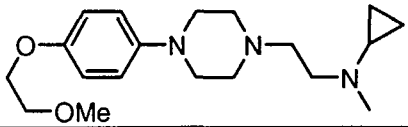
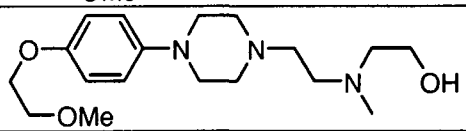
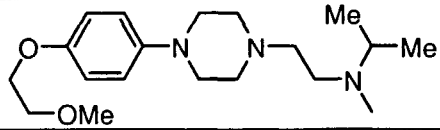
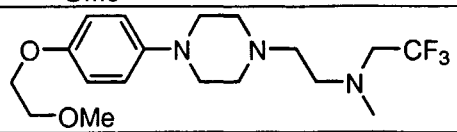
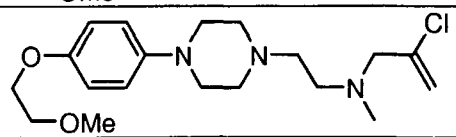
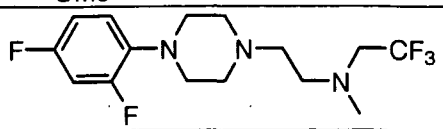
Step 2: Add the product of Step 1 (0.50 g, 2.13 mmol) to BSA (15 ml). Heat at 120 ºC 18 h, allow to cool, and pour into $CH_3OH$ (20 ml). Concentrate and heat at reflux in 50% EtOH (40 ml) 1 h. Remove EtOH and extract with $CH_2Cl_2$. Dry and concentrate to obtain the product as a white solid.

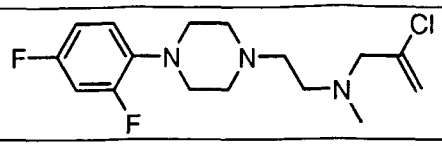
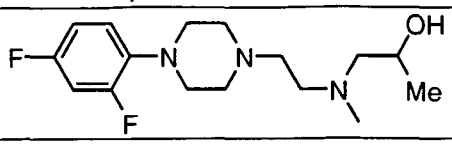
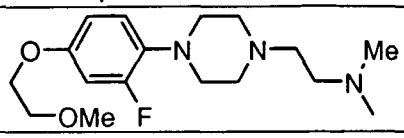
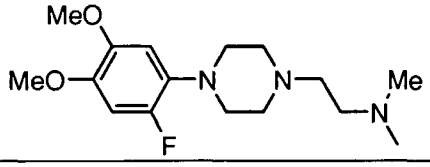
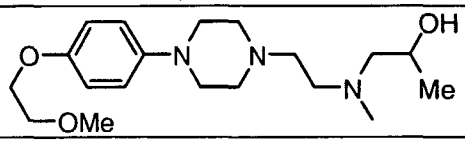
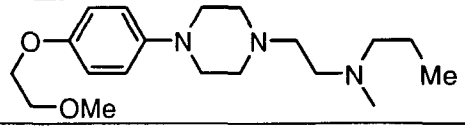
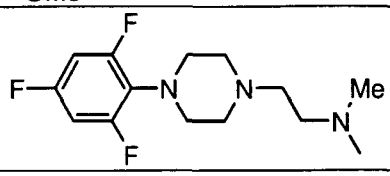
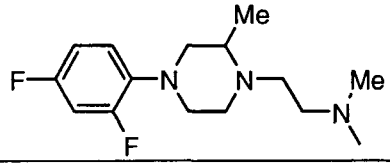
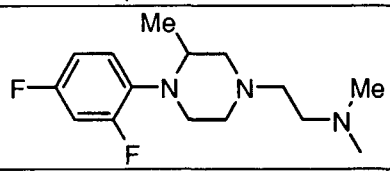
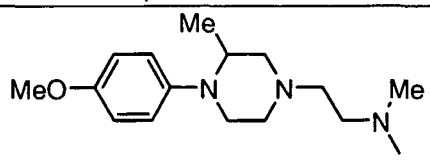
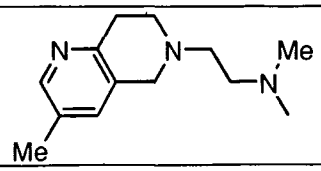
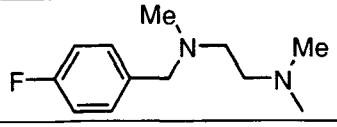
Step 3: Combine the product of Step 2 (0.093 g, 0.39 mmol), the product of Preparation 3-2 (0.127 g, 0.43 mmol), and DBU (0.059 ml, 0.42 mmol) in DMF (2 ml). Heat at 140 ºC 2 h, concentrate and purify on PLC to obtain the title compound as a yellow solid, MS: m/e 493 (M+1).

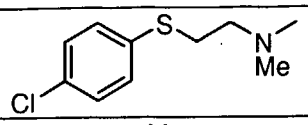
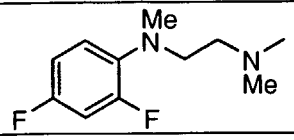
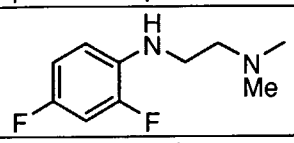
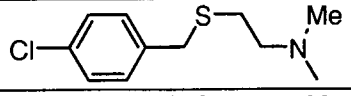
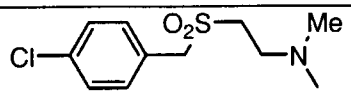
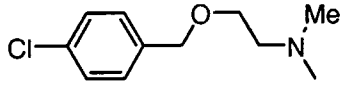
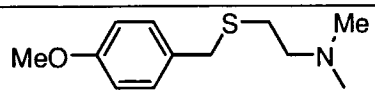
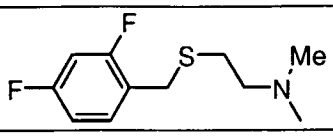
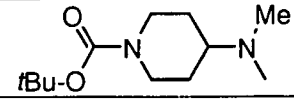
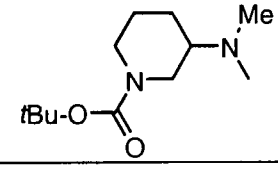
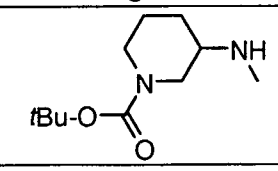
In a similar manner, employing the appropriate amine from Preparation 1 or Preparation 3, prepare the following:



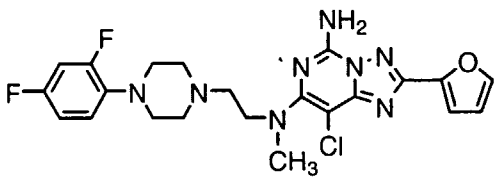

| Example | $R^2$-Y-$(CH_2)_n$-N($R^9$)- | MS m/e |
|---|---|---|
| 5-2 |  | 339 |
| 5-3 |  | 499 |
| 5-4 |  | 495 |
| 5-5 |  | 469 |
| 5-6 |  | 507 |

| | | |
|---|---|---|
| 5-7 |  | 537 |
| 5-8 |  | 533 |
| 5-9 |  | 449 |
| 5-10 |  | 481 |
| 5-11 |  | 519 |
| 5-12 |  | 481 |
| 5-13 |  | 483 |
| 5-14 |  | 485 |
| 5-15 |  | 519 |
| 5-16 |  | 523 |
| 5-17 |  | 521 |
| 5-18 |  | 561 |
| 5-19 |  | 553, 555 |
| 5-20 |  | 523 |

| | | |
|---|---|---|
| 5-21 |  | 515, 517 |
| 5-22 |  | 499 |
| 5-23 |  | 511 |
| 5-24 |  | 497 |
| 5-25 |  | 537 |
| 5-26 |  | 521 |
| 5-27 |  | 473 |
| 5-28 |  | 469 |
| 5-29 |  | 469 |
| 5-30 |  | 463 |
| 5-31 |  | 405 |
| 5-32 |  | 396 |

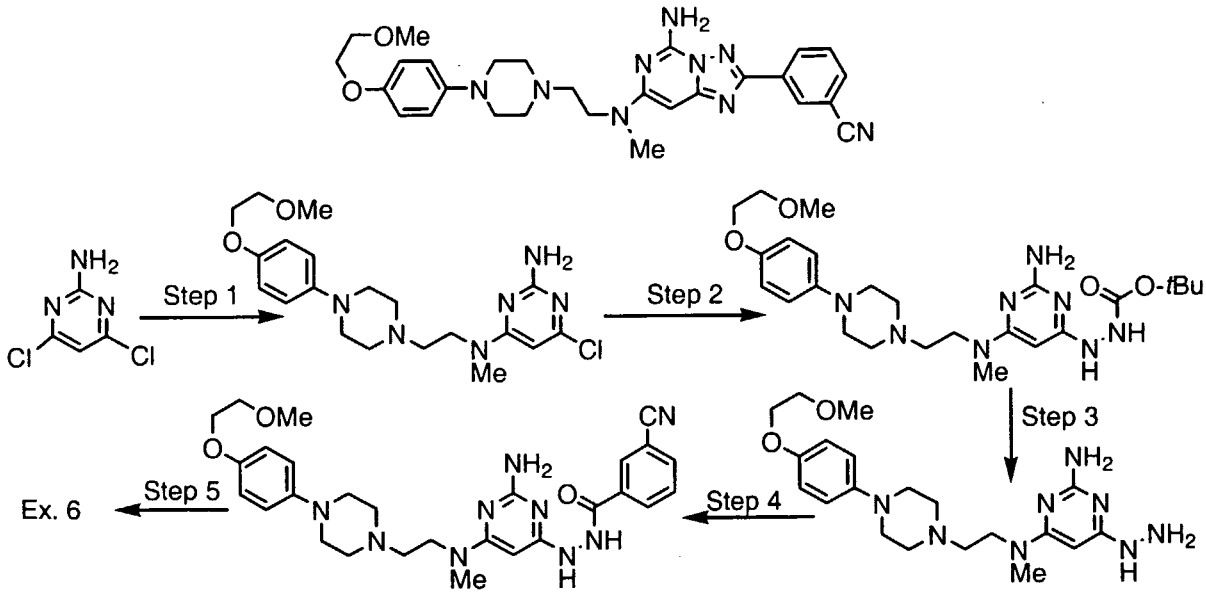
| | | |
|---|---|---|
| 5-33 |  | 401, 403 |
| 5-34 |  | 400 |
| 5-35 |  | 386 |
| 5-36 |  | 415, 417 |
| 5-37 |  | 447, 449 |
| 5-38 |  | 399, 401 |
| 5-39 |  | 411 |
| 5-40 |  | 417 |
| 5-41 |  | 414 |
| 5-42 |  | 414 |
| 5-43 |  | 400 |

In a similar fashion, employ 2-amino-4,5,6-trichloropyrimidine as starting material to obtain Example 5-44 as a yellow solid.



5-44: MS m/e 489, 491 (M+1)

Example 6




Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.477g, 2.73mmol), the product of Preparation 3-2 (0.800g, 2.73mmol) and DIPEA (0.57ml, 3.27mmole) in DMF (5ml). Heat in a sealed tube at 90 ºC 14h. Allow to cool, concentrate, and chromatograph on silica to obtain the product as a yellow solid.

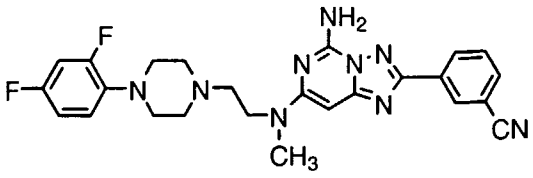
Step 2: Combine the product of Step 1 (1.07g, 2.54mmol), *t*-butyl carbazate (1.01g, 7.61mmol) and 4.0M HCl/dioxane (0.76ml, 3.04mmole) in EtOH (12ml). Heat in a sealed tube at 100 ºC 18h, allow to cool, and add 2N $NH_3$/MeOH M (10ml). Concentrate and chromatograph on silica to obtain the product as a yellow solid.

Step 3: Dissolve the product of Step 2 (0.90g, 1.74mmol) in $CH_2Cl_2$-MeOH (1:17, 20ml). Add 4.0M HCl/dioxane (5.0ml, 20mmole). Stir 18h, concentrate, add 1N NaOH (10ml), and extract with $CH_2Cl_2$. Dry ($MgSO_4$), concentrate, and chromatograph on silica to obtain the product as a yellow solid.

Step 4: To a solution of 3-cyanobenzoic acid (0.047g, 0.32mmol) in DMF (3ml) add the product of Step 3 (0.110g, 0.26mmol), EDCI (0.061g, 0.32mmol), HOBt•$H_2O$ (0.043g, 0.32mmol), and NMM (0.035ml, 0.32mmol). Stir 3h, concentrate, and purify by PLC to obtain the product as a yellow solid.

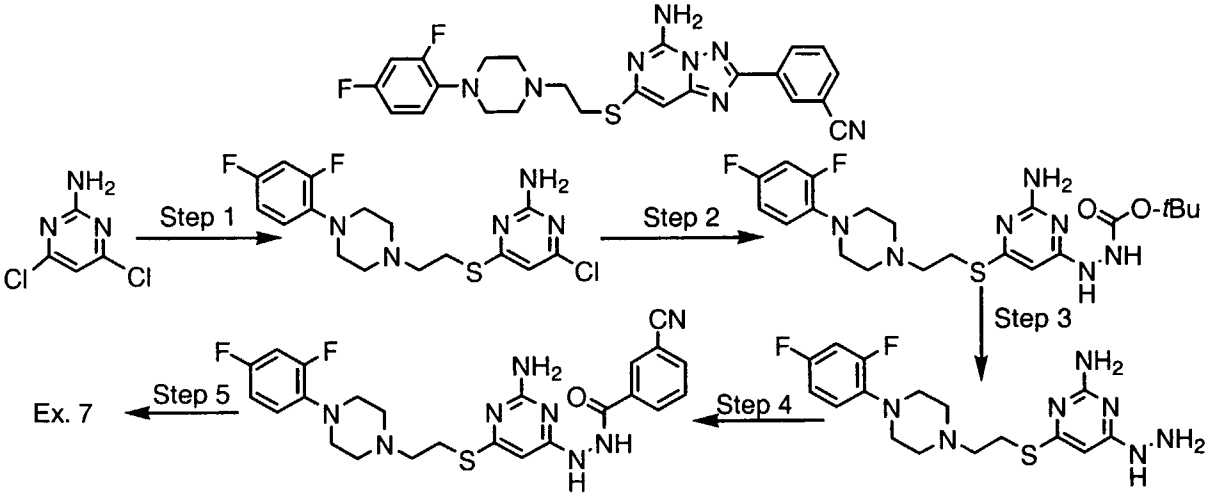
Step 5: Add the product of Step 4 (0.101g, 0.18mmol) to BSA (6.0ml). Heat at 120 ºC 18h, allow to cool, concentrate, add MeOH (20ml), stir 0.5h, concentrate, and purify by PLC to obtain the title compound as a yellow solid, MS: m/e 528 (M+1).

In a similar fashion, employ the product of Preparation 3 as starting material to obtain Example 6-2 as a white solid.



EX. 6-2: MS: m/e 490 (M+1)

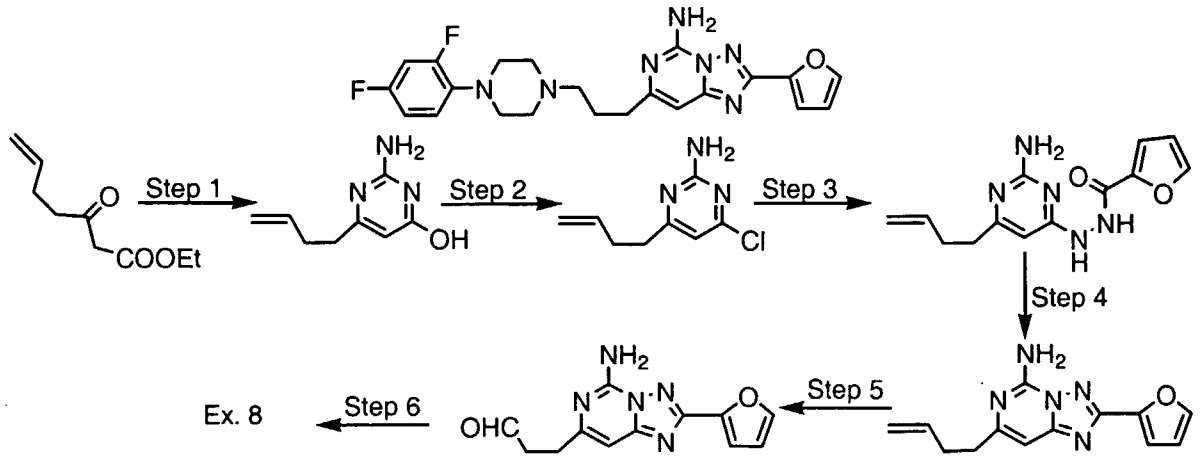
Example 7




Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.515g, 3.14mmol) and $Na_2S$ (0.294g, 3.76mmole) in DMF (3ml). Stir for 1h. Add the product of Preparation 3, Step 1 (0.900g, 3.45mmol) in DMF (2ml) and heat at 80 ºC 18h. Allow to cool, add $CH_2Cl_2$, and filter. Concentrate and chromatograph on silica to obtain the product as a yellow solid.

Steps 2-5: Treat the product of Step 1 according to Example 6, Steps 2-5, to obtain the title compound as an off-white solid, MS: m/e 493 (M+1).

Example 8




Step 1: Combine ethyl 3-oxo-6-heptenoate (6.68g, 39.2mmol) and guanidine carbonate (12.7g, 70.6mmol) in EtOH (100ml). Heat at reflux 20h, allow to cool, and

add $CH_2Cl_2$ (100ml). Filter, concentrate, and chromatograph on silica to obtain a white solid.

Step 2: Treat the product of Step 1 (2.35g, 14.2mmol) with $POCl_3$ (20ml). Heat at reflux 2h, concentrate, pour onto ice water, and basify with NaOH to pH9. Extract with $CH_2Cl_2$, dry ($MgSO_4$), concentrate, and chromatograph on silica to obtain a yellow oil.

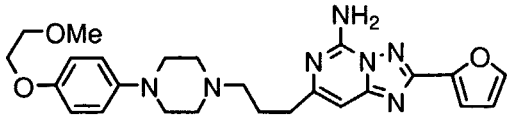
Step 3: Combine the product of Step 2 (0.90g, 4.9mmol), 2-furoic hydrazide (0.865g, 6.86mmol) and 4.0M HCl/dioxane (1.47ml, 5.88mmol) in EtOH (10ml). Heat in a sealed tube at 100 ºC 18h, allow to cool, and add 2N $NH_3$/MeOH (10ml). Concentrate and chromatograph on silica to obtain the product as a yellow solid.

Step 4: Add the product of Step 3 (0.8g, 2.9mmol) to BSA (10ml). Heat at 130 ºC 6h, allow to cool, and concentrate. Wash with water to obtain a yellow solid.

Step 5: Dissolve the product of Step 4 (0.10g, 0.39mmol) in THF (8ml), cool in ice, add water (5ml), then $NaIO_4$ (0.419g, 1.96mmol). Add two crystals $OsO_4$ and stir 5h. Partition with $CH_2Cl_2$ and water, dry ($MgSO_4$), concentrate, and purify by PLC to obtain a yellow solid.

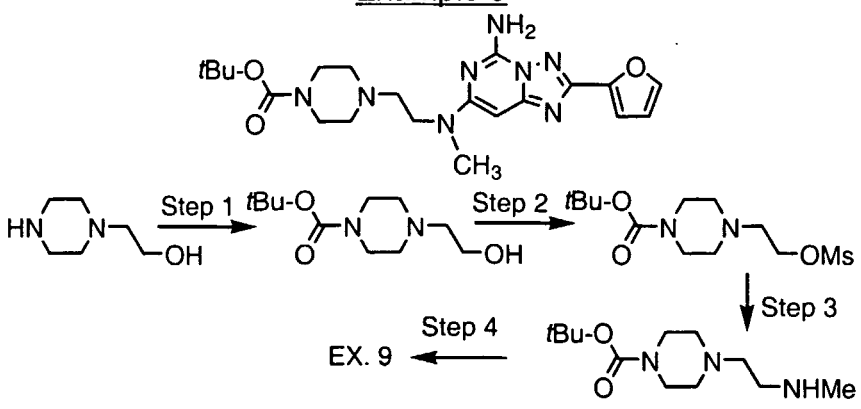
Step 6: Dissolve the product of Step 5 (0.080g, 0.31mmol) in $CH_2Cl_2$ (5ml). Add 1-(2,4-difluorophenyl)piperazine (0.185g, 0.93mmol), AcOH (0.30ml), and $NaCNBH_3$ (0.066g, 0.31mmol). Stir 18h, concentrate, and purify by PLC to obtain the title compound as a white solid, MS: m/e = 440 (M+1).

In a similar fashion, employ the appropriate aryl-piperazine to obtain Example 8-2 as a yellow powder.



EX. 8-2: MS: m/e = 478 (M+1)

Example 9



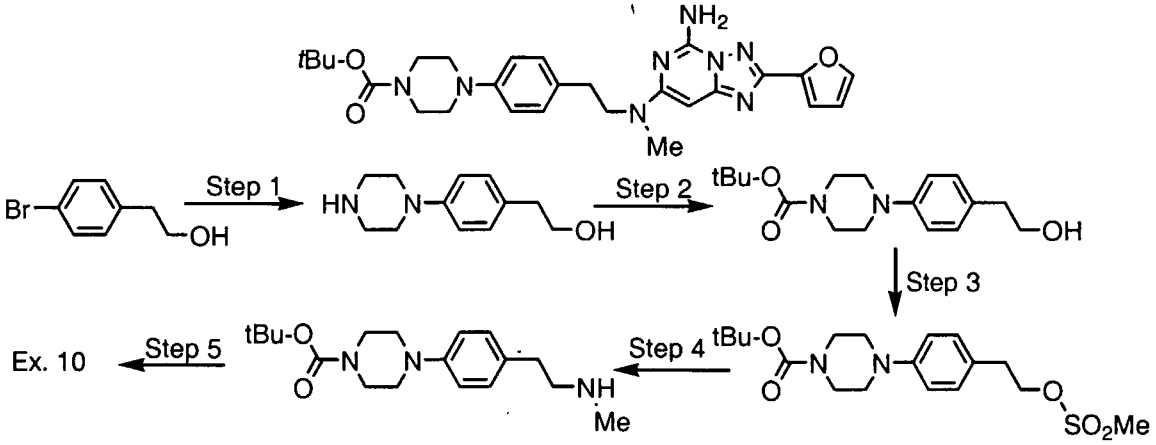
Step 1: Dissolve 1-(2-hydroxyethy)piperazine (3.25g, 25mmol) in THF (40ml) and cool in ice. Add, portionwise, $Boc_2O$ (5.45g, 25mmol). Allow to warm, stir 3h, concentrate, and treat with hot hexane (50ml). Cool to –15 ºC and decant the hexane to leave a viscous orange oil.

Step 2: Combine the product of Step 1 (3.49g, 15.0mmol) and $Et_3N$ (1.72g, 17.0mmol) in $CH_2Cl_2$ (40ml) and cool in ice. Add, dropwise, MsCl (1.96g, 17.0mmol) in $CH_2Cl_2$ (10ml). Allow to warm, stir 0.5h, and concentrate. Partition between $Et_2O$ and water, dry ($MgSO_4$) and concentrate to give the crude product as viscous oil with solid.

Step 3: Combine the crude product of Step 2 (4.6g, ~15mmol) with 40% aqueous $MeNH_2$ (35g, 0.45mol) and EtOH (35ml). After 1h, concentrate and partition between $CH_2Cl_2$ and 1N NaOH. Dry ($MgSO_4$) and concentrate to obtain the crude product as a yellow oil.

Step 4: Combine the crude product of Step 3 (0.46g, ~1.5mmol) with the product of Example 5, Step 2 (0.236g, 1.00 mmol), and $K_2CO_3$ (0.207g, 1.50mmol) in DMF (8ml). Heat in a sealed tube at 130 ºC 18h, concentrate and partition between EtOAC (10% MeOH) and water. Dry ($MgSO_4$), concentrate and chromatograph on silica and triturate with $Et_2O$ to obtain the title compound as yellow solid, MS: m/e = 443 (M+1).

Example 10




Step 1: Combine 2-(4-bromophenyl)ethanol (4.88g, 24.3mmol), piperazine (12.5g, 146mmol), NaO-*t*Bu (3.27g, 34.0mmol), ±-BINAP (0.91g, 1.5mmol), and $Pd_2(dba)_3$ (0.28g, 0.49mmol) in toluene (40ml). Heat at reflux 2h, allow to cool, and extract with 1N HCl (4x50ml). Basify with NaOH to pH 13 and extract with $CH_2Cl_2$. Dry ($MgSO_4$) and concentrate to give a brown oil.

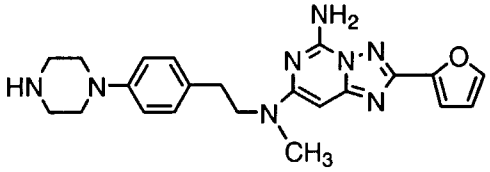
Step 2: Dissolve the product of Step 1 (4.02g, 19.5mmol) in $CH_2Cl_2$ (50ml). Add $Boc_2O$ (4.51g, 20.5mmol) and then $Et_3N$ (3.26ml, 23.4mmol). Stir 1h and wash with 1N NaOH. Dry ($MgSO_4$), concentrate and chromatograph on silica to obtain a brown oil.

Step 3: Combine the product of Step 2 (1.00g, 3.26mmol) and $Et_3N$ (0.73ml, 5.2mmol) in $CH_2Cl_2$ (20ml). Cool in ice and add gradually MsCl (0.30ml, 3.9mmol). Stir 1h, wash with sat. $NaHCO_3$, dry ($MgSO_4$) and concentrate to obtain a yellow oil.

Step 4: Dissolve the product of Step 3 (1.15g, 2.99mmol) in EtOH (10ml). Add 40% aqueous $MeNH_2$ (10ml) and heat in a sealed tube at 100 ºC 16h, allow to cool, concentrate, and partition between $CH_2Cl_2$ and 1N NaOH. Dry ($MgSO_4$), concentrate, and purify by PLC to obtain a yellow oil.

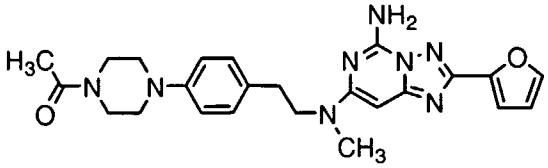
Step 5: Combine the product of Step 4 (0.466g, 1.46mmol), the product of Example 5, Step 2 (0.229g, 0.97 mmol), and $K_2CO_3$ (0.202g, 1.46mmol) in DMF (8ml). Heat in a sealed tube at 140 ºC 18h, concentrate and purify on PLC to obtain the title compound as a yellow foam, concentrate, and purify by PLC to obtain the product as a yellow oil MS: m/e = 519 (M+1).

Example 11



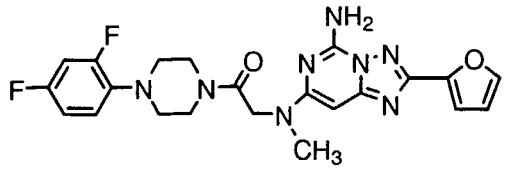
Dissolve the compound of Example 10 (0.215g, 0.41mmol) in 1:1 $CH_2Cl_2$-MeOH (10ml) and add 4M HCl/dioxane (2.0ml). Stir 18h and add 7M $NH_3$/MeOH (4.0ml). Concentrate, and chromatograph on silica to obtain the product as a white foam, MS: m/e = 419 (M+1).

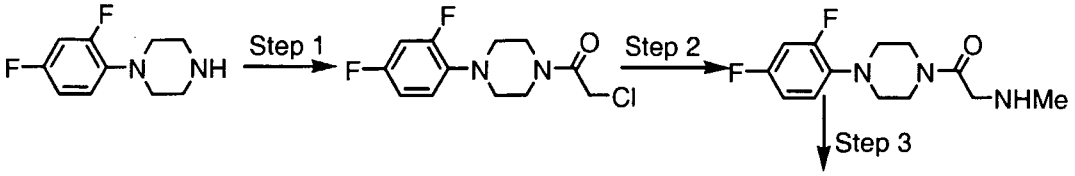
Example 12



Dissolve the compound of Example 11 (0.050g, 0.12mmol) in $CH_2Cl_2$ (5ml). Add DIPEA (0.031ml, 0.18mmol) and AcCl (0.010ml, 0.14mmol). Stir 1h, concentrate, and purify by PLC to obtain the title compound as a white foam, MS: m/e = 461 (M+1).

Example 13





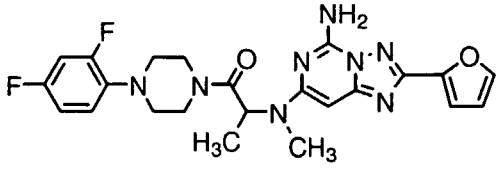

Example 13

Step 1: Dissolve 1-(2,4-difluorophenyl)piperazine (1.00g, 5.05mmol) in $CH_2Cl_2$ (5ml). Cool in ice and add N-methylmorpholine (0.66ml, 6.05mmol) together with chloroacetyl chloride (0.45ml, 5.6mmol). Stir 2h, concentrate, and partition between EtOAc and water. Dry ($MgSO_4$) and concentrate to obtain a yellow oil.

Step 2: Dissolve the product of Step 1 (1.49g, 5.4mmol) in EtOH (10ml). Add 40% aqueous $MeNH_2$ (15ml) and heat in a sealed tube at 100 ºC 48h, allow to cool, concentrate, and partition between $CH_2Cl_2$ and 1N NaOH. Dry ($MgSO_4$) and concentrate to obtain a yellow oil.

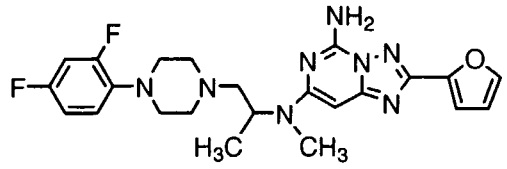
Step 3: Combine the product of Step 2 (0.137g, 0.51mmol), the product of Example 5, Step 2 (0.080g, 0.34 mmol), and $K_2CO_3$ (0.070g, 0.51mmol) in DMF (4ml). Heat in a sealed tube at 140 ºC 18h, concentrate and purify on PLC to obtain the title compound as a yellow foam, concentrate, and purify by PLC to obtain the product as a yellow solid MS: m/e = 469 (M+1).

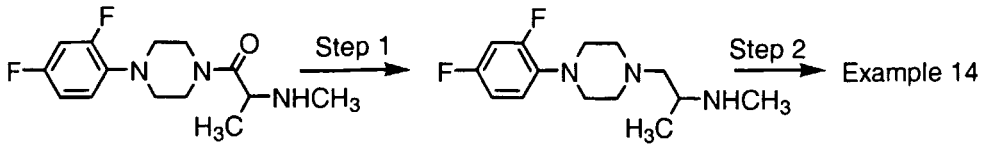
In similar fashion, using 2-bromopropionyl bromide in Step 1, prepare Example 13-2 as an off-white powder.



Ex. 13-2: MS: m/e = 483 (M+1)

Example 14

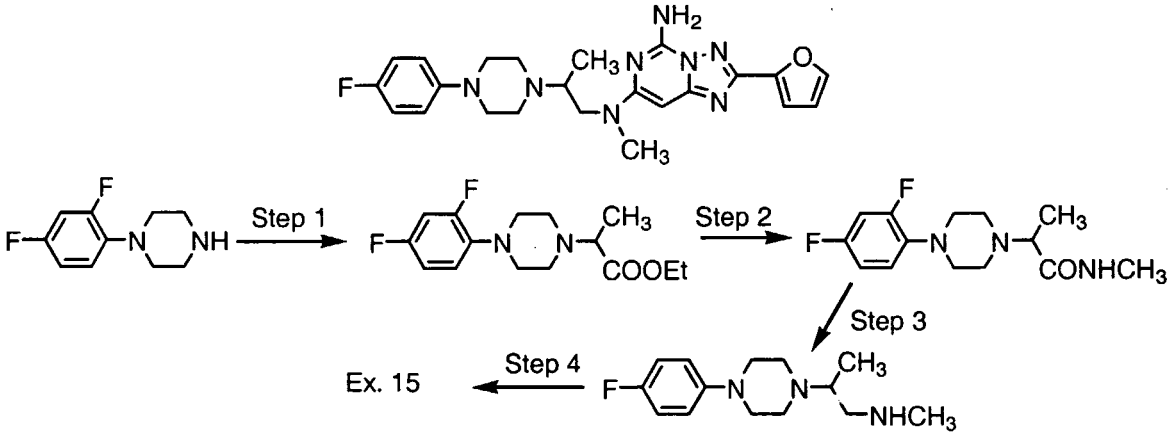





Step 1: Dissolve the product of Example 13-2, Step 2 (0.405g, 1.43mmol) in THF (10ml). Add 1.0M $LiAlH_4/Et_2O$ (0.86ml, 0.86mmol). Heat at 60 ºC 4h, allow to cool, add water (0.065ml), then 15% NaOH (0.065ml), then water (3x0.065ml). Filter and concentrate. Partition between $CH_2Cl_2$ and 1N HCl. Basify the aqueous to pH 12 with NaOH, extract with $CH_2Cl_2$, dry ($MgSO_4$) and concentrate. Purify by PLC to obtain a colorless oil.

Step 2: Treat the product of Step 1 with the product of Example 5, Step 2, following the procedure of Example 13, Step 3, to obtain the title compound as a yellow oil, MS: m/e = 469 (M+1).

Example 15



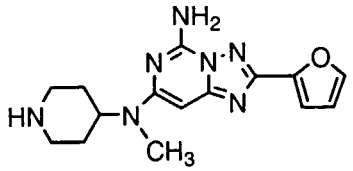

Step 1: Combine 1-(2,4-difluorophenyl)piperazine (1.98g, 10.0mmol), ethyl 2-bromo-propionate (1.81g, 10.0mmol), and $K_2CO_3$ (1.38g, 10.0mmol) in EtOH (15ml). Heat at 80 ºC 18h, add more bromide (0.07g), heat another 5h, allow to cool, filter, and concentrate. Partition between $Et_2O$ and water. Dry ($MgSO_4$) and concentrate to obtain a colorless liquid.

Step 2: Combine the product of Step 1 (2.38g, 8.0mmol) with 40% aqueous $MeNH_2$ (9.3g, 0.12mol) and EtOH (5ml). Heat in a sealed tube at 80 ºC 18h, allow to cool, concentrate, and partition between EtOAc and water. Dry ($MgSO_4$) and concentrate to obtain a yellow solid. Recrystallization from MeOH-water gives white needles, m.p. 112-3 ºC.

Step 3: Treat the product of Step 2 with $LiAlH_4$ as in Example 14, Step 1 (24h heating) to obtain a yellow oil.

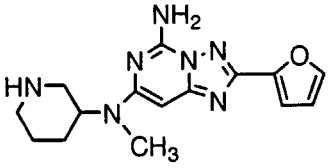
Step 4: Treat the product of Step 3 with the product of Example 5, Step 2, following the procedure of Example 13, Step 3), to obtain the title compound as a colorless oil, MS: m/e = 451 (M+1).

Example 16

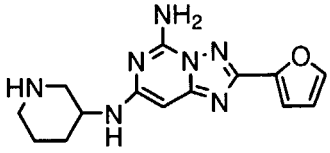


Dissolve the compound of Example 5-41 (0.206g, 0.50mmol) in 1:1 MeOH-$CH_2Cl_2$ (10ml). Add 4.0M HCl/dioxane (4.0ml). Stir 2h and quench with 2M $NH_3$/MeOH. Concentrate and chromatograph on silica to obtain the title compound as a yellow oil, MS: m/e 314 (M+1).

In a similar manner prepare Examples 16-2 and 16-3.

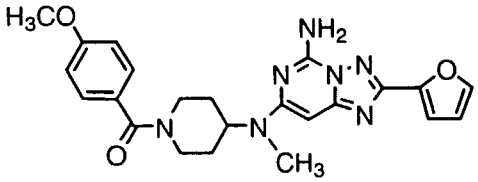


Ex. 16-2: MS: m/e 314 (M+1)



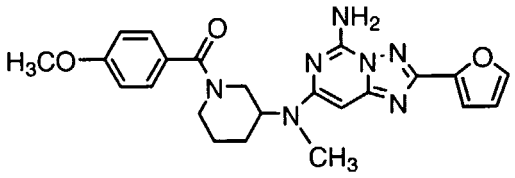
Ex. 16-3: MS: m/e 300 (M+1)

Example 17

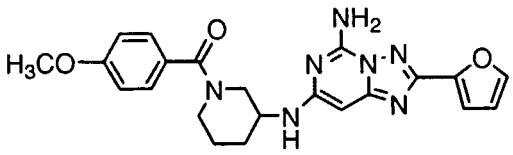


Combine the compound of Example 16 (0.070g, 0.22mmol), 4-methoxybenzoyl chloride (0.058g, 0.34mmol), and DIPEA (0.058g, 0.45mmol) in DMF (4ml). Stir 2h, concentrate, and purify by PLC to obtain the title compound as a yellow solid, MS: m/e 448 (M+1).

In similar fashion, convert the respective compounds of Example 16 to Examples 17-2 and 17-3.

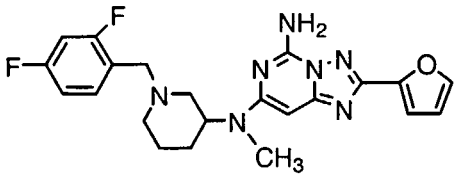


Ex. 17-2: MS: m/e 448 (M+1)



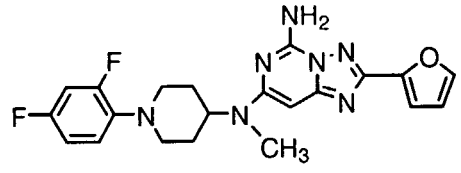
Ex. 17-3: MS: m/e 434 (M+1)

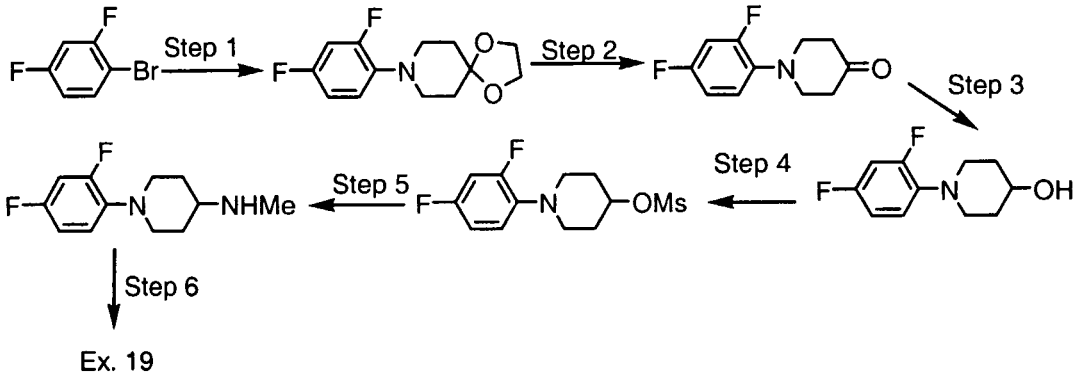
Example 18



Combine the compound of Example 17-2 (0.119g, 0.38mmol), 2,4-difluoro-benzaldehyde (0.054g, 0.38mmol) and $NaBH(OAc)_3$ (0.157g, 0.74mmol) in $CH_2Cl_2$ (10ml). Stir 3h and add more aldehyde (0.016g) and borohydride (0.045g). Stir 18h, dilute with $CH_2Cl_2$, and wash with sat. $NaHCO_3$, then brine. Dry ($MgSO_4$) and concentrate. Purify on PLC to obtain the title compound as a colorless oil, MS: m/e 440 (M+1).

Example 19






Step 1: Combine 2,4-difluorobromobezene (2.00g, 10.4mmol), 4-piperazinone ethylene ketal (2.27g, 15.5mmol), NaO-*t*Bu (1.39g, 14.5mmol), ±-BINAP (0.387g, 0.65mmol), and $Pd_2(dba)_3$ (0.119g, 0.21mmol) in toluene (20ml). Heat at reflux 18h, allow to cool, and oncentrate. Chromatograph on silica to obtain a brown oil.

Step 2: Combine the product of Step 1 (2.55g, 10.0mmol) and 5N HCl (40ml) in THF (25ml). Stir 5d and basify with $NH_4OH$. Concentrate and partition between $CH_2Cl_2$ and water. Wash with brine, dry ($MgSO_4$) and concentrate to obtain a brown oil.

Step 3: Cool the product of Step 2 (1.75g, 8.3mmol) in MeOH (15ml) in ice and add $NaBH_4$ (0.16g, 4.1mmol). Stir 1h, pour on ice and extract with $CH_2Cl_2$. Wash with brine, dry ($MgSO_4$) and concentrate to obtain a yellow oil.

Step 4: Combine the product of Step 3 (1.65g, 7.7mmol) and $Et_3N$ in $CH_2Cl_2$ (30ml). Cool in ice and add methanesulfonyl chloride (1.07g, 9.4mmol). Stir 1h and wash with sat. $NaHCO_3$. Dry ($MgSO_4$) and concentrate to obtain a yellow oil.

Step 5: Dissolve the product of Step 4 (1.00g, 3.4mmol) in EtOH (10ml). Add 40% aqueous $MeNH_2$ (20ml, 0.2mol). Heat in a sealed tube at 100 ºC for 3h, allow to cool, and concentrate. Partition between $CH_2Cl_2$ and water. Wash with brine, dry ($MgSO_4$) and concentrate. Purify on PLC to obtain a yellow oil.

Step 6: Combine the product of Step 5 (0.035g, 0.15mmol) with the product of Example 5, Step 2 (0.041mg, 0.18mmol) and $K_2CO_3$ (0.031g, 0.23mmol) in DMF (3ml). Heat at 140 ºC for 18h. Concentrate and purify by PLC to obtain the title compound as a colorless gum, MS: m/e 426 (M+1).

Because of their adenosine $A_{2a}$ receptor antagonist activity, compounds of the present invention are useful in the treatment of depression, cognitive function diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin. In particular, the compounds of the present invention can improve motor-impairment due to neurodegenerative diseases such as Parkinson's disease.

The other agents known to be useful in the treatment of Parkinson's disease that can be administered in combination with the compounds of formula I include: L-DOPA; dopaminergic agonists such as quinpirole, ropinirole, pramipexole, pergolide and bromocriptine; MAO-B inhibitors such as deprenyl and selegiline; DOPA decarboxylase inhibitors such as carbidopa and benserazide; and COMT inhibitors such as tolcapone and entacapone. One to three other agents can be used in combination with the compounds of formula I, preferably one.

The pharmacological activity of the compounds of the invention was determined by the following *in vitro* and *in vivo* assays to measure $A_{2a}$ receptor activity.

Human Adenosine $A_{2a}$ and $A_1$ Receptor Competition Binding Assay Protocol

Membrane sources:

$A_{2a}$: Human $A_{2a}$ Adenosine Receptor membranes, Catalog #RB-HA2a, Receptor Biology, Inc., Beltsville, MD. Dilute to 17 μg/100 μl in membrane dilution buffer (see below).

Assay Buffers:

Membrane dilution buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM $MgCl_2$.

Compound Dilution Buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM $MgCl_2$ supplemented with 1.6 mg/ml methyl cellulose and 16% DMSO. Prepared fresh daily.

Ligands:

$A_{2a}$: [3H]-SCH 58261, custom synthesis, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 1 nM in membrane dilution buffer. Final assay concentration is 0.5 nM.

$A_1$: [3H]- DPCPX, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 2 nM in membrane dilution buffer. Final assay concentration is 1 nM.

Non-specific Binding:

$A_{2a}$: To determine non-specific binding, add 100 nM CGS 15923 (RBI, Natick, MA). Working stock is prepared at 400 nM in compound dilution buffer.

$A_1$: To determine non-specific binding, add 100 μM NECA (RBI, Natick, MA). Working stock is prepared at 400 μM in compound dilution buffer.

Compound Dilution:

Prepare 1 mM stock solutions of compounds in 100% DMSO. Dilute in compound dilution buffer. Test at 10 concentrations ranging from 3 μM to 30 pM. Prepare working solutions at 4X final concentration in compound dilution buffer.

Assay procedure:

Perform assays in deep well 96 well plates. Total assay volume is 200 μl. Add 50 μl compound dilution buffer (total ligand binding) or 50 μl CGS 15923 working solution ($A_{2a}$ non-specific binding) or 50 μl NECA working solution ($A_1$ non-specific binding) or 50 μl of drug working solution. Add 50 μl ligand stock ([3H]-SCH 58261 for $A_{2a}$, [3H]- DPCPX for $A_1$). Add 100 μl of diluted membranes containing the appropriate receptor. Mix. Incubate at room temperature for 90 minutes. Harvest

using a Brandel cell harvester onto Packard GF/B filter plates. Add 45 μl Microscint 20 (Packard), and count using the Packard TopCount Microscintillation Counter. Determine $IC_{50}$ values by fitting the displacement curves using an iterative curve fitting program (Excel). Determine Ki values using the Cheng-Prusoff equation.

Haloperidol-induced catalepsy in the rat

Male Sprague-Dawley rats (Charles River, Calco, Italy) weighing 175-200 g are used. The cataleptic state is induced by the subcutaneous administration of the dopamine receptor antagonist haloperidol (1 mg/kg, sc), 90 min before testing the animals on the vertical grid test. For this test, the rats are placed on the wire mesh cover of a 25x43 plexiglass cage placed at an angle of about 70 degrees with the bench table. The rat is placed on the grid with all four legs abducted and extended ("frog posture"). The use of such an unnatural posture is essential for the specificity of this test for catalepsy. The time span from placement of the paws until the first complete removal of one paw (*decent latency*) is measured maximally for 120 sec.

The selective $A_{2A}$ adenosine antagonists under evaluation are administered orally at doses ranging between 0.3 and 3 mg/kg, 1 and 4 h before scoring the animals.

6-OHDA Lesion of the Middle Forebrain Bundle in Rats

Adult male Sprague-Dowley rats (Charles River, Calco, Como, Italy), weighing 275-300 g, are used in all experiments. The rats are housed in groups of 4 per cage, with free access to food and water, under controlled temperature and 12 hour light/ dark cycle. The day before the surgery the rats are fasted over night with water *ad libitum.*

Unilateral 6-hydroxydopamine (6-OHDA) lesion of the middle forebrain bundle is performed according to the method described in Ungerstedt et al, *Brian Research, 24* (1970), p. 485-493, and Ungerstedt, *Eur. J. Pharmacol., 5* (1968), p. 107-110, with minor changes. Briefly, the animals are anaesthetized with chloral hydrate (400 mg/kg, ip) and treated with desipramine (10 mpk, ip) 30 min prior to 6-OHDA injection in order to block the uptake of the toxin by the noradrenergic terminals. Then, the animals are placed in a stereotaxic frame. The skin over the skull is reflected and the stereotaxic coordinates (-2.2 posterior from bregma (AP), +1.5 lateral from bregma (ML), 7.8 ventral from dura (DV) are taken, according to the atlas of Pellegrino et al (Pellegrino L.J., Pellegrino A.S. and Cushman A.J., A Stereotaxic Atlas of the Rat

Brain, 1979, New York: Plenum Press). A burr hole is then placed in the skull over the lesion site and a needle, attached to a Hamilton syringe, is lowered into the left MFB. Then 8 µg 6-OHDA-HCl is dissolved in 4 µl of saline with 0.05% ascorbic acid as antioxidant, and infused at the constant flow rate of 1 µl /1 min using an infusion pump. The needle is withdrawn after additional 5 min and the surgical wound is closed and the animals left to recover for 2 weeks.

Two weeks after the lesion the rats are administered with L-DOPA (50 mg/kg, ip) plus Benserazide (25 mg/kg, ip) and selected on the basis of the number of full contralateral turns quantified in the 2 h testing period by automated rotameters (*priming test*). Any rat not showing at least 200 complete turns /2h is not included in the study.

Selected rats receive the test drug 3 days after the priming test (maximal dopamine receptor supersensitivity). The new $A_{2A}$ receptor antagonists are administered orally at dose levels ranging between 0.1 and 3 mg/kg at different time points (i.e., 1, 6, 12 h) before the injection of a subthreshold dose of L-DOPA (4 mpk, ip) plus benserazide (4 mpk, ip) and the evaluation of turning behavior.

Using the above test procedures, the following results were obtained for preferred and/or representative compounds of the invention.

Results of the binding assay on compounds of the invention showed $A_{2a}$ Ki vaules of about 0.3 to about 50 nM, with preferred compounds showing Ki values between 0.3 and 10 nM.

Selectivity is determined by dividing Ki for A1 receptor by Ki for A2a receptor. Compounds of the invention have a selectivity ranging from about 1 to about 1600. Preferred are compounds are those wherein the selectivity is >100.

Preferred compounds showed about a 50-75% decrease in descent latency when tested orally at 1-3 mg/kg for anti-cataleptic activity in rats.

One to three compounds of formula I can be administered in the method of the invention, preferably one.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the

art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound of formula I in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of

the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen for compounds of formula I is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from central nervous system diseases such as Parkinson's disease. The compounds are non-toxic when administered within this dosage range.

The doses and dosage regimen of the other agents used in the treatment of Parkinson's disease will be determined by the attending clinician in view of the approved doses and dosage regimen in the package insert, taking into consideration the age, sex and condition of the patient and the severity of the disease. It is expected that when the combination of a compound of formula I and a another anti-Parkinson's disease agent is administered, lower doses of the components will be effective compared to the doses of the components administered as monotherapy. When administered in combination, the compound(s) of formula I and the other agent(s) for treating Parkinson's disease can be administered simultaneously or sequentially. This is particularly useful when the components of the combination are preferably given on different dosing schedules, e.g., one component is administered daily and another every six hours, or when the preferred pharmaceutical compositions are different, e.g. one is preferably a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. Those skilled in the art will recognize that dosage forms can be modified to contain both a compound of formula I and a dopaminergic agent. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A-Tablets

| No. | Ingredients | mg/tablet | mg/tablet |
|---|---|---|---|
| 1. | Active compound | 100 | 500 |
| 2. | Lactose USP | 122 | 113 |
| 3. | Corn Starch, Food Grade, as a 10% paste in Purified Water | 30 | 40 |
| 4. | Corn Starch, Food Grade | 45 | 40 |
| 5. | Magnesium Stearate | 3 | 7 |
| | Total | 300 | 700 |

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

| No. | Ingredient | mg/capsule | mg/capsule |
|---|---|---|---|
| 1. | Active compound | 100 | 500 |
| 2. | Lactose USP | 106 | 123 |
| 3. | Corn Starch, Food Grade | 40 | 70 |
| 4. | Magnesium Stearate NF | 7 | 7 |
| | Total | 253 | 700 |

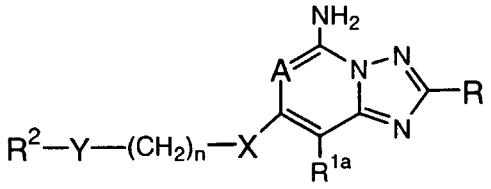
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

1. A compound represented by the structural formula



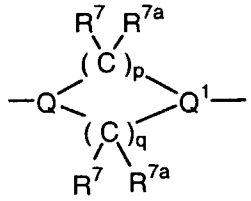
I

or a pharmaceutically acceptable salt thereof, wherein:

A is $C(R^1)$ or N;

$R^1$ and $R^{1a}$ are independently selected from the group consisting of H, $(C_1\text{-}C_6)$-alkyl, halo, CN and $-CF_3$;

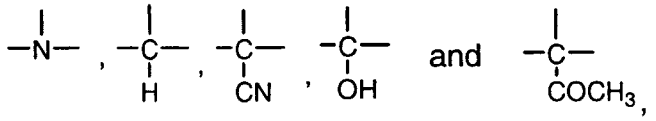
Y is –O-, -S-, -SO-, $-SO_2$-, $R^5$-heteroaryldiyl, $R^5$-arylene or



;

p and q are independently 2-3;

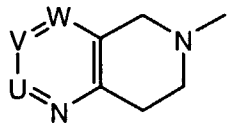
Q and $Q^1$ are independently selected from the group consisting of



provided that at least one of Q and $Q^1$ is ;

R is $R^5$-aryl, $R^5$-heteroaryl, $R^6$-$(C_2\text{-}C_6)$alkenyl or $R^6$-$(C_2\text{-}C_6)$alkynyl;

$R^2$ is $R^5$-aryl, $R^5$-heteroaryl, $R^5$-aryl$(C_1\text{-}C_6)$alkyl or $R^5$-heteroaryl$(C_1\text{-}C_6)$alkyl; or $R^2$-Y is



;

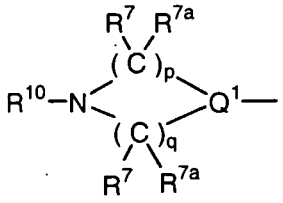
U, V, and W are independently selected from the group consisting of N and $CR^1$, provided that at least one of U, V and W is $CR^1$;

n is 1, 2 or 3; and

(a) A is $C(R^1)$ and X is $-C(R^3)(R^{3a})$-, -C(O)-, -O-, -S-, -SO-, $-SO_2$-, $R^4$-arylene, $R^4$-heteroaryldiyl, or $-N(R^9)$-; or A is $C(R^1)$, Y is a bond, and X is

$-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, $R^4$-arylene, $-N(R^9)-$ or $R^4$-heteroaryldiyl, provided that when X is $-N(R^9)-$ or $R^4$-heteroaryldiyl, $R^2$ is not phenyl or phenyl-$(C_1-C_6)$alkyl; or

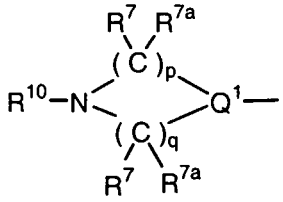
(b) A is N, X is $-N(R^9)-$, Y is $R^5$-arylene and $R^2$ is



;

or n is 2 or 3; and

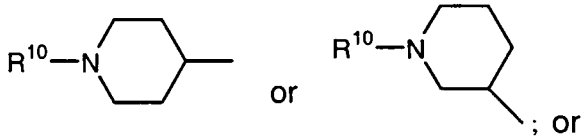
(c) A is N and X is $-C(R^3)(R^{3a})-$, -C(O)-, -O-, -S-, -SO-, $-SO_2-$, $-N(R^9)-$, $R^4$-arylene or $R^4$-heteroaryldiyl; or A is N, Y is a bond and X is -C(O)-, $-N(R^9)-$, $R^4$-arylene or $R^4$-heteroaryldiyl; or A is N, Y is $-N(R^{9a})-$, $-C(O)N(R^{9a})-$ or $-O-(CH_2)_2-N(R^{9a})-$, and X is $-N(R^9)-$; or A is N, X is $-N(R^9)-$, and Y and $R^2$ together are



;

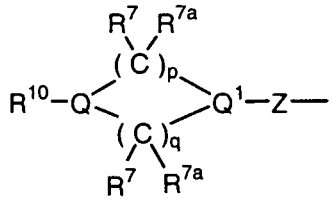
or n is 0; and

(d) A is N, Y is a bond, X is $-N(R^9)-$, and $R^2$ is



; or

(e) A is N, X is $-N(R^9)-$ and Y and $R^2$ together are



,

wherein Z is $-C(O)-CH_2-$, $-C(O)-CH(C_1-C_6$ alkyl)-, $-CH_2-CH(C_1-C_6$ alkyl)-, or $-CH(C_1-C_6$ alkyl)$-CH_2-$;

$R^3$ and $R^{3a}$ are independently selected from the group consisting of H, -OH, $C_1-C_6$ alkyl, hydroxy$(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy$(C_1-C_6)$alkyl, amino$(C_1-C_6)$alkyl, $(C_1-C_6)$alkylamino$(C_1-C_6)$alkyl and di$(C_1-C_6)$alkylamino$(C_1-C_6)$alkyl;

$R^4$ is 1-3 substituents selected from the group consisting of H, $(C_1$-$C_6)$alkyl, -OH, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo, $-CF_3$, and –CN;

$R^5$ is 1-3 substituents independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, -OH, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$-alkoxy, halo, $-CF_3$, -CN, $-NH_2$, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, amino$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl-amino, $(C_1$-$C_6)$alkanesulfonylamino, $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylthio$(C_1$-$C_6)$alkyl, $R^6$-$(C_2$-$C_6)$alkenyl, $R^6$-$(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy-C(O)-amino, or heterocycloalkyl$(C_1$-$C_6)$alkyl;

$R^6$ is 1 to 3 substituents independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, -OH, $(C_1$-$C_6)$alkoxy and halo;

$R^7$ and $R^{7a}$ are independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $R^8$-aryl and $R^8$-heteroaryl, or an $R^7$ and an $R^{7a}$ substituent on the same carbon can form =O;

$R^8$ is 1 to 3 substituents independently selected from H, $(C_1$-$C_6)$alkyl, -OH, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo, $-CF_3$, and –CN;

$R^9$ and $R^{9a}$ are independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, hydroxy$(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_2$-$C_6)$alkyl, amino$(C_2$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkyl, halo-$(C_3$-$C_6)$alkenyl, $CF_3$-$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$alkenyl, -$(C_3$-$C_6)$cycloalkyl and $(C_3$-$C_6)$cycloalkyl-$(C_1$-$C_6)$alkyl; and

$R^{10}$ is H, -C(O)-O-$(C_1$-$C_6)$alkyl, $R^5$-aryl, -C(O)-$(C_1$-$C_6)$alkyl, -C(O)-$(R^5$-aryl) or $R^5$-aryl-$(C_1$-$C_6)$alkyl.

2. The compound of claim 1 wherein A is N.

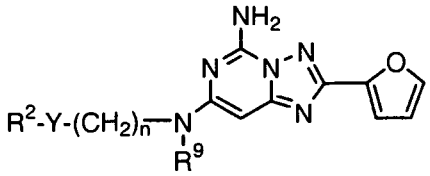
3. The compound of claim 1 wherein X is –O-, -S-, -N($R^9$)- or $R^4$-arylene.

4. The compound of claim 1 wherein Y is a bond or piperazinyl.

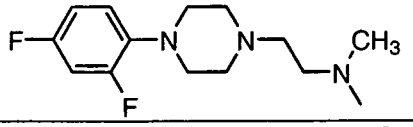
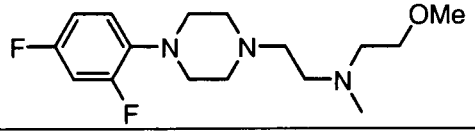
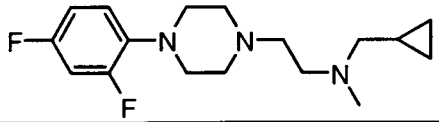
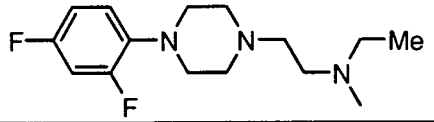
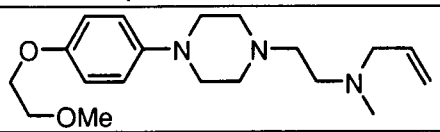
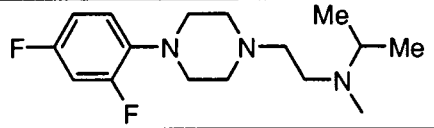
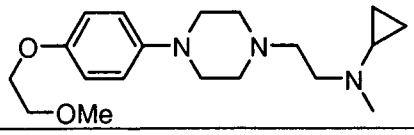
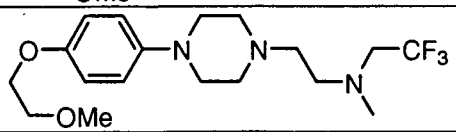
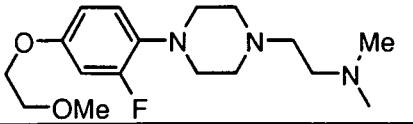
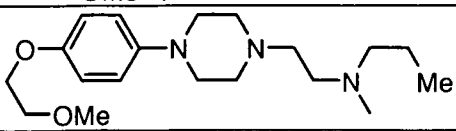
5. The compound of claim 1 wherein $R^2$ is $R^5$-aryl.

6. The compound of claim 1 wherein R is furyl.

7. A compound of claim 1 selected from the group consisting of compounds of the formula



wherein $R^2$-Y-$(CH_2)_n$-N($R^9$)- is as defined in the table:

| $R^2$-Y-$(CH_2)_n$-N($R^9$)- |
|---|
|  |
|  |
|  |
|  |
|  |
|  |
|  |
|  |
|  |
|  |

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

9. The use of a compound of claim 1 for the preparation of a medicament for treating a central nervous system disease or stroke.

10. The use of claim 9 for treating depression, cognitive diseases or neurodegenerative diseases.

11. A method of claim 10 for treating Parkinson's disease, senile dementia or psychoses of organic origin.

12. A pharmaceutical composition comprising a therapeutically effective amount of a combination of a compound of claim 1 and one to three other agents useful in treating Parkinson's disease in a pharmaceutically acceptable carrier

13. The use of a combination of a compound of claim 1 and one to three other agents useful in treating Parkinson's disease for the preparation of a medicament for treating Parkinson's disease.

14. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Parkinson's disease wherein one container comprises a pharmaceutical composition comprising an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and wherein, in separate containers, one or more pharmaceutical compositions each comprise an effective amount of an agent useful in the treatment of Parkinson's disease in a pharmaceutically acceptable carrier.