

5-substituted quinazolinone derivatives

This invention relates to quinazolinone compounds, more particularly, to substituted quinazolinone compounds and salts thereof which are useful as alpha-1-adrenergic receptor antagonists. The invention further relates to pharmaceutical compositions containing said compounds and to methods for their use as therapeutic agents.

- 5 Alpha-1-adrenergic receptors are G-protein coupled transmembrane receptors that mediate various actions of the sympathetic nervous system through the binding of the catecholamines, epinephrine, and norepinephrine (NE). Currently, several subtypes of the alpha-1 adrenergic receptors are known to exist for which the genes have been cloned: alpha-1A (previously known as alpha-1C), alpha-1B and alpha-1D.
- 10 Alpha-1 adrenoceptor antagonists have been shown in numerous clinical studies to be effective in relieving the symptoms associated with benign prostatic hypertrophy, also known as benign prostatic hyperplasia (BPH), an illness typically affecting men over fifty. The symptoms of the condition include, but are not limited to, increased difficulty in urination and sexual dysfunction. Drugs such as prazosin, indoramin, doxazosin and
- 15 tamsulosin are in common clinical use for BPH, and are effective in reducing both "obstructive" symptoms (*e.g.* weak stream) and "irritative" symptoms (*e.g.* nocturia, urinary urge and frequency). However, these compounds are all non-subtype-selective and have the potential to cause significant side-effects, particularly cardiovascular effects such as postural hypotension, dizziness, and syncope, and CNS effects such as asthenia
- 20 (tiredness). These effects can limit dosing and the clinical efficacy in reducing symptoms associated with BPH.

Pharmacological studies resulting in the subdivision of alpha-1 adrenoceptors into alpha-1A, alpha-1B, and alpha-1D adrenoceptors have led to the suggestion that development of subtype-selective antagonists may allow for an improved symptomatic treatment of

25 BPH with a lower incidence of dose-limiting side-effects. Recently, much interest has been focused on the role of the alpha-1A adrenoceptor subtype in BPH, as studies have shown that this subtype predominates in the urethra and prostate of man and appears to be the receptor mediating NE-induced smooth muscle contraction in these tissues. See,

- e.g., Price et al., J. Urol. 150:546-551 (1993); Faure et al., Life Sci. 54:1595-1605 (1994); Taniguchi et al., Naunyn Schmiedeberg's Arch. Pharmacol. 355:412-416 (1997), Forray et al., Mol. Pharmacol. 45:703-708 (1994); Hatano et al., Br. J. Pharmacol. 113:723-728 (1994); and Marshall et al., Br J. Pharmacol. 115:781-786 (1995). Smooth muscle tone is
- 5 believed to contribute substantially to the total urinary outflow obstruction observed in patients with BPH [Furuya et al., J. Urol. 128:836-839 (1982)]. Increased prostate mass is also a contributing factor. These observations have fuelled the hypothesis that an alpha-1A subtype-selective antagonist may, via a selective and significant decrease in outlet resistance, lead to improved pharmacotherapy for BPH.
- 10 However, in BPH, it is often the irritative symptoms which prompt the patient to seek treatment, and these irritative symptoms may be present in patients with no demonstrable obstruction (*i.e.* normal urine flow rates). Thus, it would be advantageous to provide a therapy for treating patients exhibiting obstructive symptoms and/or irritative symptoms. It is believed that reduction of obstructive and irritative symptoms
- 15 in patients with BPH may be achieved via a combination of alpha-1A and alpha-1B subtype selectivity in a drug molecule. The lack of alpha-1D adrenoceptor antagonism is expected to lead to reduced or fewer side effects than those associated with the use of non-subtype-selective agents.

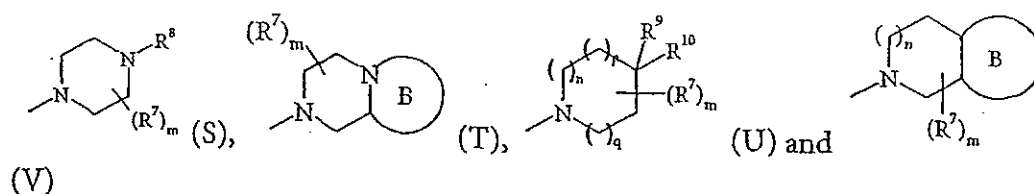
20 All publications, patents, and patent applications cited herein, whether *supra* or *infra*, are each hereby incorporated by reference in its entirety.

In a first aspect, there is provided a compound of the Formula I



wherein

- Z is $-C(=O)-$ or $-S(=O)_2-$;
- 25 R and R' are lower alkoxy;
- R⁵ is selected from halogen, cyano, hydroxy, optionally substituted phenyl, $-R^6$, and $-OR^6$;
- R⁶ is alkyl, alkoxyalkyl, hydroxyalkyl, optionally substituted benzyloxyalkoxy, optionally substituted phenoxy, aminoalkyl, optionally substituted aryl, optionally
- 30 substituted heteroaryl, cycloalkyl, or cycloalkyloxy; and
- Q is a monocyclic or bicyclic heterocyclic ring selected from (S), (T), (U), and (V)



wherein

B is an optionally-substituted fused aryl or heteroaryl ring;

5 R^7 is attached to any available carbon atom of the piperidinyl or piperazinyl ring and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, cyano, hydroxy, alkoxy, haloalkoxy, amino, and alkylamino; or alternatively, wherein Q is ring (T), two R^7 groups attached to different carbon atoms may be taken together to form a carbon-carbon bridge of one to two
10 bridgehead carbon atoms;

R^8 is $-K-R^{14}$;

R^9 and R^{10} are (i) independently selected from $-L-R^{15}$, or alternatively, (ii) R^9 and R^{10} are taken together to form an optionally-substituted spirocyclic ring;

K and L are independently selected from a bond, optionally-substituted C_{1-4} alkylene, $-M_1-O-M_2-$, $-M_1-C(=O)-M_2-$, $-M_1-C(O)_2-M_2-$, $-M_1-$
15 $C(=O)NR^{16}-M_2-$, and $-M_1-NR^{16}-M_2-$, wherein M_1 and M_2 are selected from a bond and optionally-substituted C_{1-4} alkylene;

R^{14} and R^{15} are independently selected from hydrogen, optionally-substituted alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclo, provided that if K or L is a bond or
20 $-NR^{16}-$, then R^{14} and R^{15} are not selected from phenyl, pyridyl, or pyrimidinyl having a para substituent that is CO_2R^{22} , wherein R^{22} is selected from hydrogen, alkyl, aryl, arylalkyl, guanidinyl, hydroxy, alkoxy, aryloxy, and arylalkyloxy;

R^{16} is selected from hydrogen and alkyl;

m is 0, 1, 2, 3, or 4;

25 n is 0 or 1;

p is 0, 1 or 2; and

q is 0 or 1; or

an isomer or pharmaceutically-acceptable salt, hydrate, or prodrug thereof.

In a second aspect, there is provided the compound as defined above for use as therapeutic active substance.

In a third aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of at least one compound as defined above and at least one pharmaceutically acceptable carrier.

In a fourth aspect, there is provided the use of a compound as defined above for the manufacture of a medicament comprising a compound as defined above for treating a disease state in a patient modulated via an alpha-1A/B adrenoceptor.

In a fifth aspect, there is provided a process for the preparation of a compound as defined above.

The compounds of Formula (I) above are surprisingly advantageous in selectively antagonizing the alpha-1A and alpha-1B subtype receptors with selectively lesser activity in antagonizing the alpha-1D adrenergic receptor. Accordingly, said compounds of

Formula (I) are surprisingly advantageous for use in treating diseases responsive to alpha-1A and alpha-1B receptor antagonism with reduced side effects.

Disclosed herein is the use of compounds of Formula (I) in the treatment of a subject having a disease state that is alleviated by treatment with an alpha
5 1A/B adrenergic receptor antagonist, which comprises administering to such a subject in need of treatment therefor, a therapeutically effective amount of at least one compound of Formula I.

Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used
10 in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

In general, the nomenclature used in this Application is based on AutoNom[®], a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein were prepared using ISIS[®] version 2.2. Any open
15 valency shown on a carbon, nitrogen or oxygen in the structures herein indicates the presence of a hydrogen.

As used herein, the term "alkyl" means a linear or branched, saturated monovalent hydrocarbon moiety of one to eight carbon atoms (preferably one to six carbon atoms), e.g., methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, and the like. "Lower alkyl"
20 means an alkyl of one to four carbon atoms. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms the named group may contain. Thus, e.g., C₁₋₄alkyl means an alkyl of one to four carbon atoms (*i.e.*, lower alkyl) including methyl, ethyl, propyl, iso-propyl, butyl, and *tert*-butyl; hydroxy(C₁₋₄)alkyl means an alkyl of one to four carbon atoms substituted with a hydroxy group; and
25 so forth.

"Alkylene" means a linear or branched, saturated divalent hydrocarbon moiety of one to eight (preferably one to six) carbon atoms, e.g., methylene, ethylene, propylene, and the like. When reference is made to a linker group including an alkylene, e.g., as in
-M₁-C(=O)-M₂-, -M₁-C(O)₂-M₂-, -M₁-C(=O)NR-M₂-, etc. wherein M₁ and M₂ may
30 be selected from an optionally-substituted alkylene, it should be understood that the alkylene may be a straight or branched-chain alkylene.

When the term "alkyl" is used as a suffix following another term, as in "phenylalkyl," or "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one or more (preferably one) substituent selected from the other, specifically-named group. Thus, "phenylalkyl" includes benzyl, phenylethyl, 2-phenylbutyl, and so forth. "Hydroxyalkyl" includes 2-hydroxyethyl, 1-(hydroxymethyl)-2-methylpropyl, 3,4-dihydroxybutyl, and so forth. Accordingly, as used herein, the term "hydroxyalkyl" is used to define a subset of heteroalkyl groups defined below.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, three or four substituents (preferably one to two substituents), independently selected from the group consisting of halo, haloalkoxy, trifluoromethyl, cyano, nitro, $-R^d$, $-OR^a$, $-SR^a$, $-S(O)R^c$, $-S(O)_2R^c$, $-C(=O)R^a$, $-C(=O)NR^aR^b$, $-C(O)_2R^a$, $-C(O)_2NR^aR^b$, $-S(O)_2NR^aR^b$ and $-NR^aR^b$, wherein R^a and R^b are independently selected from hydrogen, C_{1-6} alkyl, benzyl, aryl, heteroaryl, cycloalkyl, and heterocyclo; R^c is selected from C_{1-6} alkyl, benzyl, aryl, heteroaryl, cycloalkyl, and heterocyclo; and R^d is selected from aryl, heteroaryl, cycloalkyl, and heterocyclo, and each of R^a , R^b , R^c and R^d in turn is optionally substituted with one, two, or three of alkyl, halo, haloalkyl, hydroxy, O(alkyl), haloalkoxy, cyano, amino, alkylamino, SO_2 (alkyl), CO_2H , CO_2 (alkyl), $C(=O)H$, $C(=O)$ alkyl, $-C(=NR^e)-R^f$, $-N(R^e)-C(=NR^e)-R^f$, $-N=C(R^e)-NR^fR^g$, and $-N=R^f$, and/or a C_{1-6} alkyl substituted with one to two of halo, hydroxy, O(alkyl), haloalkoxy, trifluoromethyl, cyano, amino, alkylamino, $-SO_2$ (alkyl), CO_2H , CO_2 (alkyl), $C(=O)H$, and/or $C(=O)$ alkyl, $-C(=NR^e)-R^f$, $-N(R^e)-C(=NR^e)-R^f$, $-N=C(R^e)-NR^fR^g$, and/or $-N=R^f$, wherein

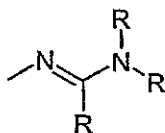
R^e is hydrogen or lower alkyl, and R^f and R^g are selected from hydrogen, alkyl, C_{1-4} alkylene-OH, and C_{1-4} alkylene-O(alkyl).

The term "substituted lower alkyl" means an alkyl of one to four carbon atoms having one, two, or three substituents selected from halo, haloalkyl, hydroxy, O(alkyl), haloalkoxy, cyano, amino, alkylamino, SO_2 (alkyl), CO_2H , CO_2 (alkyl), $C(=O)H$, and/or $C(=O)$ alkyl.

The term "substituted alkylene" means an alkylene group as defined above wherein one, two or three carbon atoms of the alkylene straight or branched chain is substituted with a group selected from halo, haloalkyl, hydroxy, O(alkyl), haloalkoxy, cyano, amino, alkylamino, SO_2 (alkyl), CO_2H , CO_2 (alkyl), $C(=O)H$, and/or $C(=O)$ alkyl.

"Alkoxy" refers to the group OR', wherein R' is alkyl or substituted alkyl. A "lower alkoxy" is a group -OR' wherein R' is C₁₋₄alkyl.

"Amidinyl" means a group of the formula



- 5 wherein each R is independently hydrogen or alkyl as defined herein. Amidinyl includes acetamidinyl, formamidinyl, butyramidinyl-, cyclobutanecarboxamidinyl-, furan-2-yl-carboxamidinyl-, N,N-dimethylacetamidinyl-, and the like.

"Alkoxyalkyl" means a group R-OR' wherein R is alkylene as defined herein and R' is alkyl as defined herein.

- 10 When the term "oxy" is used as a suffix following another specifically-named group, as in "aryloxy", "heteroaryloxy," or "arylalkyloxy", this means that an oxygen atom is present as a linker to the other, specifically-named group. Thus, e.g., "aryloxy" refers to the group -O-R, wherein R is aryl; "heteroaryloxy" refers to the group -O-R', wherein R' is heteroaryl; and "arylalkyloxy" refers to the group -O-R", wherein R" is arylalkyl such as
- 15 benzyl. Similarly, a "substituted aryloxy" means the group -O-R, wherein R is substituted aryl, and a "substituted heteroaryloxy" means the group -O-R', wherein R' is substituted heteroaryl. Phenoxy is an example of aryloxy, the phenyl moiety of which may be optionally substituted as defined below for "aryl".

"Alkylcarbonyl" means a group -(C=O)-R wherein R is alkyl as defined herein.

- 20 "Alkoxy carbonyl" means a group -(C=O)-R wherein R is alkoxy as defined herein.

"Alkoxy carbonylalkyl" means a group -R'-(C=O)-R wherein R' is alkylene as defined herein and R is alkoxy as defined herein.

"Dialkylaminocarbonyl" means a group -(C=O)-NRR wherein R is alkyl as defined herein.

- 25 "Phenylaminocarbonyl" means a group -(C=O)-NRR' wherein R is hydrogen or alkyl and R' is phenyl, which may be optionally substituted in the manner described below for "aryl".

"Cycloalkylalkylcarbonyl means a group $-(C=O)-R-R'$ wherein R is alkylene as defined herein and R' is cycloalkyl as defined herein.

"Amino" refers to the group NH_2 . Thus, an aminoalkyl refers to an alkyl group having an amino substituent, e.g., $-CH_2-NH_2$, $-CH_2-CH(NH_2)-CH_3$, $-CH_2-CH(CH_2NH_2)-CH_3$, and so forth. "Alkylamino" refers to monoalkylamino groups having the formula $-NHR$, as well as dialkylamino groups having the formula $-NRR$, wherein each R is an alkyl group. A "lower aminoalkyl" refers to a group $-NHR'$ or $-NR'R'$, wherein each R' is C_{1-4} alkyl. A "substituted alkylamino" refers to an alkylamino wherein the alkyl portion is substituted from a group selected from those recited above for substituted alkyl groups.

10 "Aminoalkyl" means a group of the formula $R-NH_2$, $R'-NHR$ or $R'-NRR$ wherein R' is alkylene as defined herein and each R is alkyl as defined herein. The group $R'-NHR$ may be more specifically referred to herein as "alkylaminoalkyl", and the group $R'-NRR$ may be more specifically referred to herein as "dialkylaminoalkyl".

"Alkylaminoalkylcarbonylaminoalkyl" means a group $-R-NR'-(C=O)-R-NHR$ wherein each R is alkylene as defined herein, R' is hydrogen or alkyl, and R" is alkyl.

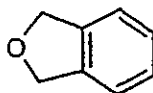
The term "aryl" refers to a monovalent, monocyclic or bicyclic moiety in which at least one of the rings is an aromatic, carbocyclic moiety. Thus, the term "aryl" includes phenyl, 1-naphthyl, and 2-naphthyl. The term "aryl" also includes phenyl rings having fused thereto a second non-aromatic carbocyclic ring, or second fused heteroaryl or heterocyclic ring (thus, the term aryl includes groups such as benzothienyl, benzopyrazolyl, benzopiperadiny, benzocyclohexyl, and the like), with the understanding, however, that in the case of bicyclic aryl groups, the point of attachment will be to a phenyl or benzo ring.

A "substituted aryl" is an aryl group as defined above having one to four (preferably one to two) substituents independently selected from the group consisting of halo, haloalkyl, haloalkoxy, cyano, hydroxy, alkoxy, $-A_1-R^P$, $-A_1-NR^qR^r$, $-A_1-C(=O)R^q$, $-A_1-C(O)_2R^q$, $-A_1-C(=O)NR^qR^r$, $-A_1-C(O)_2NR^qR^r$, $-A_1-S(O)_{0-2}R^q$, $-A_1-NR^sS(O)_2R^P$, $-A_1-N(S(O)_2R^q)_2$, $-A_1-S(O)_2NR^qR^r$, $-A_1-NR^sC(=O)NR^qR^r$, $-A_1-NR^qC(=O)R^r$, $-A_1-NR^q-A_2-NR^rC(=O)R^t$, $-A_1-C(=NH)-A_2-R^P$, $-A_1-NR^s-C(=NR^s)-A_2-R^P$, $-A_1-N=CR^s-NR^s-A_2-R^q$ and/or $-A_1-N=C(R^u)R^v$ wherein A_1 and A_2 are independently selected from a bond and optionally substituted C_{1-4} alkylene; R^P is selected from alkyl, aryl, heteroaryl, heterocyclo, and cycloalkyl; each R^q , R^r and R^t is independently selected from hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclo, except when the substituent is $-A_1-S(O)_{1-2}R^q$,

then R^q in these instances will not be hydrogen; each R^s is independently hydrogen, lower alkyl, or hydroxy C_{1-4} alkyl; and R^u and R^v are taken together to form a cycloalkyl or heterocyclo ring. In each instance, each of R^p , R^q , R^r , R^t and/or R^u and R^v in turn is optionally substituted with up to three groups selected from alkyl, halo, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, amino, alkylamino, aminoalkyl, alkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, $-SO_2$ (alkyl), CO_2H , CO_2 (alkyl), $C(=O)H$, $C(=O)$ alkyl, pyrrolidinyl, and phenyl, said phenyl and pyrrolidinyl in turn being optionally substituted with one to two of lower alkyl, lower alkoxy, cyano and/or halogen. A preferred group of aryl substituents are those selected from $-R^p$, $-(C_{1-4}alkylene)-R^p$, $-C(=NH)-R^p$, $-NR^s-C(=NR^s)-R^p$, $-N=CR^s-NR^s-R^p$, and $-N=R^p$, wherein R^s is hydrogen or lower alkyl; and R^p is selected from alkyl, pyrrolidinyl, pyrrolinyl, imidazolinyl, imidazolidinyl, morpholinyl, cyclobutyl, cyclopentyl, cyclohexyl, and furyl (except in the case of $-N=R^p$, then R^p will not be furyl), wherein each R^p in turn is optionally substituted with one to two groups selected from lower alkyl, halogen, cyano, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, hydroxy, lower alkoxy, amino, (C_{1-4} alkyl)amino, (C_{1-4} alkyl)aminoalkyl, hydroxy(C_{1-4})alkyl, (loweralkoxy)(C_{1-4})alkyl, SO_2 (C_{1-4} alkyl), $-C(=O)H$, $-C(=O)$ (C_{1-4} alkyl), pyrrolidinyl, and phenyl (said phenyl in turn being optionally substituted with one to two of lower alkyl, lower alkoxy, cyano, and/or halogen). "Optionally substituted aryl", such as optionally substituted phenyl means an aryl that is optionally substituted with from one to four (preferably one or two) of the above substituents.

The term "carbocyclic" means a cyclic moiety in which all ring atoms are carbon atoms, including saturated, partially unsaturated, and unsaturated rings.

The term "spirocyclic ring" refers to saturated and partially saturated carbocyclic or heterocyclic rings wherein the spirocyclic ring is attached to another moiety via a carbon ring atom. One or two ring carbon atoms of the "spirocyclic ring" may be replaced with a carbonyl ($-C(=O)-$) group. The term "spirocyclic ring" includes such rings having a second ring fused thereto, wherein the second fused ring may be an aryl, cycloalkyl, heteroaryl or heterocyclo ring, provided, however, that the term "spirocyclic ring" is not intended to encompass bicyclic ring systems in which a tetrahydrofuryl group has a six membered aromatic ring fused thereto (i.e., wherein the tetrahydrofuryl group is attached in a spiro fashion as in



attached in a spiro fashion at the tetrahydrofuryl group). An "optionally-substituted spirocyclic ring" means the spirocyclic ring portion of this moiety may have one, two or three substituents selected from those recited herein for cycloalkyl and heterocyclo groups, and in the situation where the optionally-substituted spirocyclic ring has a
5 second ring fused thereto, said second ring optionally may have one, two or three substituents selected from those recited herein for aryl, heteroaryl, cycloalkyl, and heterocyclo rings, as appropriate given the genus of which the second fused ring is a member.

The term "cycloalkyl" as used herein refers to saturated or partially unsaturated, mono-
10 valent, monocyclic carbocyclic moieties of three to seven ring carbon atoms and further includes such rings having a carbon-carbon bridge of one, two, or three bridgehead carbon atoms, and/or having a second ring fused thereto, with the understanding that the point of attachment will be to the non-aromatic carbocyclic ring moiety. Thus, the term "cycloalkyl" includes such rings as cyclopropyl, cyclopentyl, cyclopentenyl, cyclohexyl,
15 cyclohexenyl, and the like. Additionally, one or two carbon atoms of a cycloalkyl group may optionally contain a carbonyl oxygen group, e.g., one or two atoms in the ring may be a moiety of the formula $-C(=O)-$.

"Benzylamino" means a group $-NHR-R'$ or $-NRR-R'$ wherein each R is alkyl, R' is benzyl.

"Benzyloxy" means a group $-O-R$ wherein R is benzyl.

20 A "substituted cycloalkyl" is a cycloalkyl group as defined above having one to four (preferably one to two) substituents independently selected from the group of substituents recited above for substituted aryl groups.

"Cycloalkyloxy" means a group $-OR$ wherein R is cycloalkyl as defined herein.

The term "amidinyl" as used herein refers to the group $-N=C(R)NH_2$, wherein R is
25 hydrogen or lower alkyl. The term alkyl-amidinyl refers to the group $-N=C(R)NR'R''$, wherein R is hydrogen or lower alkyl and R' and R'' are selected from hydrogen and lower alkyl, provided that at least one of (or both of) R' and R'' is lower alkyl.

"Guanidinyl" means a group $-NR-(C=NR)-NRR$ wherein each R is independently hydrogen or alkyl.

30 "Furanylcabonyl" means a group of the formula $-(C=O)-R$ wherein R is furanyl, preferably furan-2-yl, the furanyl moiety of which may be optionally substituted.

"Morpholinylcarbonyl" means a group of the formula $-(C=O)-R$ wherein R is morpholinyl, preferably morpholin-4-yl.

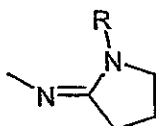
"Imidazoliny" means a 4,5-dihydro-imidazolyl. Imidazoliny may be optionally substituted in the manner defined herein for heteroaryl.

- 5 "Imidazolylalkyl" means a group $-R-R'$ wherein R is alkylene as defined herein and R' is imidazolyl, which may be optionally substituted as described for heteroaryl.

"Imidazolinyalkyl" means a group $-R-R'$ wherein R is alkylene as defined herein and R' is imidazoliny as defined herein.

- 10 "Iminomorpholinylmethyl" means a group $-(C=NR)-R'$ wherein R is hydrogen or alkyl, and R' is morpholinyl, preferably morpholin-4-yl.

"Pyrrolidinylideneamino" means a group



wherein R is hydrogen or alkyl.

- 15 The term "halo," "halide" or "halogen" when referring to a substituent means fluoro, chloro, bromo, or iodo (preferably fluoro or chloro).

The term "haloalkyl" means alkyl substituted with one or more same or different halo atoms, *e.g.*, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and the like, and further includes those alkyl groups such as perfluoroalkyl in which all alkyl hydrogen atoms are replaced by fluorine atoms.

- 20 The term "haloalkoxy" means a haloalkyl group as defined above linked through an oxygen atom, *e.g.*, it includes $-O-CH_2Cl$, $-O-CF_3$, $-O-CH_2CF_3$, $-O-CH_2CCl_3$, and the like.

"Hydroxyalkyl" means a group $-R-OH$ wherein R is alkylene as defined herein.

- 25 "Heterocydo" "heterocyclyl" or "heterocyclic" refers to a saturated or partially-unsaturated non-aromatic monocyclic or bicyclic moiety in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_x$ (where x is an integer from 0 to 2), the remaining ring atoms being carbon atoms, and additionally, one or two carbon atoms

may optionally contain a carbonyl oxygen group, *e.g.*, one or two atoms in the ring may be a moiety of the formula $-C(=O)-$. Thus, the term heterocyclo includes rings such as tetrahydropyranyl, tetrahydrofuryl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, tetrahydropyrimidinyl and the like. In the case of a bicyclic heterocyclo, one of the two rings may be a carbocyclic, heteroaromatic or aromatic ring, with the understanding that in such cases the point of attachment will be to the non-aromatic heterocyclic ring. Heterocyclics may be optionally substituted one, two or three times with alkyl, alkoxy, halo or haloalkyl.

A "substituted heterocyclo" or "substituted heterocycle" refers to a heterocyclo group as defined above having one to four substituents (preferably one to two substituents) selected from the group of substituents recited above for substituted aryl groups.

"Heteroaryl" means a monovalent, monocyclic aromatic moiety of 5 to 6 ring atoms containing one, two, three, or four ring heteroatoms, each independently selected from N, O, N(O) or S, the remaining ring atoms being carbon, and it also includes such rings having a second ring fused thereto of five to six ring atoms, wherein the second fused ring may be aromatic or nonaromatic and may be carbocyclic, heterocyclic, or a heteroaryl ring, with the understanding, however, that in such cases the point of attachment will be to an aromatic ring containing at least one heteroatom. Thus, the term heteroaryl includes, but is not limited to, pyridyl, pyridinyl, furyl, thiophenyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofuryl, isobenzofuryl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, isoquinolyl, benzimidazolyl, benzisoxazolyl, benzothiophenyl, dibenzofuran, and benzodiazepin-2-one-5-yl, and derivatives thereof.

A "substituted heteroaryl" is a heteroaryl ring as defined above having one to four (preferably one or two) substituents selected from the group of substituents recited above for substituted aryl groups. Preferred substituents for substituted heteroaryl groups include those selected from $-R^P$, $-(C_{1-4}\text{alkylene})-R^P$, $-C(=NH)-R^P$, $-NR^S-C(=NR^S)-R^P$, $-N=CR^S-NR^S-R^P$, and $-N=R^P$; wherein R^S is hydrogen or lower alkyl; and R^P is selected from alkyl, pyrrolidinyl, pyrrolinyl, imidazoliny, imidazolidinyl, morpholinyl, cyclobutyl, cyclopentyl, cyclohexyl, and furyl (except in the case of $-N=R^P$, then R^P will not be furyl), wherein each R^P in turn is optionally substituted with one to two groups selected from lower alkyl, halogen, cyano, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, hydroxy, lower alkoxy, amino, (C_{1-4} alkyl)amino, (C_{1-4} alkyl)aminoalkyl, hydroxy(C_{1-4})alkyl, (loweralkoxy)(C_{1-4})alkyl, $SO_2(C_{1-4}\text{alkyl})$, $-C(=O)H$, $-C(=O)(C_{1-4}\text{alkyl})$, pyrrolidinyl, and

phenyl (said phenyl in turn being optionally substituted with one to two of lower alkyl, lower alkoxy, cyano, and/or halogen). "Optionally substituted heteroaryl", such as optionally substituted imidazolyl, means a heteroaryl that is optionally substituted with from one to four (preferably one or two) of the above substituents.

- 5 "Phenylcarbonyl" means a group $-(C=O)-R$ wherein R is phenyl, which may be optionally substituted as described herein for "aryl".

"Sulfonamidyl" refers to the group $-SO_2NRR'$, wherein R and R' are selected from hydrogen, alkyl, cycloalkyl, and lower substituted alkyl, and also is intended to include "reverse sulfonamides" wherein the group is attached to another moiety via the nitrogen
10 atom, *i.e.*, groups of the formula $-NR''SO_2R$ and/or $-N(SO_2R)_2$, wherein in this instance R'' is hydrogen or lower alkyl, and R is alkyl, cycloalkyl, or lower substituted alkyl.

"Pyrrolidinylalkyl means a group $-R-R'$ wherein R is alkylene as defined herein and R' is pyrrolidinyl, which may be optionally substituted as described herein for heterocyclo.

- "Pyridinylalkyl" means a group $-R-R'$ wherein R is alkylene as defined herein and R' is
15 pyridinyl, which may be optionally substituted as described herein for heteroaryl.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, *i.e.*, an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy,
20 trifluoromethanesulfonyloxy, aryloxy (*e.g.*, 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino, and the like.

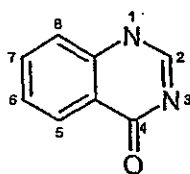
"Optional" or "optionally" means that the subsequently described event may but need not occur, and it includes instances where the event occurs and instances in which it does not. For example, "optionally-substituted cycloalkyl" refers to both cycloalkyl groups
25 and substituted cycloalkyl groups, as defined above. When the term "optionally-substituted" precedes a number of different types of rings in one line or string, *e.g.*, as in "optionally-substituted cycloalkyl or heterocyclo", or "optionally-substituted carbocyclic or heterocyclic ring," or "optionally-substituted aryl, heteroaryl, cycloalkyl, or heterocyclo," it is intended that the term "optionally-substituted" modifies each of the
30 rings identified in the line or string.

When the term "optionally-substituted" is used with respect to a particularly-named cyclic group, such as "optionally-substituted imidazolyl," or "optionally-substituted

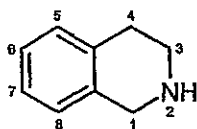
fused benzo or pyridyl,” it should be understood that the optional substituents for such particularly-named rings may be selected from the group of substituents recited above with respect to the genus of which the particularly-named group is a member. Thus, e.g., an “optionally-substituted imidazolyl” may be an unsubstituted imidazolyl or an
5 imidazolyl group having one, two, or three substituents selected from those recited above for substituted heteroaryl groups. An optionally-substituted fused benzo ring will include an unsubstituted fused benzo ring, and a benzo ring having substituents selected from those recited above for substituted aryl groups.

An optionally-substituted benzyl group means a benzyl group wherein the phenyl
10 portion of the group is unsubstituted or substituted as defined above in the definition for substituted aryl.

When reference is made herein to substituents on the quinazolinone core, e.g., the “five position substituent,” the numbering of the ring atoms is intended to be as follows



15 When reference is made herein to a tetrahydroisoquinolyl group, this means a derivative of 1,2,3,4-tetrahydroisoquinoline wherein the ring atoms are numbered as follows



“Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor
20 otherwise undesirable. The term includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

“Pharmaceutically acceptable salt” of a compound means a salt that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and which possesses the
25 desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid,

pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 5 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) 10 salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, and the like.

The terms "pro-drug" and "prodrug" are used interchangeably herein and refer to any 15 compound which releases an active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula I are prepared by modifying one or more functional group(s) present in the compound of Formula I in such a way that the modification(s) may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of Formula I wherein a 20 hydroxy, amino, or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, esters (*e.g.* acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates of hydroxy functional groups (*e.g.* *N,N*-dimethylcarbonyl), esters of carboxyl 25 functional groups (*e.g.* ethyl esters, morpholinoethanol esters), *N*-acyl derivatives (*e.g.* *N*-acetyl), *N*-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals, and enol esters of ketones and aldehyde functional groups in compounds of Formula I, and the like.

The prodrug can be metabolized before absorption, during absorption, after absorption, 30 or at a specific site. Although metabolism occurs for many compounds primarily in the liver, almost all other tissues and organs, especially the lung, are able to carry out varying degrees of metabolism. Prodrug forms of compounds may be utilized, *e.g.*, to improve bioavailability, improve subject acceptability such as by masking or reducing unpleasant characteristics such as bitter taste or gastrointestinal irritability, alter solubility such as for 35 intravenous use, provide for prolonged or sustained release or delivery, improve ease of

formulation, or provide site-specific delivery of the compound. Reference to a compound herein includes prodrug forms of a compound. Prodrugs are described in The Organic Chemistry of Drug Design and Drug Action, by Silverman, Academic Press, San Diego (1992), Chapter 8: "Prodrugs and Drug delivery Systems" pp.352-401; Design of Prodrugs, edited by Bundgaard, Elsevier Science, Amsterdam (1985); Design of Biopharmaceutical Properties through Prodrugs and Analogs, Ed. by Roche, American Pharmaceutical Association, Washington (1977); and Drug Delivery Systems, ed. by Juliano, Oxford Univ. Press, Oxford (1980).

"Solvate" means solvent addition form that contains either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate.

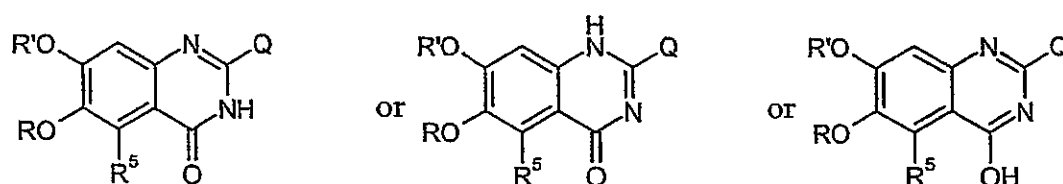
"Protecting group" refers to an atom or group of atoms that is attached to a reactive group in a molecule and masks, reduces, or prevents the reactivity of the group to which it is attached. Examples of protecting groups can be found in Green and Wuts, Protective Groups in Organic Chemistry (Wiley, 2nd ed. 1991), and Harrison et al., Compendium of Synthetic Organic Methods, Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc), nitro-veratryloxycarbonyl (NVOC), and the like. Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as with benzyl or lower alkyl and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers, and allyl ethers.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers," and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, e.g., if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric centers which are described by the (R) and (S) sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or

levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either an individual enantiomer or as a mixture thereof. A mixture containing different enantiomers is called a "racemic mixture".

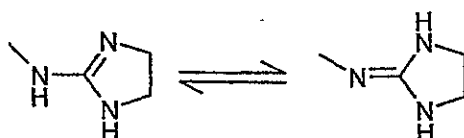
The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures (racemic or otherwise) thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see* March, Advanced Organic Chemistry, Chap. 4, 4th edition, John Wiley and Sons, New York [1992]).

"Tautomers" refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium. It is to be understood that compounds of Formula I may be depicted as different tautomers. For example, compounds of Formula I wherein Z is -C(O)-, may be depicted in the following tautomer forms



Compounds of Formula I may also contain other groups that exist in tautomeric equilibrium. For example some of the compounds contain an imidazolin-2-yl amino group which may be in equilibrium with a imidazolin-2-ylidenamino group

20



It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be within the scope of the invention, and the naming of the compounds does not exclude any tautomer form.

"Treating" or "treatment" of a disease includes: (1) preventing the disease, *i.e.*, causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the progression of the disease, *i.e.*, arresting or reducing the

development of the disease or its symptoms; and (3) relieving the disease, *i.e.*, causing regression of the disease or its symptoms.

"A therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect a treatment for the disease. The "therapeutically effective amount" will vary depending on such factors as
5 the compound being administered, the type of disease being treated, the progression or severity of the disease state, and the age, weight, and general health of the mammal being treated.

"Patient" means mammals and non-mammals. Mammals means any member of the
10 mammalia class including, but not limited to, humans, non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; and laboratory animals such as rats, mice, and guinea pigs. Examples of non-mammals include, but are not limited to, birds, reptiles, and the like.

"Pharmacological effect" as used herein encompasses effects produced in the patient that
15 achieve the intended purpose of a therapy. In one preferred embodiment, a pharmacological effect means that primary indications of the patient being treated are prevented, alleviated, or reduced. For example, a pharmacological effect would be one that results in the prevention, alleviation or reduction of primary indications in a treated
20 patient. In another preferred embodiment, a pharmacological effect means that disorders or symptoms of the primary indications of the patient being treated are prevented, alleviated, or reduced.

"Disease state" means any disease, condition, symptom, or indication.

"Disorders of the urinary tract" or "uropathy" refer to pathologic changes in the urinary
25 tract and symptoms thereof. Disorders of the urinary tract include overactive bladder (also known as detrusor hyperactivity), outlet obstruction, outlet insufficiency, pelvic hypersensitivity, incontinence, benign prostatic hypertrophy or hyperplasia (BPH), prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity, urge incontinence, urethritis, prostatodynia, cystitis, and idiopathic
30 bladder hypersensitivity.

"Overactive bladder" or "Detrusor hyperactivity" includes, but is not limited to, changes symptomatically manifested as urgency, frequency, reduced bladder capacity, and incontinence episodes; changes urodynamically manifested as changes in bladder

capacity, micturition threshold, unstable bladder contractions, and sphincteric spasticity; and symptoms usually manifested in detrusor hyperreflexia (neurogenic bladder), in conditions such as outlet obstruction, outlet insufficiency, pelvic hypersensitivity, or in idiopathic conditions such as detrusor instability.

- 5 "Outlet obstruction" includes, but is not limited to, benign prostatic hypertrophy or benign prostatic hyperplasia (BPH), urethral stricture disease, tumors and the like. It is usually symptomatically manifested as obstructive (low flow rates, difficulty in initiating urination, and the like), or irritative (urgency, suprapubic pain, and the like).

- 10 "Outlet insufficiency" includes, but is not limited to, urethral hypermobility, intrinsic sphincteric deficiency, or mixed incontinence. It is usually symptomatically manifested as stress incontinence.

- "Pelvic Hypersensitivity" includes but is not limited to, pelvic pain, interstitial (cell) cystitis, prostatic pain, prostatitis, vulvodynia, urethritis, orchialgia, and the like. It is symptomatically manifested as pain, inflammation or discomfort referred to the pelvic
15 region, and usually includes symptoms of overactive bladder.

"Sexual dysfunction" means the inability to achieve a normal sexual response and includes such conditions in males and females. Thus, it includes male erectile dysfunction (MED) and female sexual dysfunction (FSD).

- "Disease states associated with the Central Nervous System (CNS) " or "CNS disease
20 states" mean neurological and/or psychiatric changes in the CNS, e.g., brain and spinal cord, which manifest in a variety of symptoms. Examples of CNS disease states include, but are not limited to, migraine headache; cerebrovascular deficiency; psychoses including paranoia, schizophrenia, attention deficiency, and autism; obsessive/compulsive disorders including anorexia and bulimia; posttraumatic stress
25 disorders, sleep disorders, convulsive disorders including epilepsy and withdrawal from addictive substances; cognitive diseases including Parkinson's disease and dementia; and anxiety/depression disorders such as anticipatory anxiety (e.g., prior to surgery, dental work and the like), depression, mania, seasonal affective disorder (SAD), and convulsions and anxiety caused by withdrawal from addictive substances such as opiates,
30 benzodiazepines, nicotine, alcohol, cocaine, and other substances of abuse; and improper thermoregulation.

The compounds of this invention demonstrate selectivity for the alpha-1A/B subtype over the alpha-1D subtype. The compounds of this invention may reduce both

obstructive and irritative symptoms in patients with BPH. The attenuated antagonism of alpha 1D-adrenoceptor is expected to lead to reduced or fewer side effects than those associated with the use of non-subtype-selective agents.

According to one aspect of the invention, preferred compounds are those having
 5 Formula (I) wherein R^5 is selected from C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, -
 $O(CH_2)_rNH_2$, $-O(CH_2)_rOH$, $-O(CH_2)_rO(C_{1-4}alkyl)$, $-O(CH_2)_rO(phenyl)$, -
 $O(CH_2)_rO(benzyl)$, $-O(CH_2)_scycloalkyl$, $-O(CH_2)_s(phenyl)$, $-(CH_2)_scycloalkyl$, and -
 $(CH_2)_s(phenyl)$, wherein each of said phenyl, benzyl, and cycloalkyl rings is optionally
 substituted with one to two of lower alkyl, substituted lower alkyl, cyano, and/or halogen;
 10 r is 1 or 2; and s is 0, 1 or 2. More preferably R^5 is selected from methyl, ethyl, n-propyl,
 isopropyl, halogen, methoxy, and ethoxy. Even more preferred are compounds wherein
 R^5 is selected from fluoro, chloro, methyl, ethyl, isopropyl, methoxy, and ethoxy. Most
 preferred are compounds wherein R^5 is methoxy or methyl.

According to another aspect of the invention, preferred compounds are those having the
 15 Formula (I), wherein m is 0.

According to another aspect of the invention, preferred compounds are those having the
 Formula (I), wherein R and R' are both CH_3 .

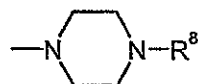
In one embodiment the present invention provides a compound of the Formula I
 wherein Z is $-C(=O)-$; R and R' are CH_3 ; R^5 is selected from C_{1-4} alkyl, halogen, cyano,
 20 hydroxy, C_{1-4} alkoxy, $-O(CH_2)_rNH_2$, $-O(CH_2)_rOH$, $-O(CH_2)_rO(C_{1-4}alkyl)$, -
 $O(CH_2)_rO(benzyl)$, $-O(CH_2)_scycloalkyl$, $-O(CH_2)_s(phenyl)$ and $-(CH_2)_s(phenyl)$, wherein
 each of said phenyl is optionally substituted with one to two of lower alkyl, cyano,
 trifluoromethyl, and/or halogen; R^7 is attached to any available carbon atom of the
 piperidiny or piperazinyl ring and at each occurrence is independently selected from
 25 alkyl, halogen, cyano, hydroxy, alkoxy, haloalkoxy, amino, and alkylamino; K and L are
 independently selected from C_{1-4} alkylene, $-M_1-O-M_2-$, $-M_1-C(=O)-M_2-$, $-M_1-$
 $C(O)_2-M_2-$, $-M_1-C(=O)NR^{16}-M_2-$, $-M_1-S(O)_2-M_2-$, and $-M_1-S(O)_2NR^{16}-M_2-$,
 wherein M_1 and M_2 are selected from a bond and C_{1-4} alkylene, except when K is $-M_1-$
 $O-M_2-$, then M_1 is not a bond; R^{14} and R^{15} are independently selected from hydrogen,
 30 alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclo, provided, however, that if K is $-M_1-$
 $S(O)_2-$, then R^{14} is not hydrogen, wherein each R^{14} and R^{15} group in turn is optionally
 substituted with one to three groups selected from R^{19} and R^{20} ; R^{16} is hydrogen or C_{1-4}
 alkyl; R^{19} and R^{20} are independently selected from lower alkyl, halogen, cyano, halo(C_{1-4} alkyl).

- 4)alkyl, halo(C₁₋₄)alkoxy, hydroxy, lower alkoxy, amino, (C₁₋₄alkyl)amino, (C₁₋₄alkyl)amino(C₁₋₄)alkyl, hydroxy(C₁₋₄)alkyl, (loweralkoxy)(C₁₋₄)alkyl, SO₂(C₁₋₄alkyl), -C(=O)H, -C(=O)(C₁₋₄alkyl), sulfonamidyl, CO₂H, CO₂(C₁₋₄alkyl), guanidiny, alkyl-guanidiny, pyrrolidiny, and phenyl (said phenyl in turn being optionally substituted with one to two of lower alkyl, lower alkoxy, cyano, and/or halogen); *m* is 0, 1, or 2; *n*, *p* and *q* are each 1; *r* is 2, 3 or 4; and *s* is 0, 1 or 2.

In still another embodiment the present invention provides a compound of the formula I wherein R⁵ is selected from methyl, ethyl, n-propyl, isopropyl, halogen, cyano, methoxy, ethoxy, hydroxy, 2-methoxyethoxy, 2-hydroxyethoxy, 2-aminoethoxy, cyclopropylmethoxy, phenoxy, 2-benzyloxyethoxy, and 4-fluorophenyl.

In still another embodiment the present invention provides a compound of the formula I wherein Z is -C(=O)-. In yet another embodiment the present invention provides a compound of the formula I wherein Z is -C(=O)- and *m* is 0. In yet another embodiment the present invention provides a compound of the formula I wherein Z is -C(=O)-, *m* is 0 and *n*, *p* and *q* are each 1.

In another embodiment the present invention provides a compound of formula I wherein Q is a group



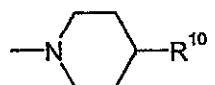
wherein R⁸ is

- (i) K-R¹⁴;
 K is selected from a bond, -C(=O)-, -C(=O)C₁₋₂alkylene-, -C(O)₂-, -C₁₋₂alkylene-C(O)₂-, -C(=O)NR¹⁶-, and -C₁₋₂alkylene-C(=O)NR¹⁶-, wherein R¹⁶ is hydrogen or methyl; and R¹⁴ is selected from lower alkyl, furyl, cyclopentyl, phenyl, pyridyl, imidazolyl, and imidazoliny, wherein each R¹⁴ in turn is optionally substituted with one to three groups selected from R¹⁹; and R¹⁹ is selected from lower alkyl, lower alkoxy, halogen, cyano, trifluoromethyl, and phenyl (said phenyl in turn being optionally substituted with one to two of methyl, halogen, and/or cyano);
 (ii) selected from -C(=O)furyl, -C(=O)alkyl, -C(O)₂alkyl, -C₁₋₂alkylene-C(O)₂-(alkyl), -C₁₋₂alkylene-C(=O)NH(alkyl), -C₁₋₂alkylene-C(=O)N(lower alkyl)(alkyl), -C(=O)NH-(phenyl), phenyl, -C(=O)C₁₋₂alkylene(cyclopentyl), pyridyl, imidazolyl, and imidazoliny, wherein each of said phenyl, pyridyl, imidazolyl, and imidazoliny groups is in turn optionally substituted with one to three of lower alkyl, trifluoromethyl, halogen, cyano,

methoxy, and phenyl, said phenyl in turn optionally substituted with one to two of methyl, halogen, and/or cyano;

- (iii) selected from alkylcarbonyl, furanylcarbonyl, alkoxy carbonyl, alkoxy carbonylalkyl, dialkylaminocarbonyl, optionally substituted phenylaminocarbonyl, cycloalkylalkylcarbonyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted imidazolyl, and optionally substituted imidazolyl; or
- (iv) selected from 4-methyl-pentanoyl-, furan-2-carbonyl-, ethoxycarbonyl-, ethoxycarbonylmethyl-, 3-trifluoromethylphenyl-, dimethylaminocarbonylmethyl-, 3-chlorophenyl-, cyclopentyl-methylcarbonyl-, 3-fluorophenyl-aminocarbonyl-, 3,4-difluorophenyl-aminocarbonyl-, 3-cyanophenyl-aminocarbonyl-, pyridin-2-yl-, imidazol-2-yl-, 6-methyl-pyridin-2-yl-, 4-methyl-pyridin-2-yl-, 1-oxypyridin-2-yl-, 1-methyl-imidazol-2-yl-, 1-methyl-imidazol-2-yl-, 1,4,5-trimethyl-imidazol-2-yl-, 4-methoxy-pyridin-2-yl-, 3-methylbutyryl-, 3-trifluoromethyl-4-chlorophenyl-, 1-(3-fluorophenyl)-imidazol-2-yl-, and 1-isopropyl-imidazol-2-yl-.

- 15 In another embodiment the present invention provides a compound of formula I wherein Q is



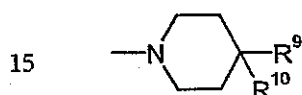
wherein R^{10} is

- (i) selected from alkyl, pyrrolidinyl, $-C_{1-2}$ alkylene(pyrrolidinyl), $-C(=O)$ phenyl, $-C_{1-2}$ alkylene(phenyl), $-C_{1-2}$ alkylene(pyridyl), $-N(H)(C_{1-2}$ alkylene)(phenyl), $-N(CH_3)(C_{1-2}$ alkylene)(phenyl), $-C_{1-2}$ alkylene(imidazolyl), $-O-(C_{1-2}$ alkylene)(phenyl), and tetrahydropyrimidinyl, wherein each of said pyrrolidinyl and tetrahydropyrimidinyl groups optionally has one to two carbon ring atoms replaced with a carbonyl group, and each of said pyrrolidinyl, phenyl, pyridyl, imidazolyl, and tetrahydropyrimidinyl groups optionally is substituted with one to three of lower alkyl, halogen, cyano, methoxy, methoxy(C_{1-2})alkyl, amino, (C_{1-4} alkyl)amino, sulfonamidyl, CO_2H , $CO_2(C_{1-4}alkyl)$, $N=C(CH_3)N(CH_3)_2$, and/or pyrrolidinyl;
- (ii) selected from alkyl, optionally substituted pyrrolidinyl, optionally substituted pyrrolidinylalkyl, optionally substituted tetrahydropyrimidinyl, optionally substituted benzyl, optionally substituted phenylcarbonyl, optionally substituted benzylamino, optionally substituted imidazolylalkyl, optionally substituted imidazolylalkyl, optionally substituted pyridinylalkyl, optionally substituted phenylalkylamino, optionally

substituted benzyloxy, optionally substituted phenyl, and optionally substituted morpholinylcarbonyl; or

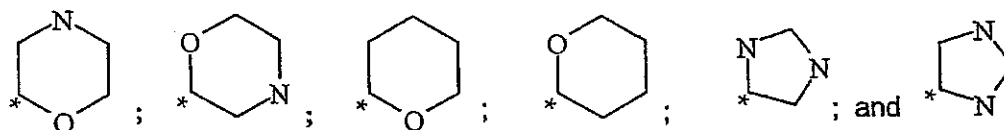
- (iii) selected from 2-(2-methoxymethylpyrrolidin-1-yl)-ethyl-, 2-oxo-tetrahydropyrimidin-1-yl-, 2-oxo-pyrrolidin-1-yl-, benzyl, 4-chlorophenylcarbonyl, 3-(pyrrolidin-1-yl)-benzylamino-, 2-(2-amino-imidazol-1-yl)-ethyl-, 2-(2-methyl-imidazolin-1-yl)-ethyl-, 2-(imidazol-1-yl)-ethyl-, 2-dimethylaminosulfonyl-benzyloxy-, 2-fluoro-benzyl-N-methyl-amino-, propyl-, pyridin-2-yl-methyl-, 2-fluoro-benzylamino-, 2-chloro-benzylamino-, 2-methoxy-benzylamino-, 2-methyl-benzylamino-, 3-methoxycarbonyl-benzyloxy-, 3-carboxy-benzyloxy-, 3-(N,N-di-methanesulfonyl)-amino-benzyloxy-, 3-methanesulfonylamino-benzyloxy-, 3-N,N-dimethylacetamidinyl-benzyloxy-, 3-(2-methylimidazolin-1-yl)-phenyl-, morpholin-1-yl-carbonyl-, 3-[(2-methylaminocarbonyl)-ethyl]-phenyl-, and 3-N,N-dimethylacetamidinyl-phenyl-.

In another embodiment the present invention provides a compound of formula I wherein Q is the group

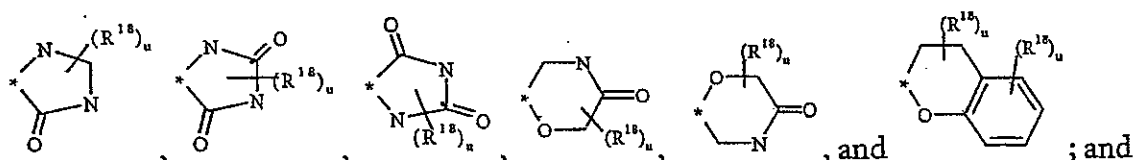


wherein R^9 and R^{10} are taken together

- (i) to form a spirocyclic ring selected from one of

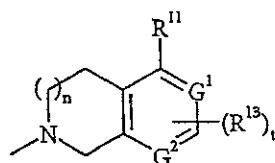


- wherein * represents the point of attachment to the carbon ring atom to which R^9 and R^{10} are attached, and wherein each of said spirocyclic rings optionally has one to two carbon ring atoms replaced with a carbonyl group, and/or optionally has a benzo ring fused thereto, and wherein each of said spirocyclic rings and/or benzo rings is optionally substituted with one to three groups selected from lower alkyl, aminoalkyl, alkylaminoalkyl, and phenyl, wherein said phenyl group is in turn optionally substituted with one to two of halogen, cyano, lower alkoxy, and/or lower alkyl; or
- (ii) to define one of



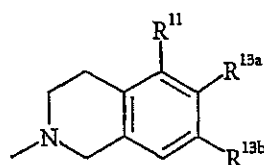
R^{18} is at each occurrence selected from hydrogen, lower alkyl, $(C_{1-4}alkyl)amino(C_{1-4}alkyl)$, and phenyl optionally substituted with one to two of halogen and/or lower alkoxy; and u is 0, 1, 2 or 3.

- In another embodiment the present invention provides a compound of formula I
 5 wherein Q is the group



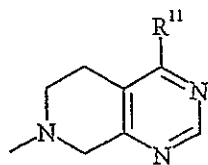
- wherein G^1 and G^2 are carbon or nitrogen; R^{11} is $-J-R^{17}$; R^{13} is selected from lower alkoxy, guanidinyll and alkylguanidinyll; J is selected from a bond, $-C_{1-2}alkylene-$, $-C(=NH)-$, $-NR^{16}-C(=NH)-$, $-N=CR^{16}-NR^{16a}-$, and $-N=$; R^{16} and R^{16a} are hydrogen or lower alkyl;
 10 R^{17} is selected from hydrogen, alkyl, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolinyll, imidazolidinyll, morpholinyl, cycloalkyl, and furyl, except R^{17} is not furyl when J is $-N=$; and wherein each of said R^{17} groups is optionally substituted with one to three groups selected from R^{21} ; R^{21} is selected from lower alkyl, lower alkoxy, halogen and cyano; and t is 0, 1 or 2.

- 15 In another embodiment the present invention provides a compound of formula I wherein Q is



- wherein R^{11} is selected from hydrogen, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolinyll, imidazolidinyll, morpholinyl, $-N=C(CH_3)N(CH_3)_2$, $-N=(pyrrolidinyl)$, $-N=(imidazolid-$
 20 $inyl)$, $-C_{1-2}alkylene(imidazolinyll)$, $-C(=NH)(morpholinyl)$, $-N(H)-C(=NH)-(alkyl)$, $-N(H)-C(=NH)-(cyclobutyl)$, and $-N(H)-C(=NH)-(furyl)$, wherein each of said pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolinyll, imidazolidinyll, and morpholinyl groups is in turn optionally substituted with one to three of methyl, ethyl, propyl, methoxy, ethoxy, and/or methoxy($C_{1-2}alkyl$); and R^{13a} and R^{13b} are selected from
 25 hydrogen, methoxy and $-N=C(CH_3)N(CH_3)_2$.

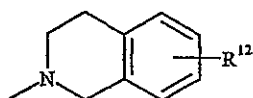
In another embodiment the present invention provides a compound of formula I wherein Q is the group



wherein R^{11} is selected from hydrogen, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, morpholinyl, $-N=C(CH_3)N(CH_3)_2$, $-N=(\text{pyrrolidinyl})$, $-N=(\text{imidazolidinyl})$, $-C_{1-2}\text{alkylene}-(\text{imidazoliny})$, $-C(=NH)-(\text{morpholinyl})$, $-N(H)-C(=NH)-(alkyl)$,
 5 $-N(H)-C(=NH)-(cyclobutyl)$, and $-N(H)-C(=NH)-(furyl)$, wherein each of said pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, morpholinyl, cyclobutyl, and/or furyl groups is in turn optionally substituted with one to three of methyl, ethyl, propyl, methoxy, ethoxy, and/or methoxy($C_{1-2}\text{alkyl}$).

In another embodiment the present invention provides a compound of formula I

10 wherein Q is the group



wherein R^{12} is selected from

- (i) hydrogen, alkoxy, dialkylaminoalkyl, alkylaminoalkyl, optionally substituted imidazolidin-2-ylideneamino, alkylaminoalkylcarbonylaminoalkyl, optionally substituted
 15 pyrrolidinylideneamino, acetamidinyl, optionally substituted imidazolylalkyl, optionally substituted imidazolyl, optionally substituted imidazoliny, iminomorpholinylmethyl, amidinyl, and morpholinyl; or
- (ii) hydrogen, methoxy, N-ethyl-N-methylamino-methyl-, N-methylamino-methyl-, 1,3-dimethyl-imidazolidin-2-ylideneamino-, N-methylamino-methylcarbonyl-N-methyl-
 20 amino-methyl-, 1-methyl-pyrrolidin-ylideneamino-, N,N-dimethylacetamidinyl-, 2-(imidazolin-2-yl)-ethyl-, imidazolin-2-yl-, imino-morpholin-4-yl-methyl-, butyramidinyl-, cyclobutanecarboxamidinyl-, furan-2-yl-carboxamidinyl-, 1-methyl-imidazolin-2-yl-, 2,4,4-trimethyl-imidazolin-1-yl-, 1-methyl-imidazol-2-yl-, 1-(2-methoxy)-ethoxy-imidazolin-2-yl-, 1-isopropyl-imidazolin-2-yl-, 2,4-dimethyl-
 25 imidazolin-2-yl-, and morpholin-4-yl-.

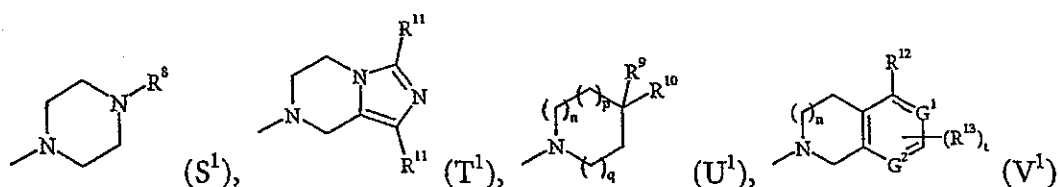
According to another aspect of the invention, preferred compounds are those having the Formula (Ia)



wherein

R^5 is selected from C_{1-4} alkyl, halogen, cyano, hydroxy, C_{1-4} alkoxy, $-O(CH_2)_rNH_2$, $-O(CH_2)_rOH$, $-O(CH_2)_rO(C_{1-4}alkyl)$, $-O(CH_2)_rO(benzyl)$, $-O(CH_2)_scycloalkyl$, $-O(CH_2)_s(phenyl)$, and $-(CH_2)_s(phenyl)$, wherein each of said phenyl is optionally substituted with one to two of lower alkyl, cyano, trifluoromethyl, and/or halogen; and

Q is selected from (S^1) , (T^1) , (U^1) and (V^1)



R^8 is $-K-R^{14}$;

R^9 is hydrogen or alkyl;

R^{10} is $-L-R^{15}$, or R^{10} together with R^9 may form an optionally substituted spirocyclic ring of five or six members that optionally includes one or two heteroatoms selected from O, N and S;

each R^{11} is independently selected from hydrogen, alkyl or cycloalkyl;

R^{12} is selected from hydrogen, halogen, cyano, alkoxy and $-J-R^{17}$;

G^1 and G^2 are selected from CR^{13} and nitrogen;

R^{13} is selected from hydrogen, halogen, cyano, and alkoxy;

J is selected from a bond, $-C_{1-4}alkylene-$, $-C(=NR^{16})-$, $-NR^{16}-C(=NR^{16})-$, $-N=CR^{16}-NR^{16a}-$, and $-N=$;

K is selected from a bond, $C_{1-4}alkylene-$, $-M_1-C(=O)-M_2-$, $-M_1-C(O)_2-M_2-$ and $-M_1-C(=O)NR^{16}-M_2-$, wherein M_1 and M_2 are selected from a bond and $C_{1-4}alkylene$;

L is selected from a bond, $C_{1-4}alkylene-$, $-M_1-O-M_2-$, and $-M_1-NR^{16}-M_2-$,

R^{13} is selected from hydrogen, halo, alkyl, haloalkyl and alkoxy;

R^{14} is selected from alkyl, cycloalkyl, optionally substituted phenyl, optionally substituted pyridinyl, and optionally substituted imidazolyl;

R¹⁵ is selected from alkyl, optionally substituted phenyl, optionally substituted pyrrolidinyl, optionally substituted imidazolyl, optionally substituted pyridinyl, and tetrahydropyrimidyl;

5 R¹⁷ is selected from hydrogen, alkyl, amino, alkylamino, dialkylamino, cycloalkyl, optionally substituted furanyl, optionally substituted imidazolyl, morpholinyl, and optionally substituted imidazolidinyl;

R¹⁶ and R^{16a} are selected from hydrogen and lower alkyl;

n is 1;

p is 0, 1 or 2;

10 q is 1; and

t is 0, 1 or 2, except if both G¹ and G² are nitrogen, then t is 0 or 1.

In certain embodiments of formula (I) and formula (Ia):

K-R¹⁴ taken together may be selected from alkylcarbonyl, furanylcarbonyl, alkoxy carbonyl, alkoxy carbonylalkyl, dialkylaminocarbonyl, optionally substituted
15 phenylaminocarbonyl, cycloalkylalkylcarbonyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted imidazolyl, and optionally substituted imidazolyl;

L-R¹⁵ taken together may be selected from alkyl, optionally substituted pyrrolidinyl, optionally substituted pyrrolidinylalkyl, optionally substituted tetrahydropyrimidinyl, optionally substituted benzyl, optionally substituted phenylcarbonyl, optionally
20 substituted benzylamino, optionally substituted imidazolylalkyl, optionally substituted imidazolylalkyl, optionally substituted pyridinylalkyl, optionally substituted phenylalkylamino, optionally substituted benzyloxy, optionally substituted phenyl, and optionally substituted morpholinylcarbonyl; and

25 J-R¹⁷ taken together may be selected from hydrogen, alkoxy, dialkylaminoalkyl, alkylaminoalkyl, optionally substituted imidazolidin-2-ylideneamino, alkylaminoalkylcarbonylaminoalkyl, optionally substituted pyrrolidinylideneamino, acetamidinyl, optionally substituted imidazolylalkyl, optionally substituted imidazolyl, optionally substituted imidazolyl, iminomorpholinylmethyl, amidinyl, and
30 morpholinyl.

Where K-R¹⁴ taken together is alkylcarbonyl K-R¹⁴ may be 4-methyl-pentanoyl-.

Where K-R¹⁴ taken together is furanylcarbonyl K-R¹⁴ may be furan-2-carbonyl-. Where K-R¹⁴ taken together is alkoxy carbonyl, K-R¹⁴ may be ethoxycarbonyl.

Where K-R¹⁴ taken together is dialkylaminocarbonyl, K-R¹⁴ may be dimethylaminocarbonylmethyl-.

Where K-R¹⁴ taken together is optionally substituted phenylaminocarbonyl, K-R¹⁴ may be 3-fluorophenylaminocarbonyl-, 3,4-difluorophenylaminocarbonyl-, or 3-
5 cyanophenylaminocarbonyl-.

Where K-R¹⁴ taken together is cycloalkylalkylcarbonyl, K-R¹⁴ may be cyclopentyl-methylcarbonyl-.

Where K-R¹⁴ taken together is optionally substituted phenyl, K-R¹⁴ may be 3-trifluoromethylphenyl-, 3-chlorophenyl-, 3-trifluoromethyl-4-chlorophenyl-, or 1-(3-fluoro-
10 phenyl)-imidazolin-2-yl-.

Where K-R¹⁴ taken together is optionally substituted pyridinyl, K-R¹⁴ may be 4-methoxypyridin-2-yl-, 4-methyl-pyridin-2-yl-, 5-methyl-pyridin-2-yl-, 6-methyl-pyridin-2-yl-, pyridin-2-yl, or 1-oxypyridin-2-yl.

Where K-R¹⁴ taken together is optionally substituted imidazolyl, K-R¹⁴ may be imidazol-
15 2-yl-, 1-methyl-imidazol-2-yl-, or 1,4,5-trimethyl-imidazol-2-yl-.

Where K-R¹⁴ taken together is optionally substituted imidazoliny, K-R¹⁴ may be 1-methyl-imidazolin-2-yl-, imidazolin-2-yl-, or 1-isopropyl-imidazolin-2-yl-.

Where L-R¹⁵ taken together is optionally substituted pyrrolidinyl, L-R¹⁵ may be 2-oxopyrrolidin-1-yl-.

20 Where L-R¹⁵ taken together is optionally substituted pyrrolidinylalkyl, L-R¹⁵ may be 2-(2-methoxymethylpyrrolidin-1-yl)-ethyl-.

Where L-R¹⁵ taken together is optionally substituted tetrahydropyrimidinyl, L-R¹⁵ taken may be 2-oxo-tetrahydropyrimidin-1-yl-.

Where L-R¹⁵ taken together is optionally substituted phenylcarbonyl, L-R¹⁵ may be 4-
25 chlorophenylcarbonyl.

Where L-R¹⁵ taken together is optionally substituted benzylamino, L-R¹⁵ may be 3-(pyrrolidin-1-yl)-benzylamino-, 2-fluoro-benzyl-N-methylamino-, 2-fluoro-benzylamino-, 2-chloro-benzylamino-, 2-methoxy-benzylamino- or 2-methylbenzylamino-.

Where L-R¹⁵ taken together is optionally substituted imidazolylalkyl, L-R¹⁵ may be 2-(2-amino-imidazol-1-yl)-ethyl-, or 2-(imidazol-1-yl)-ethyl-.

Where L-R¹⁵ taken together is optionally substituted imidazolinylalkyl, L-R¹⁵ may be 2-(2-methyl-imidazolin-1-yl)-ethyl-.

- 5 Where L-R¹⁵ taken together is optionally substituted pyridinylalkyl, L-R¹⁵ may be pyridin-2-yl-methyl-.

- Where L-R¹⁵ taken together is optionally substituted benzyloxy, L-R¹⁵ may be 2-dimethylaminosulfonyl-benzyloxy-, 2-dimethylaminosulfonyl-benzyloxy-, 3-methoxycarbonyl-benzyloxy-, 3-carboxy-benzyloxy-, 3-(N,N-di-methanesulfonyl)-
10 amino-benzyloxy-, 3-methanesulfonylamino-benzyloxy-, or 3-N,N-dimethylacetamidinyl-benzyloxy-.

Where L-R¹⁵ taken together is optionally substituted phenyl, L-R¹⁵ may be 3-(2-methyl-imidazolin-1-yl)-phenyl-, 3-[(2-methylaminocarbonyl)-ethyl]-phenyl-, or 3-N,N-dimethylacetamidinyl-phenyl-.

- 15 Where L-R¹⁵ taken together is optionally substituted morpholinylcarbonyl, L-R¹⁵ may be morpholin-1-yl-carbonyl-.

Where J-R¹⁷ taken together is dialkylaminoalkyl, J-R¹⁷ may be N-ethyl-N-methylamino-methyl-.

Where J-R¹⁷ taken together is alkylaminoalkyl, J-R¹⁷ may be N-methylamino-methyl-,

- 20 Where J-R¹⁷ taken together is optionally substituted imidazolidin-2-ylideneamino, J-R¹⁷ may be 1,3-dimethyl-imidazolidin-2-ylideneamino-.

Where J-R¹⁷ taken together is alkylaminoalkylcarbonylaminoalkyl, J-R¹⁷ may be N-methylamino-methylcarbonyl-N-methylamino-methyl-.

- Where J-R¹⁷ taken together is optionally substituted pyrrolidinylideneamino, J-R¹⁷ may
25 be 1-methyl-pyrrolidin-ylideneamino-.

Where J-R¹⁷ taken together is optionally substituted imidazolylalkyl, J-R¹⁷ may be 2-(imidazolin-2-yl)-ethyl-.

Where J-R¹⁷ taken together is optionally substituted imidazolyl, J-R¹⁷ may be 1-methyl-imidazol-2-yl-.

Where J-R¹⁷ taken together is optionally substituted imidazoliny, J-R¹⁷ may be imidazolin-2-yl-, 1-methyl-imidazolin-2-yl-, 2,4,4-trimethyl-imidazolin-1-yl-, 1-(2-methoxy)-ethoxy-imidazolin-2-yl-, 1-isopropyl-imidazolin-2-yl-, or 2,4-dimethyl-imidazolin-2-yl-.

- 5 Where J-R¹⁷ taken together is iminomorpholinylmethyl, J-R¹⁷ may be imino-morpholin-4-yl-methyl-.

Where J-R¹⁷ taken together is amidinyl, J-R¹⁷ may be butyramidinyl-, cyclobutanecarboxamidinyl-, furan-2-yl-carboxamidinyl-, or N,N-dimethylacetamidinyl-.

Where J-R¹⁷ taken together is morpholinyl, J-R¹⁷ may be morpholin-4-yl-

- 10 In certain embodiments of formula (I) and formula (Ia), K-R¹⁴ taken together may be selected from 4-methyl-pentanoyl-, furan-2-carbonyl-, ethoxycarbonyl-, ethoxycarbonylmethyl-, 3-trifluoromethylphenyl-, dimethylaminocarbonylmethyl-, 3-chlorophenyl-, cyclopentyl-methylcarbonyl-, 3-fluorophenyl-aminocarbonyl-, 3,4-difluorophenyl-aminocarbonyl-, 3-cyanophenyl-aminocarbonyl-, pyridin-2-yl-, imidazol-2-yl-, 6-
15 methyl-pyridin-2-yl-, 4-methyl-pyridin-2-yl, 1-oxypyridin-2-yl, 1-methyl-imidazolin-2-yl-, 1-methyl-imidazol-2-yl-, 1,4,5-trimethyl-imidazol-2-yl-, 4-methoxy-pyridin-2-yl-, 3-methylbutyryl-, 3-trifluoromethyl-4-chlorophenyl-, 1-(3-fluorophenyl)-imidazolin-2-yl-, and 1-isopropyl-imidazolin-2-yl-.

- In other embodiments of formula (I) and formula (Ia), L-R¹⁵ taken together may be
20 selected from 2-(2-methoxymethylpyrrolidin-1-yl)-ethyl-, 2-oxo-tetrahydropyrimidin-1-yl-, 2-oxo-pyrrolidin-1-yl-, benzyl, 4-chlorophenylcarbonyl, 3-(pyrrolidin-1-yl)-benzyl-amino-, 2-(2-amino-imidazol-1-yl)-ethyl-, 2-(2-methyl-imidazolin-1-yl)-ethyl-, 2-(imidazol-1-yl)-ethyl-, 2-dimethylaminosulfonyl-benzyloxy-, 2-fluoro-benzyl-N-methylamino-, propyl-, pyridin-2-yl-methyl-, 2-fluoro-benzylamino-, 2-chloro-
25 benzylamino-, 2-methoxy-benzylamino-, 2-methyl-benzylamino-, 3-methoxycarbonyl-benzyloxy-, 3-carboxy-benzyloxy-, 3-(N,N-di-methanesulfonyl)-amino-benzyloxy-, 3-methanesulfonylamino-benzyloxy-, 3-N,N-dimethylacetamidinyl-benzyloxy-, 3-(2-methylimidazolin-1-yl)-phenyl-, morpholin-1-yl-carbonyl-, 3-[(2-methylaminocarbonyl)-ethyl]-phenyl-, and 3-N,N-dimethylacetamidinyl-phenyl.

- 30 In still other embodiments of formula (I) and formula (Ia), J-R¹⁷ taken together may be selected from hydrogen, methoxy, N-ethyl-N-methylamino-methyl-, N-methylamino-methyl-, 1,3-dimethyl-imidazolidin-2-ylideneamino-, N-methylamino-methylcarbonyl-N-methylamino-methyl-, 1-methyl-pyrrolidin-ylideneamino-, N,N-

dimethylacetamidinyl-, 2-(imidazolin-2-yl)-ethyl-, imidazolin-2-yl-, imino-morpholin-4-yl-methyl-, butyramidinyl-, cyclobutanecarboxamidinyl-, furan-2-yl-carboxamidinyl-, 1-methyl-imidazolin-2-yl-, 2,4,4-trimethyl-imidazolin-1-yl-, 1-methyl-imidazol-2-yl-, 1-(2-methoxy)-ethoxy-imidazolin-2-yl-, 1-isopropyl-imidazolin-2-yl-, 2,4-dimethyl-imidazolin-2-yl-, and morpholin-4-yl-.

According to another aspect of the invention, certain preferred compounds are those having the above formulae (Ia) wherein Q is the group (S¹).

Within the group of compounds wherein Q is (S) or more preferably (S¹), preferred are those compounds wherein R⁸ is K-R¹⁴; K is selected from a bond, C₁₋₂alkylene, -M₁-C(=O)-M₂-, -M₁-C(O)₂-M₂-, and -M₁-C(=O)NR¹⁶-M₂-, wherein M₁ and M₂ are selected from a bond and C₁₋₂alkylene; and R¹⁶ is hydrogen or lower alkyl; R¹⁴ is selected from hydrogen, lower alkyl, furyl, cycloalkyl, phenyl, pyridyl, imidazolyl, and imidazoliny, wherein each R¹⁴ in turn is optionally substituted with one to three groups selected from R¹⁹; and R¹⁹ is selected from lower alkyl, halogen, cyano, halo(C₁₋₄)alkyl, halo(C₁₋₄)alkoxy, hydroxy, lower alkoxy, amino, (C₁₋₄alkyl)amino, (C₁₋₄alkyl)amino(C₁₋₄)alkyl, hydroxy(C₁₋₄)alkyl, (loweralkoxy)(C₁₋₄)alkyl, SO₂(C₁₋₄alkyl), -C(=O)H, -C(=O)(C₁₋₄alkyl), pyrrolidinyl, and phenyl (said phenyl in turn being optionally substituted with one to two of lower alkyl, lower alkoxy, cyano, and/or halogen).

Within the group of preferred compounds wherein Q is (S) or more preferably (S¹), even more preferred are compounds wherein R⁸ is K-R¹⁴; K is selected from a bond, -C(=O)-, -C(=O)C₁₋₂alkylene-, -C(O)₂-, -C₁₋₂alkylene-C(O)₂-, -C(=O)NR¹⁶-, and -C₁₋₂alkylene-C(=O)NR¹⁶-, wherein R¹⁶ is hydrogen or methyl; R¹⁴ is selected from lower alkyl, furyl, cyclopentyl, phenyl, pyridyl, imidazolyl, and imidazoliny, wherein each R¹⁴ in turn is optionally substituted with one to three groups selected from R¹⁹; and R¹⁹ is selected from lower alkyl, lower alkoxy, halogen, cyano, trifluoromethyl, and phenyl (said phenyl in turn being optionally substituted with one to two halogen).

Within this group of preferred compounds wherein Q is the group (S) or more preferably (S¹), even more preferred are compounds wherein R⁸ is selected from -C(=O)furyl, -C(=O)alkyl, -C(O)₂alkyl, -C₁₋₂alkylene-C(O)₂-(alkyl), -C₁₋₂alkylene-C(=O)NH(alkyl), -C₁₋₂alkylene-C(=O)N(lower alkyl)(alkyl), -C(=O)NH(phenyl), phenyl, -C(=O)C₁₋₂alkylene(cyclopentyl), pyridyl, imidazolyl, and imidazoliny, wherein each of said phenyl, pyridyl, imidazolyl, and imidazoliny groups is in turn optionally substituted with one to three of lower alkyl, trifluoromethyl, halogen, cyano, methoxy, and/or phenyl, said

phenyl in turn being optionally substituted with one to two of methyl, halogen, and/or cyano.

Within this group of preferred compounds, most preferred are those compounds wherein R^{14} is furyl optionally substituted with one to two of lower alkyl, trifluoromethyl, halogen, and/or cyano, and most preferred are those compounds wherein R^8 is $-C(=O)(\text{furyl})$.

According to another aspect of the invention, certain preferred compounds are those having the above formulae (Ia) wherein Q is a group of formula S^1 , and wherein R^8 is selected from alkylcarbonyl, furanylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, dialkylaminocarbonyl, optionally substituted phenylaminocarbonyl, cycloalkylalkylcarbonyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted imidazolyl, and optionally substituted imidazolinyl. In certain embodiments, R^8 may be selected from 4-methyl-pentanoyl-, furan-2-carbonyl-, ethoxycarbonyl-, ethoxycarbonylmethyl-, 3-trifluoromethylphenyl-, dimethylaminocarbonylmethyl-, 3-chlorophenyl-, cyclopentyl-methylcarbonyl-, 3-fluorophenyl-aminocarbonyl-, 3,4-difluorophenyl-aminocarbonyl-, 3-cyanophenyl-aminocarbonyl-, pyridin-2-yl-, imidazol-2-yl-, 6-methyl-pyridin-2-yl-, 4-methyl-pyridin-2-yl-, 1-oxypyridin-2-yl-, 1-methyl-imidazolin-2-yl-, 1-methyl-imidazol-2-yl-, 1,4,5-trimethyl-imidazol-2-yl-, 4-methoxy-pyridin-2-yl-, 3-methylbutyryl-, 3-trifluoromethyl-4-chlorophenyl-, 1-(3-fluorophenyl)-imidazolin-2-yl-, and 1-isopropyl-imidazolin-2-yl-.

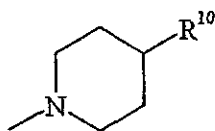
According to another aspect of the invention, preferred compounds are those having the above formulae (I) and/or (Ia) wherein Q is the group (T^1). Within this group of preferred compounds, more preferred are compounds wherein R^{11} is cycloalkyl, more preferably cyclohexyl, and wherein R^{12} is hydrogen.

According to another aspect of the invention, preferred compounds are those having the above formulae (I) and/or (Ia) wherein Q is the group (U^1). Within this group of preferred compounds wherein Q is the group (U^1), one subset of further preferred compounds are those wherein n , p and q are each 1; R^9 is hydrogen or lower alkyl; R^{10} is $-L-R^{15}$; L is selected from a bond, C_{1-2} alkylene, $-C(=O)-$, $-NH(C_{1-2}alkylene)-$, $-N(lower\ alkyl)(C_{1-2}alkylene)-$, and $-O-(C_{1-2}alkylene)-$; R^{15} is selected from alkyl, pyrrolidinyl, phenyl, pyridyl, imidazolyl, and tetrahydropyrimidinyl, wherein each of said pyrrolidinyl and tetrahydropyrimidinyl groups optionally has one to two carbon ring atoms replaced with a carbonyl group, and each of said R^{15} groups is optionally substituted with one to

three groups selected from R^{20} ; and R^{20} is at each occurrence independently selected from lower alkyl, halogen, cyano, lower alkoxy, (loweralkoxy)(C_{1-4})alkyl, amino, (C_{1-4} alkyl)amino, sulfonamidyl, CO_2H , $CO_2(C_{1-4}alkyl)$, amidinyl, alkyl-amidinyl, and pyrrolidinyl.

- 5 Within this group of preferred compounds wherein Q is the group (U^1), even further preferred compounds are those wherein n , p and q are each 1; R^9 is hydrogen; and R^{10} is selected from alkyl, pyrrolidinyl, $-C_{1-2}alkylene(pyrrolidinyl)$, $-C(=O)phenyl$, $C_{1-2}alkylene(phenyl)$, $-C_{1-2}alkylene(pyridyl)$, $-NH(C_{1-2}alkylene)(phenyl)$, $-N(CH_3)(C_{1-2}alkylene)(phenyl)$, $-C_{1-2}alkylene(imidazolyl)$, $-O-(C_{1-2}alkylene)(phenyl)$, and
- 10 tetrahydropyrimidinyl, wherein each of said pyrrolidinyl and tetrahydropyrimidinyl groups optionally has one to two carbon ring atoms replaced with a carbonyl group, and each of said pyrrolidinyl, phenyl, pyridyl, imidazolyl, and tetrahydropyrimidinyl groups optionally is substituted with one to three of lower alkyl, halogen, cyano, methoxy, methoxy(C_{1-2})alkyl, amino, ($C_{1-4}alkyl$)amino, sulfonamidyl, CO_2H , $CO_2(C_{1-4}alkyl)$, -
- 15 $N=C(CH_3)N(CH_3)_2$, and/or pyrrolidinyl.

According to another aspect of the invention, preferred compounds are those having the above formulae (I) and/or (Ia) wherein Q is

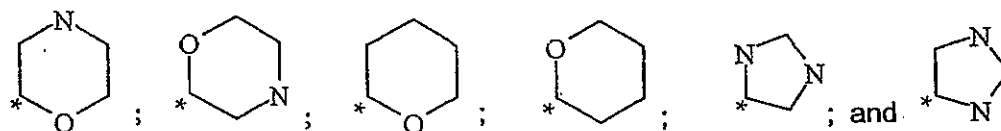


- and wherein R^{10} is selected from alkyl, optionally substituted pyrrolidinyl, optionally
- 20 substituted pyrrolidinylalkyl, optionally substituted tetrahydropyrimidinyl, optionally substituted benzyl, optionally substituted phenylcarbonyl, optionally substituted benzyl-amino, optionally substituted imidazolylalkyl, optionally substituted imidazolylalkyl, optionally substituted pyridinylalkyl, optionally substituted phenylalkylamino, optionally substituted benzyloxy, optionally substituted phenyl, and optionally substituted morpho-
 - 25 lylcarbonyl.

- R^{10} may be selected from 2-(2-methoxymethylpyrrolidin-1-yl)-ethyl-, 2-oxo-tetrahydro-pyrimidin-1-yl-, 2-oxo-pyrrolidin-1-yl-, benzyl, 4-chlorophenylcarbonyl, 3-(pyrrolidin-1-yl)-benzylamino-, 2-(2-amino-imidazol-1-yl)-ethyl-, 2-(2-methyl-imidazol-1-yl)-ethyl-, 2-(imidazol-1-yl)-ethyl-, 2-dimethylaminosulfonyl-benzyloxy-, 2-fluoro-benzyl-
- 30 N-methylamino-, propyl-, pyridin-2-yl-methyl-, 2-fluoro-benzylamino-, 2-chloro-benzylamino-, 2-methoxy-benzylamino-, 2-methyl-benzylamino-, 3-methoxycarbonyl-

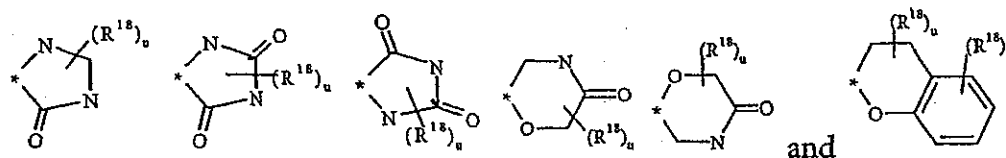
benzyloxy-, 3-carboxy-benzyloxy-, 3-(N,N-di-methanesulfonyl)-amino-benzyloxy-, 3-methanesulfonylamino-benzyloxy-, 3-N,N-dimethylacetamidinyl-benzyloxy-, 3-(2-methylimidazolin-1-yl)-phenyl-, morpholin-1-yl-carbonyl-, 3-[(2-methylaminocarbonyl)-ethyl]-phenyl-, and 3-N,N-dimethylacetamidinyl-phenyl-.

- 5 According to another aspect of the invention, preferred compounds are those having the above formulae (I) and/or (Ia) wherein Q is the group (U¹), and R⁹ and R¹⁰ are taken together to form a spirocyclic ring, more preferably a spirocyclic ring selected from one of



- wherein * represents the point of attachment to the carbon ring atom to which R⁹ and R¹⁰ are attached, and each of said spirocyclic rings optionally has one to two carbon ring atoms replaced with a carbonyl group, and/or optionally has a benzo ring fused thereto, and wherein each of said spirocyclic rings and/or fused benzo rings is optionally substituted with one to two groups selected from lower alkyl, aminoalkyl, alkylaminoalkyl, and phenyl, wherein said phenyl group is in turn optionally substituted with one to two of halogen, cyano, lower alkoxy, and/or lower alkyl, more preferably with fluoro, chloro, and/or methoxy.

In certain embodiments, R⁹ and R¹⁰ taken together define one of

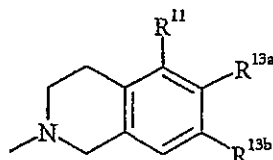


- and R¹⁸ is at each occurrence selected from hydrogen, lower alkyl, (C₁₋₄alkyl)amino-, (C₁₋₄alkyl), and phenyl optionally substituted with one to two of halogen and/or lower alkoxy; and u is 0, 1, 2 or 3.

- According to another aspect of the invention, preferred compounds are those having the above formulae (I) and/or (Ia) wherein Q is the group (V¹). Within this group of compounds, one subset of further preferred compounds are those wherein n is 1; G¹ and G² are both carbon; R¹¹ is -J-R¹⁷; R¹³ is selected from lower alkoxy, amidinyl and alkylamidinyl; J is selected from a bond, -C₁₋₂alkylene-, -C(=NH)-, -NR¹⁶-C(=NH)-, -N=CR¹⁶-NR^{16a}-, and -N=; R¹⁶ and R^{16a} are hydrogen, methyl, or ethyl; R¹⁷ is selected

from hydrogen, alkyl, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, morpholinyl, cycloalkyl, and furyl, except R^{17} is not furyl when J is $-N=$; and wherein each of said R^{17} groups is optionally substituted with one to three groups selected from R^{21} ; R^{21} is selected from lower alkyl, lower alkoxy, halogen and cyano; and t is 0, 1 or 2.

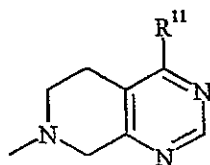
- 5 Further preferred within this group of preferred compounds [wherein Q is the group (V^1)], are those compounds wherein Q is



R^{11} is selected from hydrogen, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, morpholinyl, $-N=C(CH_3)N(CH_3)_2$, $-N=(pyrrolidinyl)$,

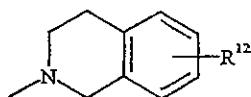
- 10 $-N=(imidazolidinyl)$, $-C_{1-2}alkylene(imidazoliny)$, $-C(=NH)(morpholinyl)$, $-N(H)-C(=NH)-(alkyl)$, $-N(H)-C(=NH)-(cyclobutyl)$, and $-N(H)-C(=NH)-(furyl)$, wherein each of said pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, morpholinyl groups, cyclobutyl, and furyl groups is in turn optionally substituted with one to three of methyl, ethyl, propyl, methoxy, ethoxy, and/or methoxy($C_{1-2}alkyl$); and
- 15 R^{13a} and R^{13b} are selected from hydrogen, methoxy and $-N=C(CH_3)N(CH_3)_2$.

According to another aspect of the invention, preferred compounds are those compounds wherein Q is the group



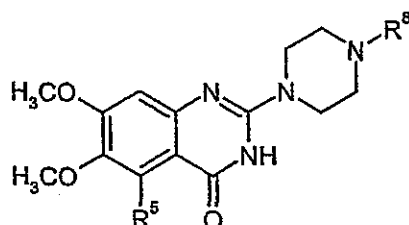
- and R^{11} is selected from hydrogen, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, morpholinyl, $-N=C(CH_3)N(CH_3)_2$, $-N=(pyrrolidinyl)$, $-N=(imidazolidinyl)$, $-C_{1-2}alkylene(imidazoliny)$, $-C(=NH)(morpholinyl)$, $-N(H)-C(=NH)-(alkyl)$, $-N(H)-C(=NH)-(cyclobutyl)$, and $-N(H)-C(=NH)-(furyl)$, wherein each of said pyrrolidinyl, pyrrolinyl, imidazolyl, imidazoliny, imidazolidinyl, and morpholinyl rings is in turn optionally substituted with one to three of methyl, ethyl, propyl, methoxy, ethoxy, and/or methoxy($C_{1-2}alkyl$). More preferred within this group of compounds are those wherein R^{11} is morpholinyl.
- 25

In certain embodiments of formula (I) and formula (Ia) wherein Q is the group



- R^{12} may be selected from hydrogen, alkoxy, dialkylaminoalkyl, alkylaminoalkyl, optionally substituted imidazolidin-2-ylideneamino, alkylaminoalkylcarbonylaminoalkyl, optionally substituted pyrrolidinylideneamino, acetamidinyl, optionally substituted imidazolylalkyl, optionally substituted imidazolyl, optionally substituted imidazolinyl, iminomorpholinylmethyl, amidinyl, and morpholinyl. In specific embodiments R^{12} may be selected from hydrogen, methoxy, N-ethyl-N-methylamino-methyl-, N-methylamino-methyl-, 1,3-dimethyl-imidazolidin-2-ylideneamino-, N-methylamino-methylcarbonyl-
 10 N-methylamino-methyl-, 1-methyl-pyrrolidin-ylideneamino-, N,N-dimethylacetamidinyl-, 2-(imidazolin-2-yl)-ethyl-, imidazolin-2-yl-, imino-morpholin-4-yl-methyl-, butyramidinyl-, cyclobutanecarboxamidinyl-, furan-2-yl-carboxamidinyl-, 1-methyl-imidazolin-2-yl-, 2,4,4-trimethyl-imidazolin-1-yl-, 1-methyl-imidazol-2-yl-, 1-(2-methoxy)-ethoxy-imidazolin-2-yl-, 1-isopropyl-imidazolin-2-yl-, 2,4-dimethyl-
 15 imidazolin-2-yl-, and morpholin-4-yl-.

In certain embodiments, the compounds of the invention are of the formula (Im)



(Im)

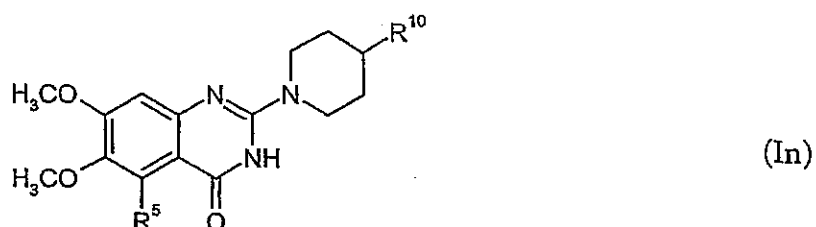
wherein

R^5 is hydrogen, alkyl or alkoxy; and

- R^8 may be selected from alkylcarbonyl, furanylcabonyl, alkoxycarbonyl, alkoxycarbonyl-alkyl, dialkylaminocarbonyl, optionally substituted phenylaminocarbonyl, cycloalkylalkylcarbonyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted imidazolyl, and optionally substituted imidazolinyl. In specific
 20 embodiments R^8 may be selected from 4-methyl-pentanoyl-, furan-2-carbonyl-, ethoxycarbonyl-, ethoxycarbonylmethyl-, 3-trifluoromethylphenyl-, dimethylaminocarbonylmethyl-, 3-chlorophenyl-, cyclopentyl-methylcarbonyl-, 3-fluorophenyl-aminocarbonyl-, 3,4-difluorophenyl-aminocarbonyl-, 3-cyanophenyl-aminocarbonyl-, pyridin-2-yl-, imidazol-2-yl-, 6-methyl-pyridin-2-yl-, 4-methyl-

pyridin-2-yl, 1-oxypyridin-2-yl, 1-methyl-imidazolin-2-yl-, 1-methyl-imidazol-2-yl-, 1,4,5-trimethyl-imidazol-2-yl-, 4-methoxy-pyridin-2-yl-, 3-methylbutyryl-, 3-trifluoromethyl-4-chlorophenyl-, 1-(3-fluorophenyl)-imidazolin-2-yl-, and 1-isopropyl-imidazolin-2-yl-.

- 5 In certain embodiments, the compounds of the invention are of the formula (In)

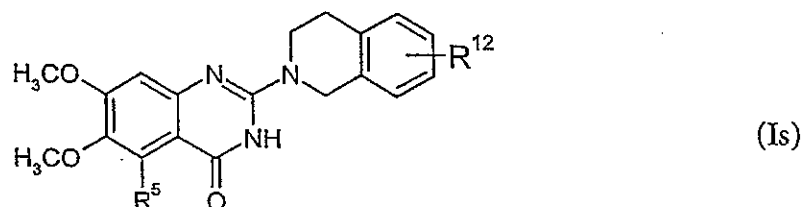


wherein

R⁵ is hydrogen, alkyl or alkoxy; and

- R¹⁰ is selected from alkyl, optionally substituted pyrrolidinyl, optionally substituted
 10 pyrrolidinylalkyl, optionally substituted tetrahydropyrimidinyl, optionally substituted benzyl, optionally substituted phenylcarbonyl, optionally substituted benzylamino, optionally substituted imidazolylalkyl, optionally substituted imidazolinylalkyl, optionally substituted pyridinylalkyl, optionally substituted phenylalkylamino, optionally substituted benzyloxy, optionally substituted phenyl, and optionally substituted
 15 morpholinylcarbonyl. In specific embodiments R¹⁰ may be selected from 2-(2-methoxymethylpyrrolidin-1-yl)-ethyl-, 2-oxo-tetrahydropyrimidin-1-yl-, 2-oxo-pyrrolidin-1-yl-, benzyl, 4-chlorophenylcarbonyl, 3-(pyrrolidin-1-yl)-benzylamino-, 2-(2-amino-imidazol-1-yl)-ethyl-, 2-(2-methyl-imidazolin-1-yl)-ethyl-, 2-(imidazol-1-yl)-ethyl-, 2-dimethylaminosulfonyl-benzyloxy-, 2-fluoro-benzyl-N-methylamino-, propyl-,
 20 pyridin-2-yl-methyl-, 2-fluoro-benzylamino-, 2-chloro-benzylamino-, 2-methoxy-benzylamino-, 2-methyl-benzylamino-, 3-methoxycarbonyl-benzyloxy-, 3-carboxy-benzyloxy-, 3-(N,N-di-methanesulfonyl)-amino-benzyloxy-, 3-methanesulfonylamino-benzyloxy-, 3-N,N-dimethylacetamidinyl-benzyloxy-, 3-(2-methylimidazolin-1-yl)-phenyl-, morpholin-1-yl-carbonyl-, 3-[(2-methylaminocarbonyl)-ethyl]-phenyl-, and 3-
 25 N,N-dimethylacetamidinyl-phenyl-.

In certain embodiments, the compounds of the invention are of the formula (Is)

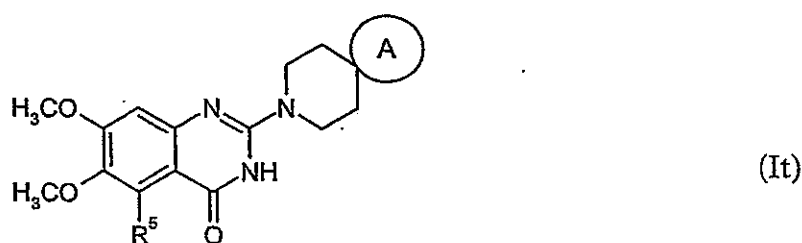


wherein:

R^5 is hydrogen, alkyl or alkoxy; and

R^{12} is selected from hydrogen, alkoxy, dialkylaminoalkyl, alkylaminoalkyl, optionally substituted imidazolidin-2-ylideneamino, alkylaminoalkylcarbonylaminoalkyl, optionally substituted pyrrolidinylideneamino, acetamidinyl, optionally substituted imidazolylalkyl, optionally substituted imidazolyl, optionally substituted imidazolyl, iminomorpholinylmethyl, amidinyl, and morpholinyl. In specific embodiments R^{12} may be selected from hydrogen, methoxy, N-ethyl-N-methylamino-methyl-, N-methylamino-methyl-, 1,3-dimethyl-imidazolidin-2-ylideneamino-, N-methylamino-methylcarbonyl-N-methylamino-methyl-, 1-methyl-pyrrolidin-ylideneamino-, N,N-dimethylacetamidinyl-, 2-(imidazolin-2-yl)-ethyl-, imidazolin-2-yl-, imino-morpholin-4-yl-methyl-, butyramidinyl-, cyclobutanecarboxamidinyl-, furan-2-yl-carboxamidinyl-, 1-methyl-imidazolin-2-yl-, 2,4,4-trimethyl-imidazolin-1-yl-, 1-methyl-imidazol-2-yl-, 1-(2-methoxy)-ethoxy-imidazolin-2-yl-, 1-isopropyl-imidazolin-2-yl-, 2,4-dimethyl-imidazolin-2-yl-, and morpholin-4-yl-.

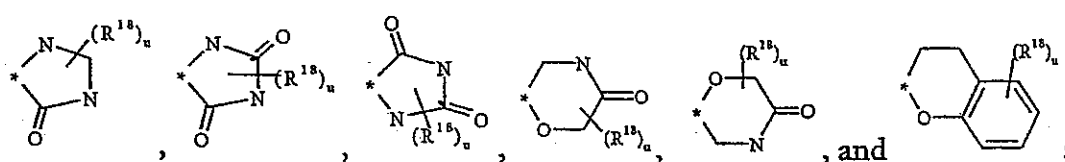
In certain embodiments, the compounds of the invention are of the formula (It)



wherein

R^5 is hydrogen, alkyl or alkoxy; and

A is a five or six-membered ring selected from:

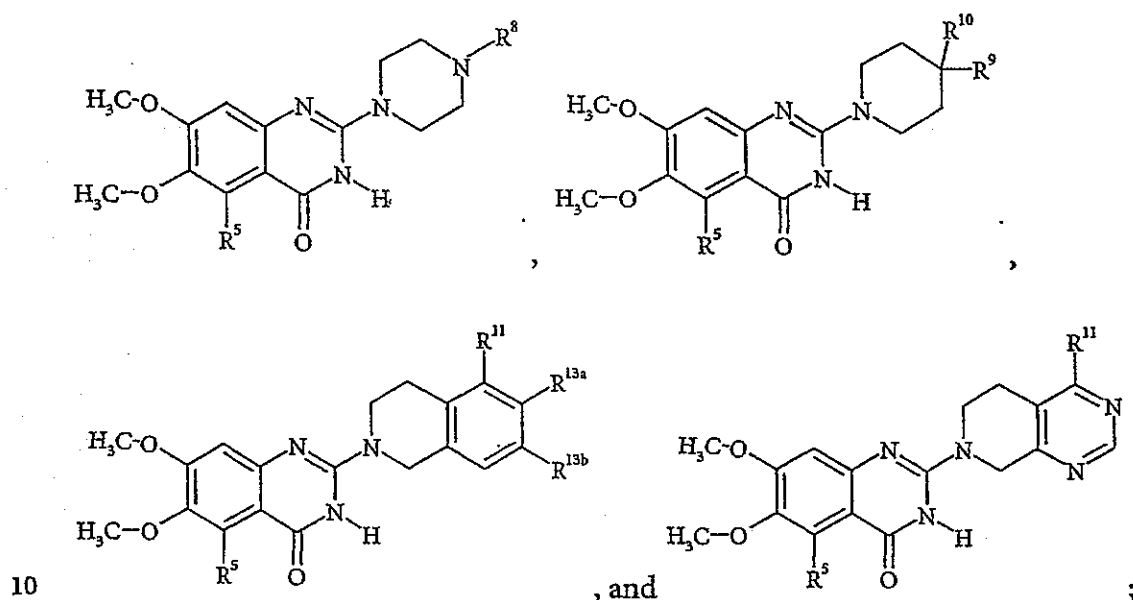


u is 0, 1 or 2;

* is the point of attachment for each ring A; and

R¹⁸ is at each occurrence selected from hydrogen, alkyl, alkylaminoalkyl, and phenyl optionally substituted with one to two of halogen and/or alkoxy.

According to another aspect of the invention, combinations of the preferred groups described herein form other preferred embodiments. In this manner, a variety of preferred compounds are embodied within the present invention. For example, another group of preferred compounds, selected from a combination of preferred groups recited above, are those compounds having a formula selected from,



wherein R⁵ is selected from C₁₋₄alkyl, halogen, hydroxy, C₁₋₄alkoxy, -O(CH₂)_rNH₂, -O(CH₂)_rOH, -O(CH₂)_rO(C₁₋₄alkyl), -O(CH₂)_rO(phenyl), -O(CH₂)_rO(benzyl), -O(CH₂)_scycloalkyl, -O(CH₂)_s(phenyl), -(CH₂)_scycloalkyl, and -(CH₂)_s(phenyl), wherein each of said phenyl, benzyl, and cycloalkyl rings is optionally substituted with one to two of lower alkyl, substituted lower alkyl, cyano, and/or halogen, *r* is 1 or 2, and *s* is 0, 1 or 2; and R⁸, R⁹, R¹⁰, R¹¹, R^{13a}, and R^{13b} are selected from preferred and further preferred groups recited above.

Even more preferred are compounds as immediately defined above wherein R⁵ is selected from methyl, ethyl, n-propyl, isopropyl, halogen, methoxy, and ethoxy. Even more preferred are compounds wherein R⁵ is selected from methyl and methoxy.

Thus, further combinations of preferred compounds may be selected from the preferred groups recited above.

Alpha-1 adrenoceptors mediate the contractile state of smooth muscle tissue and are present in the human prostate, bladder neck and urethra. Alpha-1 adrenoceptor stimulation also produces contraction of urethral and bladder neck smooth muscle, leading to increased resistance in urinary outflow. Thus, alpha-1 adrenoceptor antagonists may be
5 useful in treating disorders of the urinary tract, as previously defined.

Alpha-1B adrenoceptors are present in the liver, heart and cerebral cortex and are believed to be involved in mediating vascular contractile and blood pressure responses. Alpha-1B adrenoceptors are also present in areas of the spinal cord which receive input from sympathetic neurons originating in the pontine micturition center and are
10 presumed to be involved in the regulation of bladder function. Additionally, alpha-1B adrenoceptor antagonists are useful as analgesic/ antihyperalgesic therapies for treating pain, including symptoms of acute pain, inflammatory pain, neuropathic pain (including thermal and mechanical hyperalgesia as well as thermal and mechanical allodynia), complex regional pain syndromes (including reflex sympathetic dystrophy, causalgia and
15 sympathetically maintained pain and the like).

However, it must be noted that in BPH, it is often the irritative symptoms which prompt the patient to seek treatment, and that these irritative symptoms may be present even in patients with no demonstrable obstruction (*i.e.* normal urine flow rates). By combining both alpha-1A and alpha-1B subtype selectivity in a compound, a reduction of both ob-
20 structive and irritative symptoms in patients with BPH may be achieved. Lower levels or lack of alpha-1D adrenoceptor antagonism should lead to reduced or fewer side effects than those associated with the use of non-subtype-selective agents.

In a preferred embodiment, the compounds of this invention are useful for treating disorders and symptoms which can be ameliorated by blockade of alpha-1A/B
25 adrenoceptors, such as reduction or alleviation of urinary tract disorders, *e.g.*, pelvic hypersensitivity (including interstitial cystitis, prostatitis, pelvic pain syndrome, infectious cystitis, prostatodynia, and the like), overactive bladder, urinary frequency, nocturia, urinary urgency, detrusor hyperreflexia, outlet obstruction, BPH, prostatitis, urge incontinence, urethritis, idiopathic bladder hypersensitivity, sexual dysfunction, and
30 the like.

In another preferred embodiment, the compounds of this invention are useful for treating disorders and symptoms which can be ameliorated by blockade of alpha-1A/B adrenoceptors, such as reduction or alleviation of pain disorders, *e.g.* inflammatory pain,

neuropathic pain, cancer pain, acute pain, chronic pain or complex regional pain syndromes.

In a more preferred embodiment, the compounds of this invention are useful for treating disorders and symptoms which can be ameliorated by blockade of both alpha-1A and
5 alpha-1B adrenoceptors with diminished blockade of alpha-1D adrenoceptors, such as reduction or alleviation of both outlet obstruction, such as benign prostatic hypertrophy, and irritative symptoms associated with it, such as pain.

In another preferred embodiment, the compounds of this invention are useful for the improvement of sexual dysfunction including male erectile dysfunction (MED) and
10 female sexual dysfunction (FSD).

These and other therapeutic uses are described, e.g., in Goodman & Gilman's, The Pharmacological Basis of Therapeutics, ninth edition, McGraw-Hill, New York, 1996, Chapter 26, 601-616; and Coleman, Pharmacological Reviews 46:205-229 (1994).

The present invention includes pharmaceutical compositions comprising at least one
15 compound of the present invention, or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt or solvate thereof, together with at least one pharmaceutically acceptable carrier, and optionally other therapeutic and/or prophylactic ingredients.

In general, the compounds of the present invention will be administered in a therapeuti-
20 cally effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are typically 1-500 mg daily, preferably 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication
25 towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this Application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

30 In general, compounds of the present invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sublingual), rectal, nasal, topical, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or pulmonary in a form suitable for

administration by inhalation or insufflation. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

A compound or compounds of the present invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing about one (1) to about 20 milligram of active ingredient or, more broadly, about 0.01 to about one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salts thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active

component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations including
5 emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, e.g., in aqueous propylene glycol solutions or may contain emulsifying agents, e.g., such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in
10 water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition
15 to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, e.g. bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in
20 multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, e.g. solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such
25 as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration
30 to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, e.g., be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.
35 Formulations suitable for topical administration in the mouth include lozenges

comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

- 5 The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, e.g., by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.
- 10 The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays may contain in addition to the active ingredient, such carriers as are known in the art to be appropriate.

- The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional
- 15 means, e.g., with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the case of a dropper or pipette, dosing may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved e.g. by means of a metering atomizing spray pump.
- 20 The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size e.g. on the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, e.g. by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as
- 25 a chlorofluorocarbon (CFC), e.g., dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, e.g. a powder mix of the compound in a suitable powder base such as
- 30 lactose, starch, and starch derivatives such as hydroxypropylmethyl cellulose, and polyvinylpyrrolidone (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form e.g. in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, *e.g.*, Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into to the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, *e.g.*, silicone rubber, or a biodegradable polymer, *e.g.*, polylactic acid.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Other suitable pharmaceutical carriers and their formulations are described in Remington: The Science and Practice of Pharmacy 1995, edited by Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described in Examples below.

Throughout the application, and in the following Schemes and Examples herein, the following abbreviations are used for ease of reference: BOC: *tert*-Butoxycarbonyl; BPH: Benign prostatic hypertrophy or benign prostatic hyperplasia; CBZ: Carbobenzyloxy; CNS: Central nervous system; DCE: Dichloroethane; DCM: Dichloromethane; DMF: *N,N*-Dimethylformamide; DMSO: Dimethylsulfoxide; EtOH: Ethanol; EtOAc: Ethyl Acetate; Hal: Halogen or halide; L: Leaving group; MeOH: Methanol; P: Protective group; Pd/C: Palladium on carbon; RT: room temperature; TEA: triethylamine; THF: Tetrahydrofuran

Compounds of the present invention may be made by the methods depicted in the illustrative synthetic reaction schemes shown and described below.

The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, 1991, Volumes 1-15; Rodd's Chemistry of Carbon Compounds, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention may be synthesized, and various modifications to these synthetic reaction schemes may be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

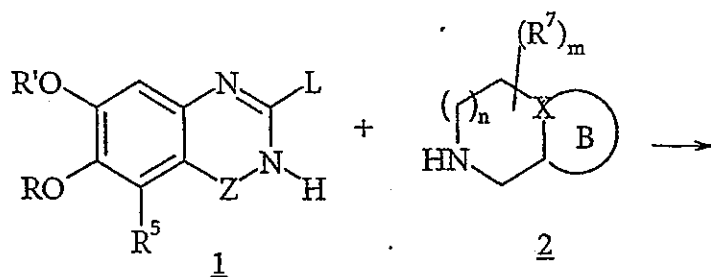
The starting materials and the intermediates of the synthetic reaction schemes may be isolated and purified if desired using conventional techniques including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

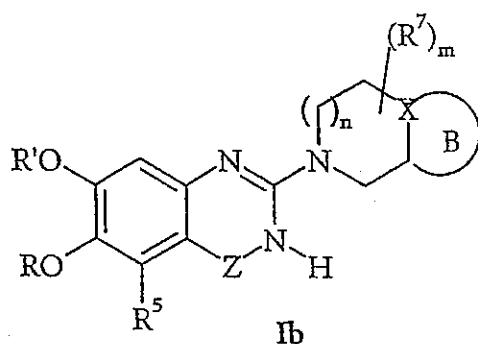
Unless specified to the contrary, the reactions described herein preferably take place at atmospheric pressure over a temperature range from about -78°C to about 150°C , more preferably from about 0°C to reflux, and most preferably and conveniently at about room (or ambient) temperature, *e.g.*, about 20°C .

Schemes 1 to 9 describe methods to prepare compounds of Formula I. Scheme 10 describes a method to prepare intermediates (1) useful in Schemes 1-9 to prepare compounds of formula (I).

Scheme 1

Scheme 1 describes a method of preparing a compound of Formula Ib wherein X is carbon or nitrogen, fused ring B is optionally present, and Z, R, R', R⁵, R⁷, *m* and *n* are as defined in the claims herein.





Reacting the free amine of compound 2, with compound 1 in an inert solvent such as lower alkanol, methoxyethanol, DMSO or DMF, optionally in the presence of a base such as, but not limited to sodium carbonate, sodium bicarbonate, triethyl amine,

5 tributylamine and the like, can give a compound of Formula Ib.

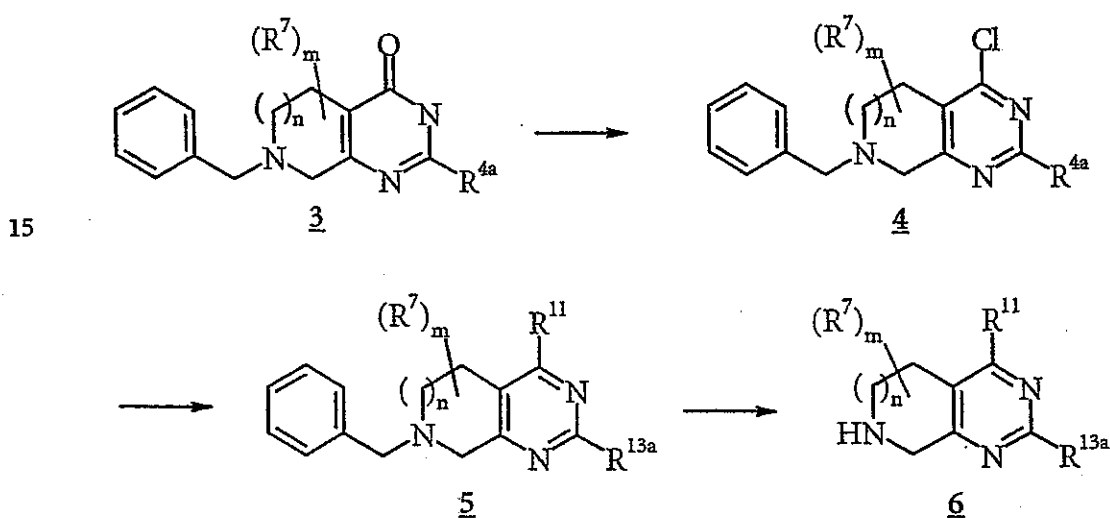
Compounds 1 wherein L is a leaving group such as halogen, preferably chloro, or SCH₃ (as in Ex. G-1, below) can be prepared according to Cronin et al., J. Med. Chem. 11:136-138 (1968) or as described in WO 02/053558 A1, incorporated herein by reference.

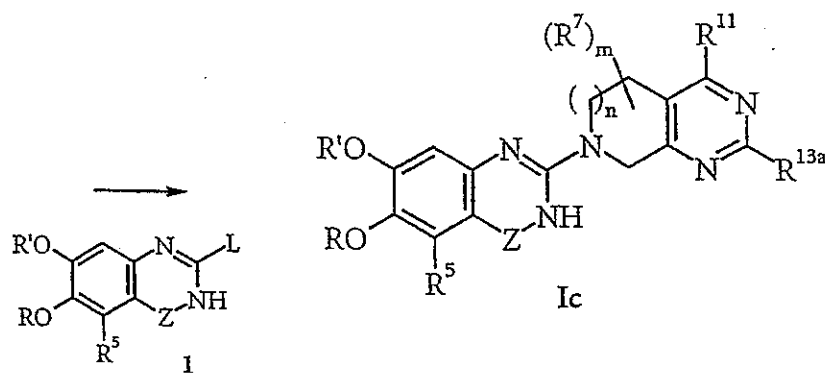
Alternatively, 2-chloro-quinazoline compounds 1 can be prepared as described below in

10 Scheme 10.

Scheme 2

Scheme 2 describes a method of preparing a compound of Formula Ic wherein R¹¹ is attached to the pyrimidinyl ring via a nitrogen atom (*i.e.*, R¹¹ is NRR), and the remaining variables are as defined herein.

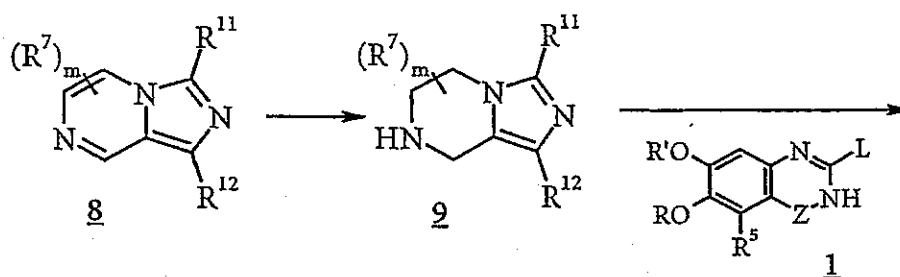


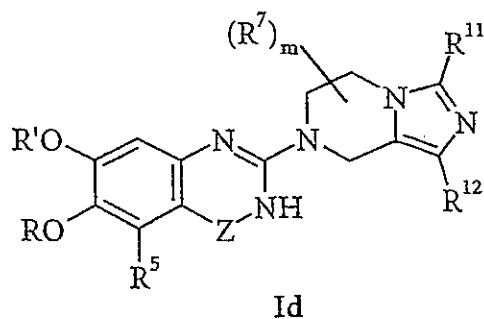


Compounds 3 can be prepared according to Ozdowska et al., Rocz.Chem. 50:1771-1775 (1976), and halogenated with phosphorous oxychloride to yield the chloro derivative 4, which can be reacted with an appropriate amine (*i.e.*, to provide the desired group R^{11}) in an inert solvent such as an alkanol, methoxyethanol, DMSO or DMF to yield the substituted 5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine 5. The benzyl group of compound 5 can be removed by procedures known to one skilled in the art to yield the free base 6. A detailed description of the techniques applicable to protective groups and their removal can be found in Greene and Wuts, Protective Groups in Organic Synthesis, Wiley and Sons, New York (1991). For example a method of debenzylation can be carried out with a suitable catalyst (*e.g.*, 10% Pd/C) in the presence of ammonium formate and in an appropriate solvent, typically an alcohol, preferably MeOH/EtOH, at about 20 °C to about 100 °C, and more preferably at reflux. Compounds of Formula Ic can be obtained by reacting the free amine 6 with a quinazolinone derivative of Formula 1, wherein L is a leaving group, preferably a halo group, and even more preferably a chloro group, in an inert solvent such as an alkanol, preferably *n*-butanol or methoxyethanol, by procedures known to one skilled in the art.

Scheme 3

Scheme 3 describes a method of preparing a compound of Formula Id wherein the variables are as defined herein.

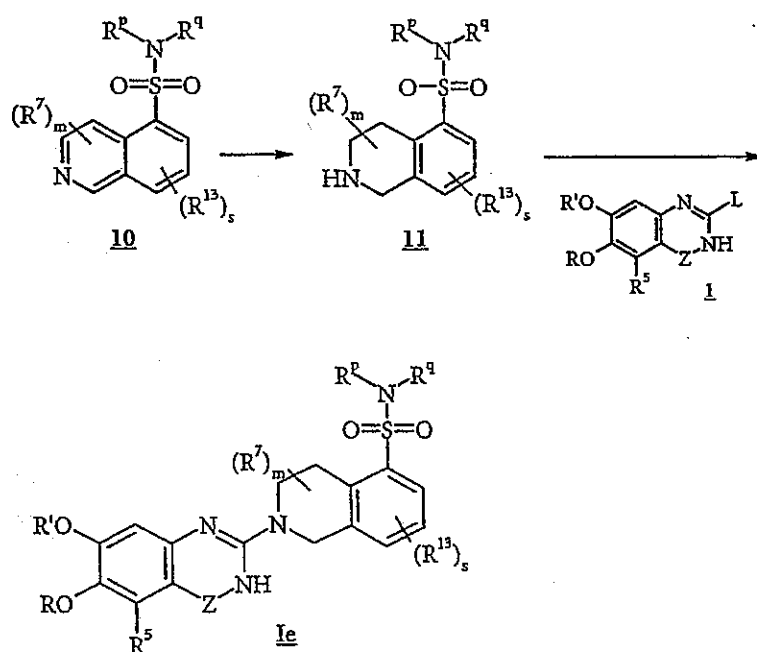




Compound 8 [prepared according to Abushanab et al. J. Heterocycl. Chem. 12:211 (1975)] can be hydrogenated in the presence of a catalyst, preferably Adam's catalyst (platinum (IV)oxide) to give compound 9. Suitable solvents are alkanols, preferably EtOH. Compounds of Formula Id can be obtained by reaction of the free amine 9, with a quinazolinone derivative of Formula 1, wherein L is a leaving group as described in the previous schemes.

Scheme 4

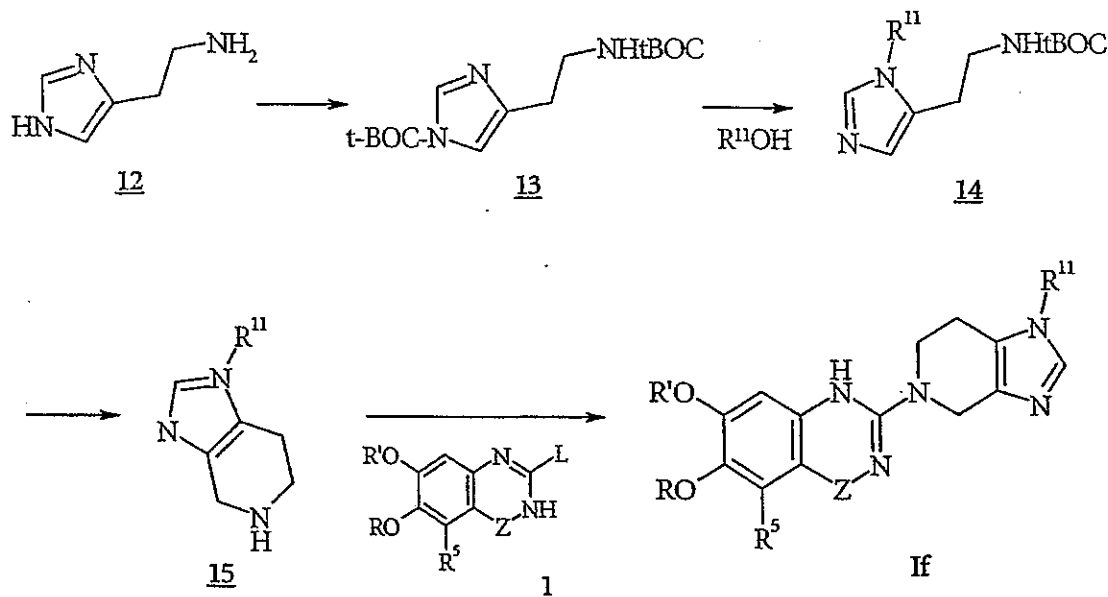
Scheme 4 describes a method of preparing a compound of Formula Ie wherein the variables are as defined herein.



Compounds 10 [prepared according to Morikawa et al., Chem. Pharm. Bull. 40:770-773 (1992)], can be hydrogenated in the presence of a catalyst, preferably platinum oxide to give compounds 11. Suitable solvents are alkanols, preferably MeOH. Compounds of Formula Ie are obtained by reaction of the free amine 11, with a quinazolinone derivative 1, wherein L is a leaving group as described in Scheme 2.

Scheme 5

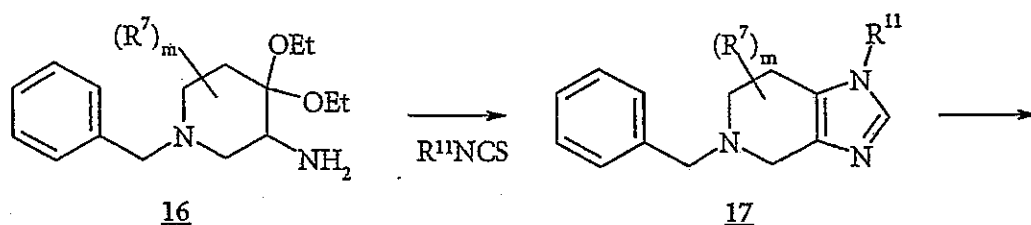
Scheme 5 describes a method of preparing a compound of Formula If wherein R^{11} is benzyl, and the remaining variables are as defined in the claims herein.

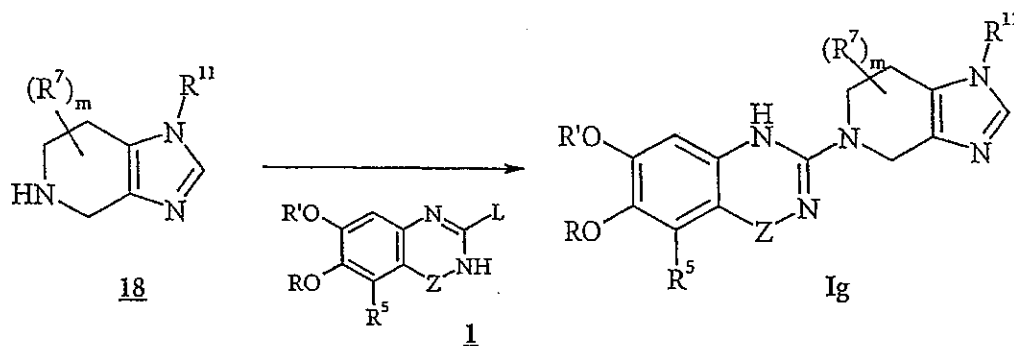


Protection of the amino groups of histamine 12 with di-*tert*-butyl dicarbonate under conditions well known to the skilled artisan can give compounds 13. Formation of the amine of Formula 14 can be effected when the protected histamine 13 is treated with a solution of benzyl alcohol and a base such as diisopropylethyl amine to which a solution of triflic anhydride in an anhydrous halogenated solvent, such as DCM, has been added. Deprotection of 14 in the presence of an acid, preferably in trifluoroacetic acid in a solvent such as DCM, followed by Mannich cyclization preferably with formaldehyde in the presence of an aqueous acid such as hydrochloric acid, provides amines 15. Compounds of Formula If can be obtained by reaction of the free amine 15, with a quinazolinone derivative of Formula 1, wherein L is a leaving group as described in the previous schemes.

Scheme 6

Scheme 6 describes a method of preparing a compound of Formula Ig wherein R^{11} is phenyl and the remaining variables are as defined in the claims herein.

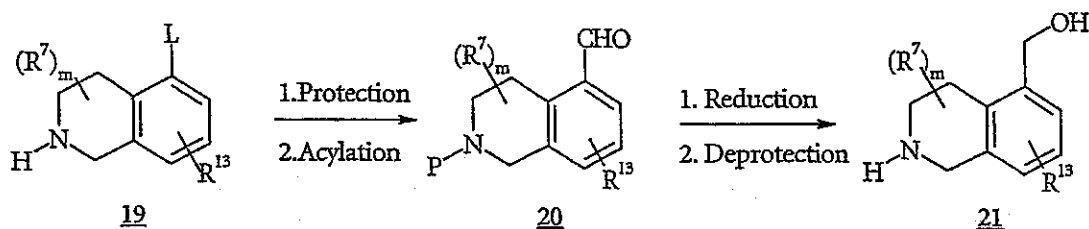


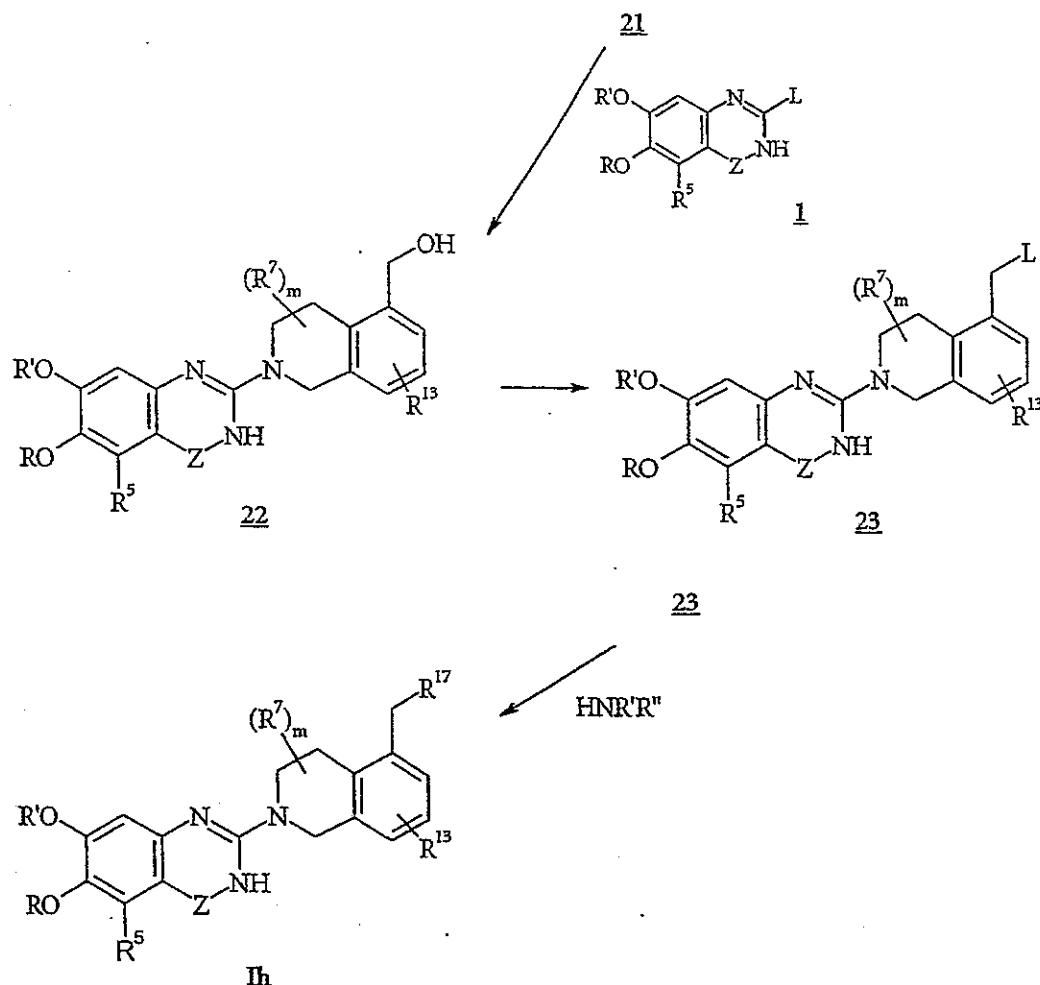


Compounds **16** (prepared as described in Tetrahedron, 1995, at 13447-13453), can be treated with a phenyl isothiocyanate of formula $R^{11}NCS$ in an inert solvent such as chloroform or DMF, preferably chloroform, followed by acid catalyzed cyclization with a diluted acid such as hydrochloric acid, to the imidazolethione, which is desulfurized by methods known in the art such as by oxidation with hydrogen peroxide or by reduction with Raney Nickel to give compounds **17**. Deprotection of the amino group in conditions well known in the art, such as by catalytic hydrogenation, i.e. 10% Pd/C, palladium hydroxide, palladium acetate, etc., in the presence of ammonium formate and in an appropriate solvent, typically an alcohol (e.g., EtOH, MeOH, isopropanol, any appropriate mixture of alcohols), preferably in the presence of Pd/C gives amines **18**. Compounds of Formula **Ig** can be obtained by reaction of the free amine **18**, with a quinazolinone derivative **1**, wherein L is a leaving group, as described in the previous schemes.

15 Scheme 7

Scheme 7 describes a method of preparing a compound of Formula **Ih** wherein R^{17} is attached to the methylene group via a nitrogen atom, and the remaining variables are as defined herein.

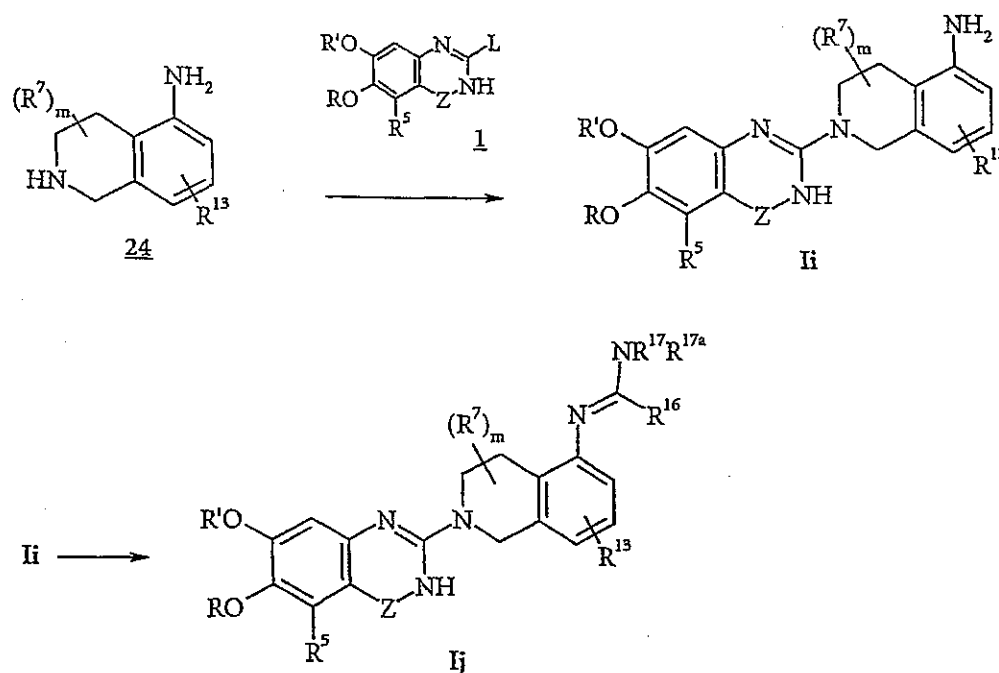




The amine functionality of a compound of Formula 19, wherein L is a halide, is protected with a protective group such as benzyl, BOC, carbamate, or CBZ, under conditions well known in the art. Formylation with a N',N' -disubstituted formyl amide such as *N*-formylmorpholine in the presence of butyllithium can afford an aldehyde of formula 20. Reduction of the aldehyde with a metallic hydride such as lithium aluminum hydride or sodium borohydride, followed by deprotection by methods well known in the art, such as with ammonium formate and Pd/C in a solvent such as MeOH in the case of benzyl, can afford the alcohol of general Formula 21. Reacting the free amine of Formula 21 with compounds 1 wherein L is a leaving group such as halogen in an inert solvent affords compounds 22. The hydroxy group can be converted to a leaving group such as a halide with halogen acids such as hydrobromic acid or with inorganic acid halides such as, e.g., SOCl_2 , POBr_3 , or POCl_3 to afford compounds 23, which can further undergo amination with an amine (i.e., R^{17} being an amine) to give a compound of general Formula 1h.

Scheme 8

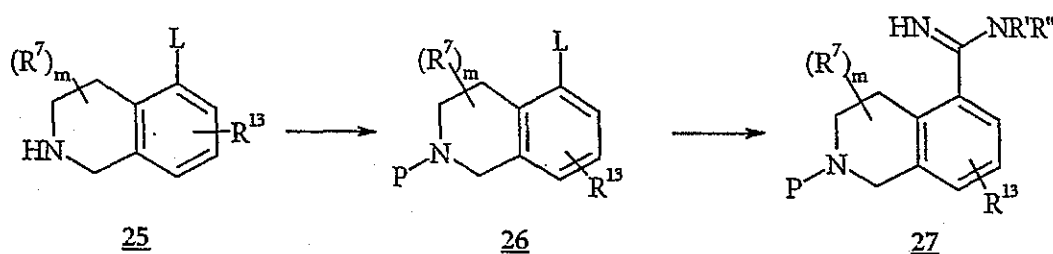
Scheme 8 describes a method of preparing compounds of Formula Ii and Ij, wherein the variables are as defined herein.

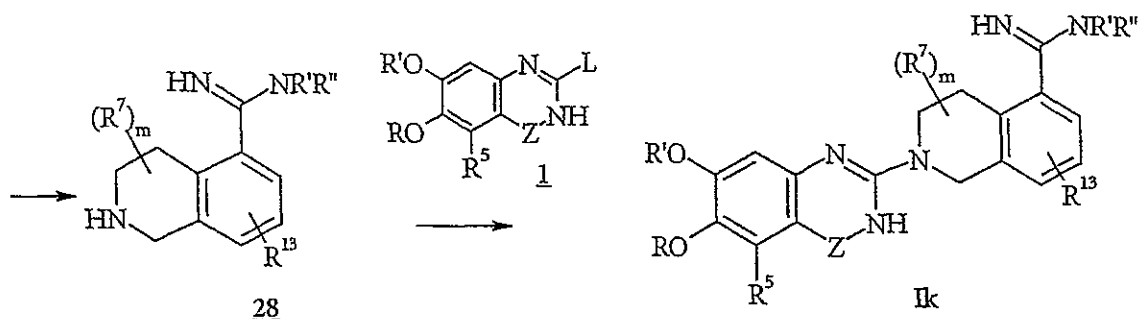


- 5 Compounds of formula Ii can be prepared from compounds 24 (prepared as described in WO 95/13274) with the quinazoline derivative 1, as described in Scheme 1. Compounds of Formula Ij, wherein R¹¹ is -N=CR¹⁶-NR^{17a}R¹⁷, can be prepared by reacting compounds of formula Ii, with a disubstituted amide and phosphorous oxychloride.

10 Scheme 9

Scheme 9 describes a method of preparing a compound of Formula Ik wherein the variables are as defined herein.

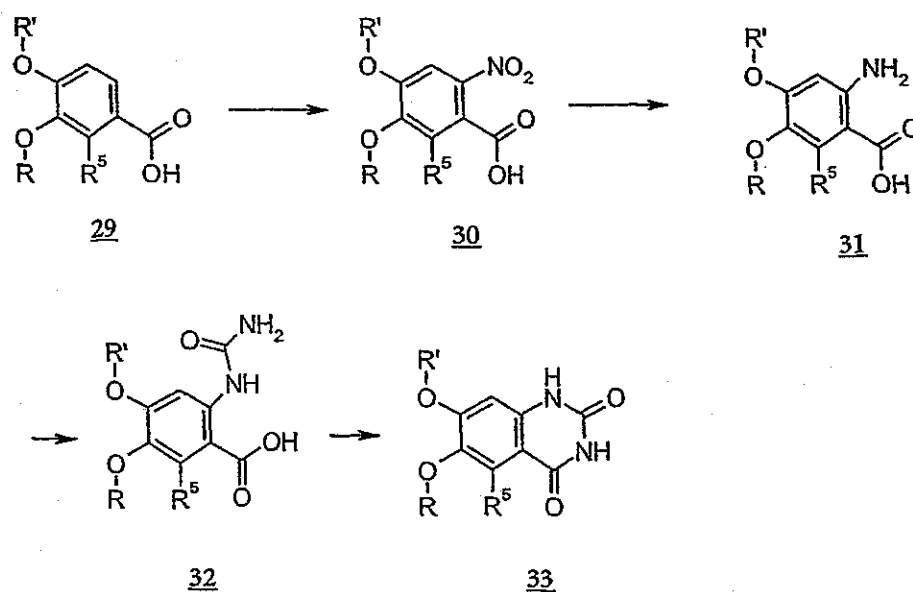


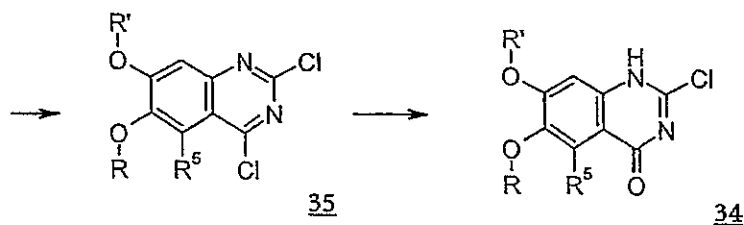


After protection of the amino group of compound of Formula **25**, wherein L is a halogen, preferably bromo or chloro, following procedures well known in the art as described
 5 herein to afford compound of Formula **26**, the halogen group can be replaced with an amidine group of general formula $-C(=NH)-NR'R''$, by treatment with butyllithium followed by an aminocarbonitrile compound to give an imino amine of general Formula **27**. Removal of the amino protecting group, e.g. with an acid, such as trifluoroacetic acid if the protective group is BOC, and coupling with the quinazoline derivative **1** afford
 10 compounds of Formula **1Ik**.

Scheme 10

Scheme 10 illustrates a method for making 2-chloro-quinazolin-4-one compounds **34, 1** (wherein L is Cl and Z is $C(=O)$), used as starting material in Schemes 1 through 9.





The procedure of Scheme 10 is described by Cronin et al., J. Med. Chem. 11:136-138

(1968) and by WO 02/053558 A1. Nitro-acids (30) are commercially available, or can be readily prepared by one skilled in the field from carboxylic acids (29) using several

5 methods, including that of Kowalczyk et al., Organic Process Research and Development 1:355-358 (1997). Carboxylic acids (29) are commercially available.

Nitro acids (30) are dissolved in water by addition of base (e.g., NaOH, KOH, LiOH). A

heterogenous catalyst on an inert support is added (e.g., palladium on carbon), and the reaction mixture is exposed to a hydrogen atmosphere either directly (hydrogen gas) or

10 indirectly (transfer hydrogenation technique using e.g., formate salts, hydrazine, etc., as the hydrogen source). The nitro-group is thereby converted to an amino group to provide compounds (31).

Compounds (31) can be converted to a urea (32) by addition of a cyanate salt (e.g., KOCN, NaOCN) and an acid (e.g., HCl, HOAc). The urea (32) is then cyclized to a

15 dione derivative (33) by adding a base (e.g., NaOH, KOH) and heating the reaction mixture. The dione (33) is precipitated by adding an acid (e.g., HCl, HOAc) to the reaction mixture, and the dione (33) may be isolated such as by filtration. Other acids also may be used, e.g., any acid that will generate HOCN in-situ from the cyanate salt and the acid.

20 Dione intermediate (33) is converted to dichloroquinazoline (35) by combining (33) with a chlorinating and dehydrating agent (e.g., phosphorous oxychloride) in an organic solvent (e.g. acetonitrile) and heating the reaction mixture. The dichloroquinazoline (35) is isolated by quenching the reaction mixture into water and filtering the precipitated product, or by quenching the reaction mixture into a mixture of water and a

25 water-immiscible solvent (e.g. methylene chloride), and extracting the product into the organic solvent. The solvent is evaporated to provide compound (35). Compound (35) is then combined with a base (e.g., KOH, NaOH) in a mixture of water and a solvent like THF. At the end of the reaction, the organic solvent is partially removed by distillation, an acid (e.g. HOAc) is added, and the compound (34) is

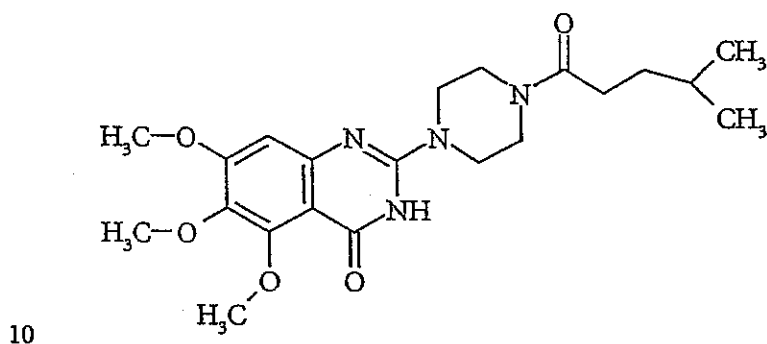
30 collected via filtration. Dione intermediates (33) are commercially available or can be readily prepared by one skilled in the field, e.g., as described in Mizuno et al., Heteroatom Chemistry 11:428-433

(2000); Mizuno et al., Tetrahedron Letters 41:1051-1051 (2000); US 6,376,667-B1; US 6,048,864; WO 97/23462; EP 775,697; and so forth.

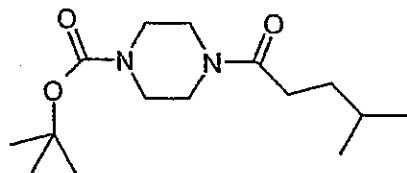
EXAMPLES

The following preparations and examples are provided to enable those skilled in the art to more clearly understand and to practice the present invention. However, these Examples should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Example A-1: 5,6,7-Trimethoxy-2-[4-(4-methyl-pentanoyl)-piperazin-1-yl]-1H-quinazolin-4-one



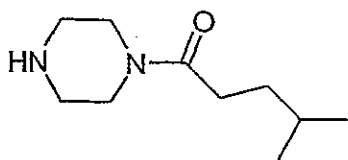
Step 1: Preparation of 4-(4-methyl-pentanoyl)-piperazine-1-carboxylic acid tert-butyl ester



A stirred mixture of EtOAc (70 mL) containing 1.6 g (8.6 mmol) of 1-BOC piperazine and 25 mL of saturated aqueous sodium carbonate was treated dropwise with 1.2 g (9 mmol) of 4-methylvaleryl chloride. After 2 h of stirring, an additional 0.2 g (1.5 mmol) of 4-methylvaleryl chloride was added and stirring was continued for an additional 2 h. The layers were separated and the organic phase was dried over potassium carbonate, filtered, and concentrated to furnish 2.45 g of 4-(4-methyl-pentanoyl)-piperazine-1-carboxylic acid tert-butyl ester. Mp 88-90.2°C.

20

Step 2: Preparation of 4-methylpentanoylpiperazine

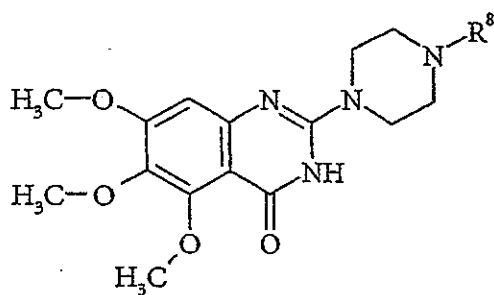


4-(4-Methyl-pentanoyl)-piperazine-1-carboxylic acid tert-butyl ester from Step 1 (2.45 g) was dissolved in 15 mL of hot EtOH and was treated with 15 mL of EtOH containing 1.5 g of HCl. The solution was kept at reflux for 5 min, and concentrated to approximately 15 mL. Addition of diethyl ether precipitated the HCl salt of 4-methylpentanoylpiperazine, 1.5 g (79%). Mp 186.2-187.5 °C.

Step 3: Example A-1

A mixture containing 300 mg of 2-chloro-5,6,7-trimethoxyquinazolin-4-one (1.1 mmol), 253 mg of 4-methylpentanoylpiperazine from Step 2 (1.15 mmol), 400 mg TEA (4 mmol) and 3-4 mL *N*-methylpyrrolidinone was stirred at 80 °C for 6 h. The *N*-methylpyrrolidinone was removed *in vacuo* and the remainder was treated with hot EtOH, and the insoluble white free base of Example A-1 was collected. This was further purified by trituration with water and recrystallization from EtOH to furnish 140 mg of Example A-1 (30%). Mp 211.4-211.7 °C, ms 418.49 (M+H). Anal. (C₂₁H₃₀N₄O₅) Calcd.: C, 60.27; H, 7.23; N, 13.39. Found: C, 60.19; H, 7.17; N, 13.45. The hydrochloride salt of Example A-1 was prepared from ethanol-diethyl ether. Mp 198-201°C, Anal. (C₂₁H₃₀N₄O₅•HCl) Calcd.: C, 55.44; H, 6.87; N, 12.32. Found: C, 55.30; H, 6.80; N, 12.39.

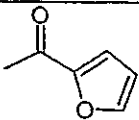
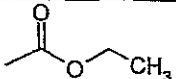
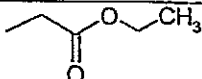
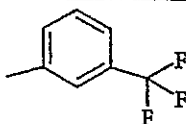
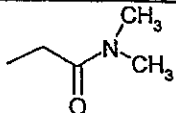
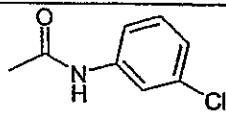
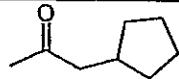
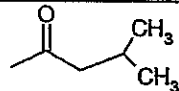
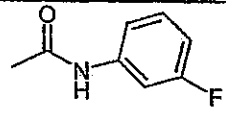
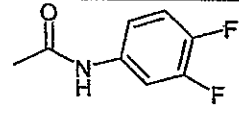
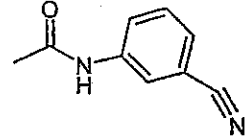
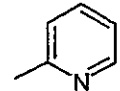
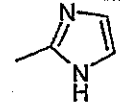
EXAMPLES A-2 to A-21

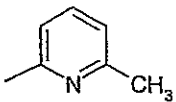
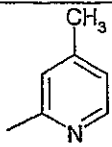
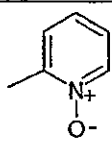
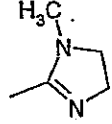
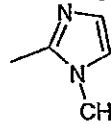
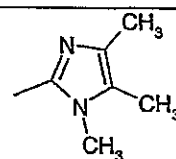
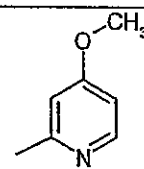


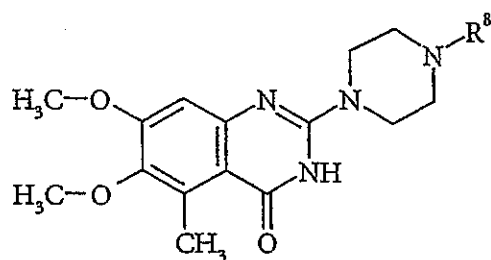
(II)

Compounds having the above formula (II), wherein R⁸ has the values reported in Table 1 were prepared following the same or similar method as described in A-1 except a differently-substituted piperazine was coupled with the chloroquinazolinone in the last step.

TABLE 1

Ex.	R ^b	MW
A-2		414.42
A-3		392.41
A-4		406.44
A-5		464.44
A-6		405.45
A-7		473.91
A-8		430.50
A-9		404.46
A-10		457.46
A-11		475.45
A-12		464.48
A-13		397.43
A-14		386.41

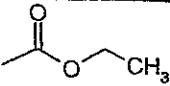
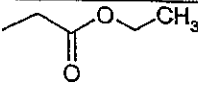
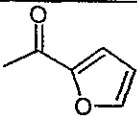
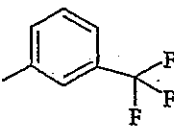
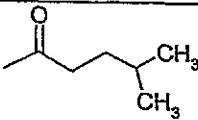
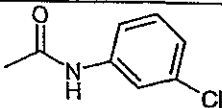
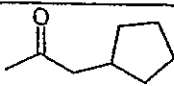
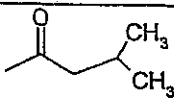
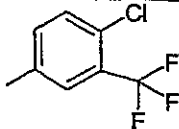
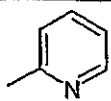
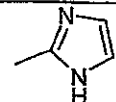
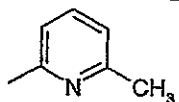
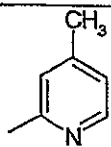
A-15		411.46
A-16		411.46
A-17		413.43
A-18		402.45
A-19		400.44
A-20		428.49
A-21		427.46

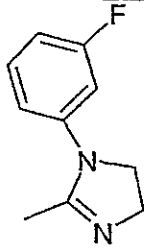
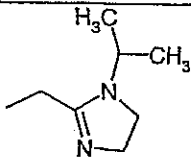
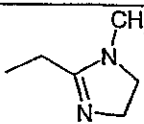
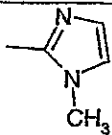
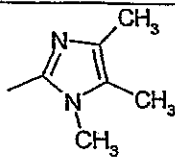
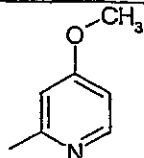
EXAMPLES A-22 to A-40

(Im)

Compounds having the above formula (Im) wherein R⁸ has the values reported in Table 2 were prepared following the same or similar method as described in A-1 except in the last step, an appropriately-substituted piperazinyl compound was coupled with 2-chloro-6,7-dimethoxy-5-methylquinazolin-4-one instead of 2-chloro-5,6,7-trimethoxyquinazolin-4-one.

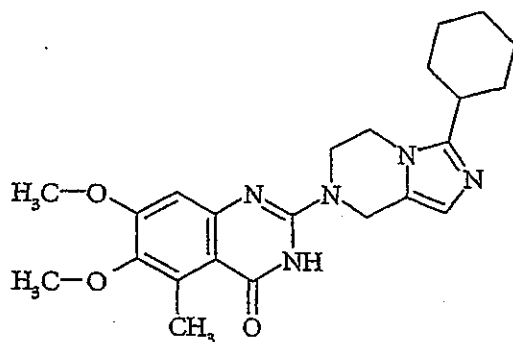
TABLE 2

Ex.	R ⁸	MW
A-22		376.41
A-23		390.44
A-24		398.42
A-25		448.44
A-26		402.49
A-27		457.92
A-28		414.50
A-29		388.46
A-30		482.89
A-31		381.43
A-32		370.41
A-33		395.46
A-34		395.46

A-35		466.51
A-36		428.53
A-37		400.48
A-38		384.44
A-39		412.49
A-40		411.46

Additional compounds prepared according to the procedure of Example A-1 are shown in Table 9.

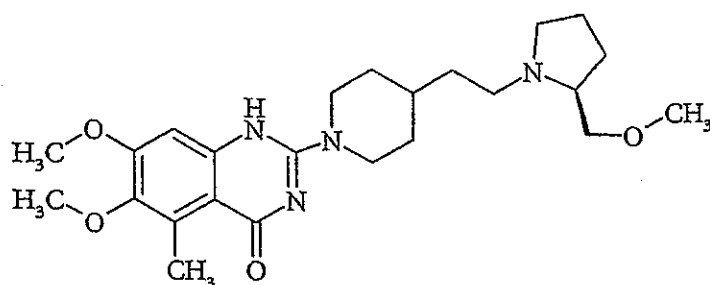
Example B-1: 2-(3-Cyclohexyl-5,6-dihydro-8H-imidazo[1,5-a]pyrazin-7-yl)-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one



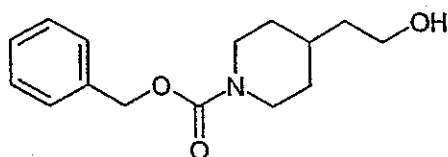
Example B-1 was made following the same or similar procedure as Example A-1, except 3-cyclohexyl-5,6-dihydro-8H-imidazo[1,5-a]pyrazine was coupled to the 2-chloroquinazolinone in the last step. MW = 423.51.

Example C-1: 6,7-Dimethoxy-2-{4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidin-1-yl}-5-methyl-1H-quinazolin-4-one

5

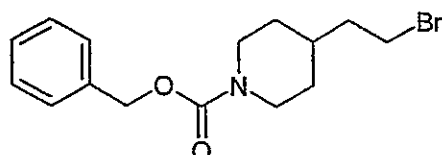


Step 1: Preparation of 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid benzyl ester



Benzyl chloroformate (12 mL, 84.1 mmol) was added dropwise via syringe to a stirred solution of 2-piperidin-4-ylethanol (10.04 g, 77.4 mmol) and TEA (11.8 mL, 84.7 mmol) in 100 mL of acetonitrile. The reaction was stirred at rt in a water bath overnight. The suspension was filtered and the filtrate was diluted with EtOAc. The solution was washed with brine and the organic extracts were dried with magnesium sulfate. The crude reaction mixture was concentrated to give 16.43 g (81%) of 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid benzyl ester as an orange/yellow oil. ¹H NMR (CDCl₃) 1.1-1.7 (m, 5H), 1.5 (t, 2H, J = 6.4), 2.7 (t, 2H, J = 12), 3.7 (t, 2H, J = 6.5), 4.2 (m, 2H), 5.1 (s, 2H), 7.25-7.4 (m, 5H).

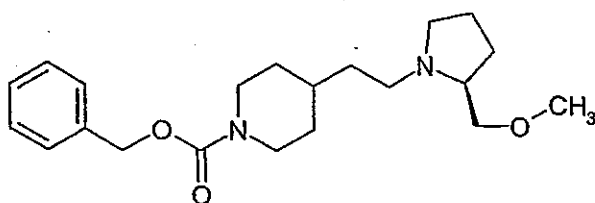
Step 2: Preparation of 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid benzyl ester



A solution of triphenylphosphine (4.4 g, 16.8 mmol) in DCM (10 mL) was added via addition funnel to a solution of 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid benzyl

ester from Step 1 (4.0 g, 15.3 mmol) and carbon tetrabromide (5.48 g, 16.5 mmol) in DCM (20 mL) at 0 °C. The reaction was gradually warmed to rt and stirred overnight. The reaction mixture was concentrated and chromatographed (6:1 hexane/EtOAc) to give 4.27 g (86%) of 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid benzyl ester as a light tan oil. TLC R_f 0.5 (4:1 hexane/EtOAc) ¹H NMR (CDCl₃) 1.1 (m, 2H), 1.7 (m, 3H), 1.8 (t, 2H, J = 6.8), 2.8 (t, 2H, J = 12), 3.4 (t, 2H, J = 6.8), 4.2 (m, 2H), 5.1 (s, 2H), 7.3 (m, 5H).

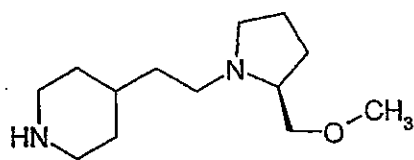
Step 3: Preparation of (S)-4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidine-1-carboxylic acid benzyl ester



10

(S)-(+)-2-(Methoxymethyl)pyrrolidine (320 µL, 2.59 mmol) was added to a stirred solution of 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid benzyl ester from Step 2 (797 mg, 2.44 mmol) and TEA (360 µL, 2.58 mmol) in acetonitrile (12 mL). The yellow solution was stirred overnight at rt and concentrated under reduced pressure. The crude residue was diluted with EtOAc, washed with saturated sodium bicarbonate solution and brine, and dried with magnesium sulfate. The solvent was removed to give 591 mg (67%) of (S)-4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidine-1-carboxylic acid benzyl ester as a yellow oil. MS (ES+) *m/z* 361 (M+H).

Step 4: Preparation of (S)-4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidine

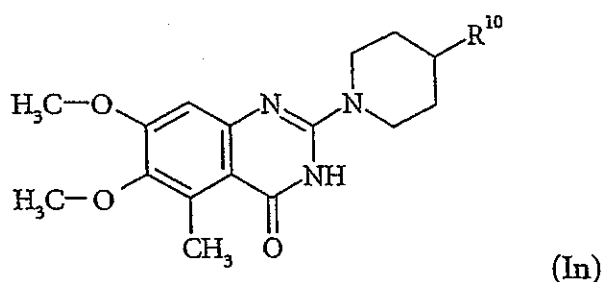


20

A solution of (S)-4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidine-1-carboxylic acid benzyl ester from Step 3 (592 mg, 1.64 mmol), palladium (10% on carbon) (85 mg, 0.08 mmol) in MeOH (5 mL) and EtOH (2 mL) was stirred at rt under an atmosphere of hydrogen. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to give 372 mg (quantitative yield) of (S)-4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidine as a light orange oil. MS (ES+) *m/z* 227 (M+H).

Step 5: A solution of (S)-4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidine from step 4 (196 mg, 0.867 mmol) and 2-chloro-6,7-dimethoxy-5-methylquinazolin-4-one (220 mg, 0.866 mmol) in methoxyethanol (3 mL) was heated at 80 °C overnight. The reaction mixture was concentrated and chromatographed (5% MeOH/DCM) to give 104 mg (27%) of Example C-1 above as a white solid. Mp = 83.1-110.9 °C; TLC R_f 0.35 (10% EtOH/DCM); [α]_D²⁴ -27.1 ° (C 5.18, MeOH); IR (KBr) $\nu_{\max}$ 3437, 2928, 1650, 1586, 1464 cm⁻¹; ¹H NMR (DMSO-*d*₆) 1.2 (m, 2H), 1.5-1.9 (m, 8H), 2.0 (m, 1H), 2.6 (s, 3H), 2.7 (m, 2H), 2.9 (t, 2H, *J* = 12), 3.3 (s, 3H), 3.4 (m, 2H), 3.6 (s, 3H), 3.8 (s, 3H), 4.3 (d, 2H, *J* = 12), 6.6 (s, 1H); MS (ES+) *m/z* 445 (M+H); Anal. (C₂₄H₃₆N₄O₄ 0.92 CH₂Cl₂) C: calcd, 57.26; found, 57.22; H: calcd, 7.30; found, 7.31; N: calcd, 10.72; found, 10.93.

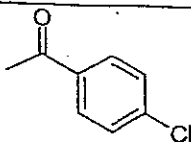
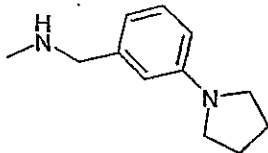
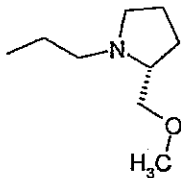
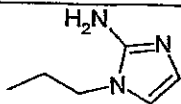
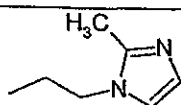
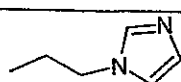
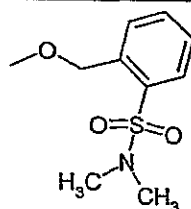
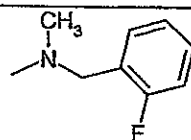
EXAMPLES C-2 to C-12



Compounds having the above formula (In), wherein R¹⁰ has the values reported in Table 3 were prepared following the same or similar method as described e.g. C-1, except a differently-substituted piperidinyl compound was used in place of 1-(2-methoxymethyl-pyrrolidin-1-yl)-2-(piperidin-4-yl)ethyl.

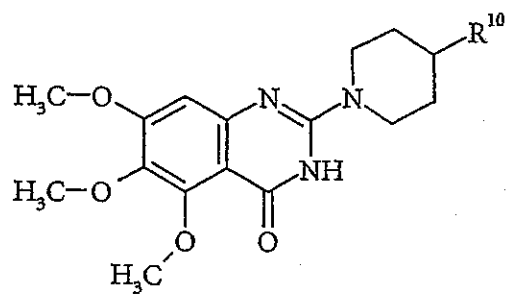
TABLE 3

Ex.	R ¹⁰	MW
C-2		401.46
C-3		386.45
C-4		393.48

C-5		441.91
C-6		477.61
C-7		444.57
C-8		412.49
C-9		413.52
C-10		397.48
C-11		516.61
C-12		440.52

Additional compounds prepared according to the procedure of Example C-1 are shown in Table 9.

EXAMPLES D-1 to D-20

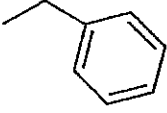
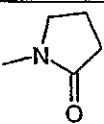
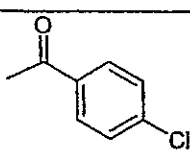
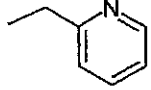
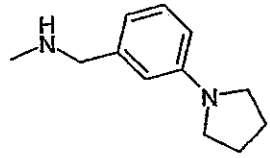
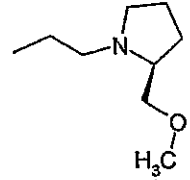
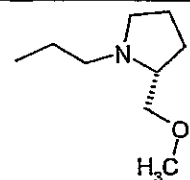
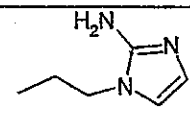


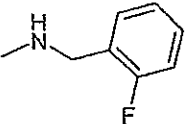
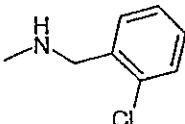
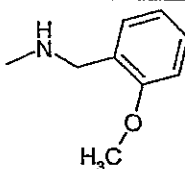
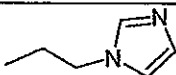
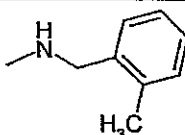
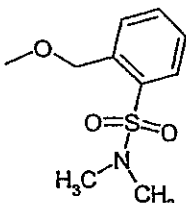
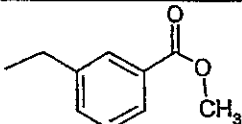
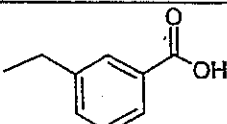
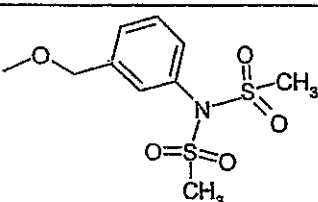
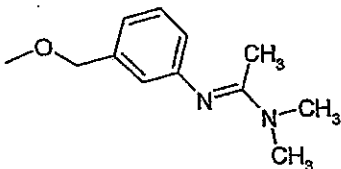
(Io)

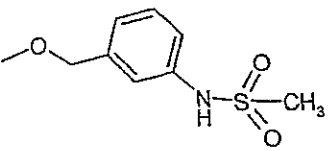
Compounds having the above formula (I_o), wherein R¹⁰ has the values reported in Table 4 were prepared following the same or similar method as described e.g. C-1, except 2-chloro-6,7-dimethoxy-5-methylquinazolin-4-one was replaced with 2-chloro-5,6,7-trimethoxyquinazolin-4-one, and an appropriately-substituted piperidinyl compound

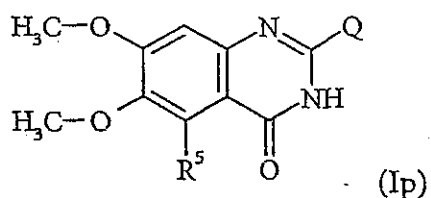
5 was used.

TABLE 4

Ex.	R ¹⁰	MW
D-1		409.48
D-2		402.45
D-3		361.44
D-4		457.91
D-5		410.47
D-6		493.60
D-7		460.57
D-8		460.57
D-9		428.49

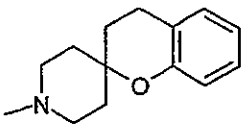
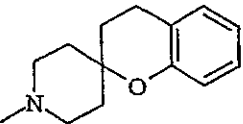
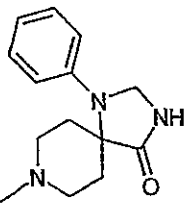
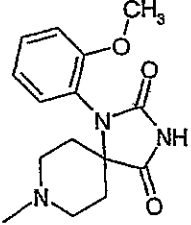
D-10		442.49
D-11		458.94
D-12		454.52
D-13		413.48
D-14		438.52
D-15		532.61
D-16		467.51
D-17		453.49
D-18		596.68
D-19		509.60

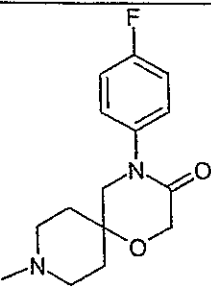
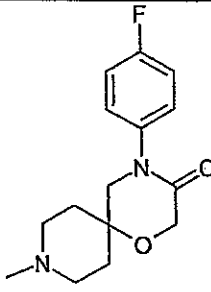
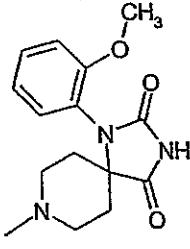
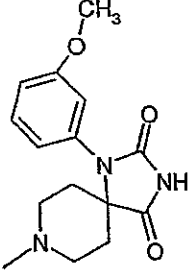
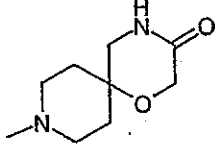
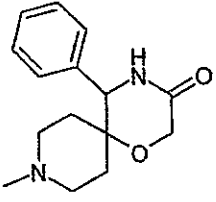
D-20		518.59
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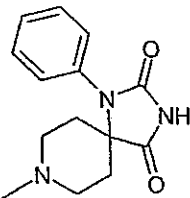
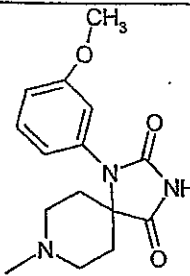
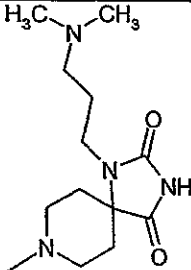
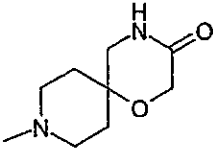
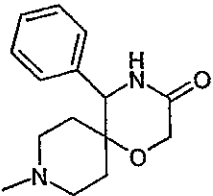
EXAMPLES E-1 to E-15

Compounds having the above formula (Ip), wherein R⁵ and Q have the values reported
 5 in Table 5 were prepared following the same or similar methods described above.

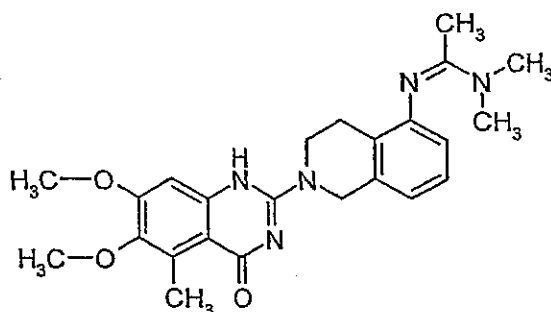
TABLE 5

Ex.	R ⁵	Q	MW
E-1	-CH ₃		421.49
E-2	-OCH ₃		437.49
E-3	-CH ₃		449.51
E-4	-CH ₃		493.52

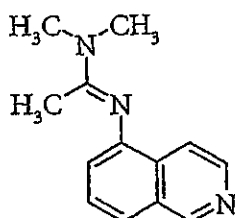
E-5	-CH ₃		482.51
E-6	-OCH ₃		498.51
E-7	-OCH ₃		509.52
E-8	-OCH ₃		509.52
E-9	-OCH ₃		404.42
E-10	-OCH ₃		480.542

E-11	-OCH ₃		465.51
E-12	-CH ₃		493.52
E-13	-CH ₃		472.54
E-14	-CH ₃		388.42
E-15	-CH ₃		464.52

Example F-1: *N'*-[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-*N,N*-dimethyl-acetamidine

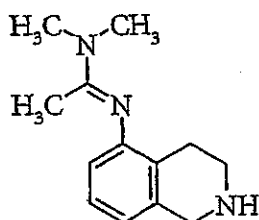


Step 1: Preparation of *N'*-isoquinolin-5-yl-*N,N*-dimethyl-acetamidine



5-Aminoisoquinoline (1.00 g, 6.926 mmol) and *N,N*-dimethylacetamide dimethylacetal (4.00 g) were heated at 80 °C for 16 h. The excess *N,N*-dimethylacetamide dimethylacetal was evaporated under reduced pressure. The crude *N'*-isoquinolin-5-yl-*N,N*-dimethyl-acetamidine was a brown oil which was taken to the next step.

Step 2: Preparation of *N,N*-dimethyl-*N'*-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamidine

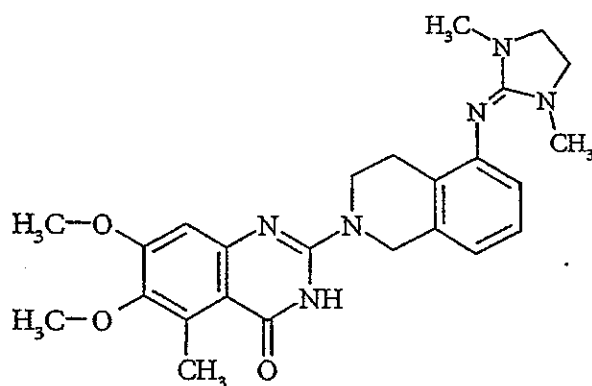


10

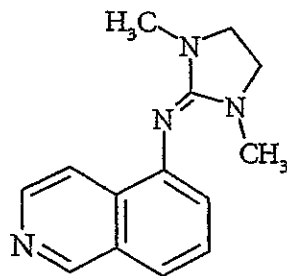
Sodium cyanoborohydride (2.6 g, 41.56 mmol) was added to a solution of *N'*-isoquinolin-5-yl-*N,N*-dimethyl-acetamidine from Step 1 (1.51 g, 6.926 mmol) in 10% HCl in MeOH (10ml) at 0 °C. The ice-bath was removed and the mixture stirred at rt for 1 h. DCM (30ml) was added, the white solid was filtered off, and the filtrate was concentrated to dryness. Purification by flash chromatography (CH₂Cl₂:MeOH:NH₄OH/300:10:1) gave 1.49 g (ca. 100%) of a brown solid, *N,N*-dimethyl-*N'*-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamidine.

Step 3: 2-Chloro-6,7-dimethoxy-5-methyl-1*H*-quinazolin-4-one (0.300g, 1.178 mmol) and the solid (2) from Step 2 (0.269 g, 1.239 mmol) in methoxyethanol (10 ml) were heated at 80°C for 18 h. The solvent was evaporated to dryness under reduced pressure. Purification by flash chromatography (CH₂Cl₂:MeOH:NH₄OH/120:10:1) followed by
 5 recrystallization (CH₂Cl₂) gave 0.241 g (47%) of the above Example F-1 as a tan solid. Mp = 270.9-273.5 °C; ¹H NMR (DMSO-*d*₆, 2.49) δ 1.74 (s, 3 H), 2.54 (t, 2 H), 2.60 (s, 3H), 2.97 (s, 6 H), 3.62 (s, 3 H), 3.75 (t, 2H), 3.86 (2, 3H), 4.72 (s, 2H), 6.40 (d, 1H), 6.67 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H), 10.99 (s, 1H); IR (KBr) ν_{max} 1575 cm⁻¹; MS (ES+) *m/z* 436(M + H); Anal. (C₂₄H₂₉N₅O₃·0.8H₂O) C: calcd, 59.16; found, 59.07; H: calcd,
 10 6.13; found, 6.06; N: calcd, 13.91; found, 13.93.

Example F-2:2-[5-(1,3-Dimethyl-imidazolidin-2-ylideneamino)-3,4-dihydro-1*H*-isoquinolin-2-yl]-6,7-dimethoxy-5-methyl-1*H*-quinazolin-4-one



Step 1: Preparation of (1,3-dimethylimidazolidin-2-ylidene)isoquinolin-5-ylamine

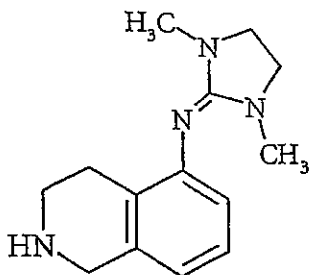


15

A mixture of 5-aminoisoquinoline (0.3 g, 2.09 mmol) and 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (0.7 g, 2.51 mmol) in 15 mL of DCE, was heated to 60°C for 72 hours. The crude was purified by flash column eluting with CH₂Cl₂:MeOH:NH₄OH (94.5:5:0.5) to afford 0.25 g (50%) of the above titled compound
 20 as a dark foam. ¹H NMR (CD₃OD 3.31) δ 2.74 (s, 6 H), 3.79 (s, 4 H), 7.75 (d, 1 H, *J* =

1.17), 7.77 (s, 1 H), 8.01 (dt, 1H, $J = 6.03, 0.96$), 8.15 (m, 1 H), 8.59 (d, 1H, $J = 6.03$), 9.35 (d, 1H, $J = 0.99$); MS (ES+) m/z 241.2 (M + H).

Step 2: Preparation of (1,3-dimethylimidazolidin-2-ylidene)(1,2,3,4-tetrahydroisoquinolin-5-yl)amine.



To a solution of (1,3-dimethylimidazolidin-2-ylidene)isoquinolin-5-ylamine from Step 1 (0.25 g, 1.04 mmol) in 10 mL of 10% HCl in MeOH, was added NaBH_3CN (0.4 g, 6.24 mmol), portion-wise over one hour while maintaining the pH acidic by adding 10% HCl in MeOH as required. After the addition was complete, stirring was continued at rt for 18 hours. Solid NaOH was slowly added until pH=10-12, and the insoluble solids removed by filtration. The filtrate was concentrated, dissolved again in 5% MeOH/ CH_2Cl_2 and filtered to remove the insoluble materials. Then it was evaporated and purified by flash chromatography eluting with CH_2Cl_2 :MeOH: NH_4OH (94.5:5:0.5) to yield the above-titled compound (0.075 g, 29.5%). ^1H NMR (CDCl_3 7.26) δ 2.58 (t, 2 H, $J = 5.97$), 2.61 (s, 6 H), 2.82 (br s, D_2O , 1H), 3.11 (t, 2 H, $J = 6.03$), 3.28 (s, 4 H), 3.96 (s, 2 H), 5.58 (dt, 1H, $J = 7.77, 1.17$), 6.70 (dt, 1H, $J = 7.77, 1.17$), 6.97 (t, 1H, $J = 7.65$); MS (ES+) m/z 245.2 (M + H).

10

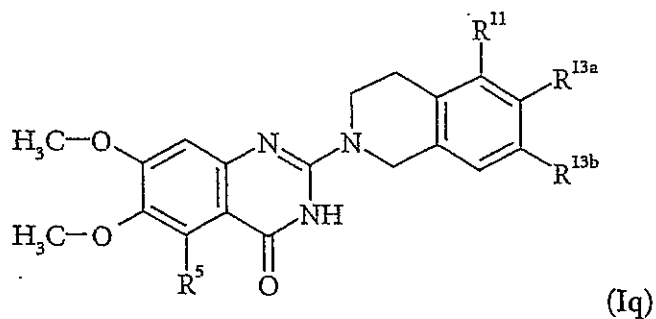
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Step 3: 2-[5-(1,3-Dimethylimidazolidin-2-ylideneamino)-3,4-dihydro-1H-isoquinolin-2-yl]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one (Example F-2).

In a screw capped test tube, a mixture of (1,3-dimethylimidazolidin-2-ylidene)(1,2,3,4-tetrahydroisoquinolin-5-yl)amine (13 mg, 0.052 mmol), 2-chloro-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one (13 mg, 0.050 mmol) and TEA (0.014 mL, 0.1 mmol) in 1 mL of DMSO, was heated to 80 °C for 18 hours. The crude mixture was purified by LCMS to afford the above titled compound, Example F-2. MS (ES+) m/z 463.3 (M + H).

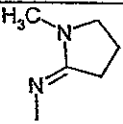
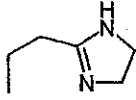
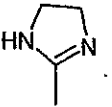
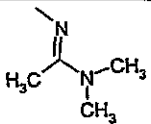
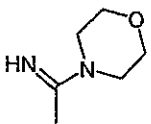
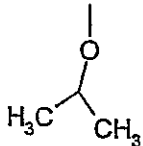
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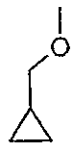
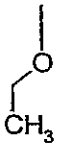
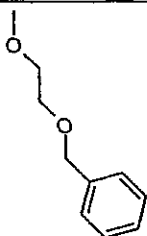
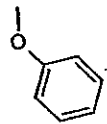
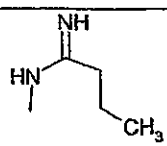
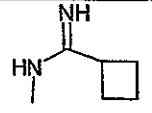
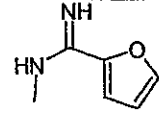
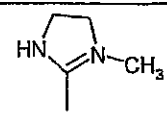
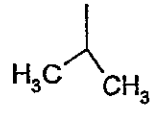
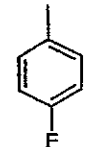
25 EXAMPLES F-3 to F-37

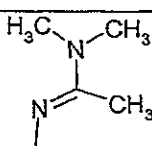
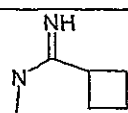
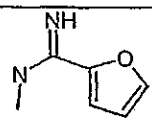
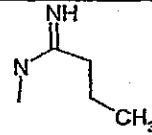
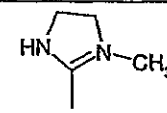
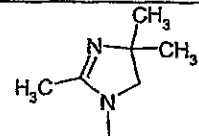
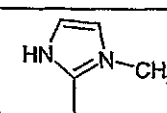
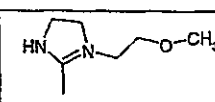
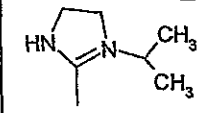
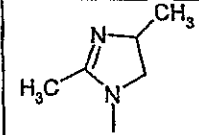
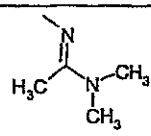


Compounds having the above formula (Iq), wherein R^5 , R^{11} , R^{13a} , and R^{13b} have the values reported in Table 6, were prepared following the same or similar method as described for Example F-1.

5 **TABLE 6**

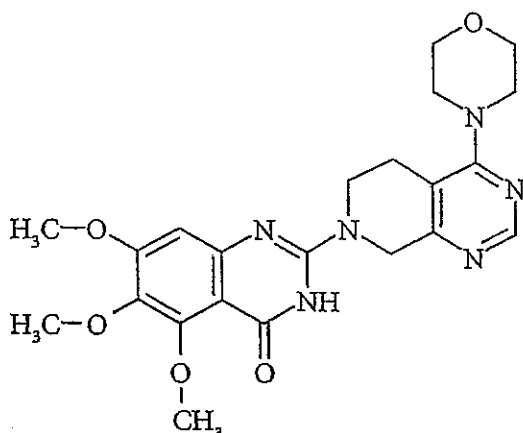
Ex.	R^5	R^{11}	R^{13a}	R^{13b}	MW
F-3	$-\text{OCH}_3$		$-\text{H}$	$-\text{H}$	463.53
F-4	$-\text{OCH}_3$		$-\text{H}$	$-\text{H}$	463.53
F-5	$-\text{OCH}_3$		$-\text{H}$	$-\text{H}$	435.48
F-6	$-\text{OCH}_3$	$-\text{H}$	$-\text{H}$		451.52
F-7	$-\text{OCH}_3$	$-\text{H}$	$-\text{OCH}_3$	$-\text{OCH}_3$	427.46
F-8	$-\text{OCH}_2\text{CH}_2\text{OCH}_3$	$-\text{H}$	$-\text{OCH}_3$	$-\text{OCH}_3$	471.51
F-9	$-\text{OCH}_3$		$-\text{H}$	$-\text{H}$	479.53
F-10		$-\text{H}$	$-\text{OCH}_3$	$-\text{OCH}_3$	455.51

F-11		-H	-OCH ₃	-OCH ₃	467.52
F-12		-H	-OCH ₃	-OCH ₃	441.48
F-13	-OH	-H	-OCH ₃	-OCH ₃	413.43
F-14	-OCH ₂ CH ₂ OH	-H	-OCH ₃	-OCH ₃	457.48
F-15		-H	-OCH ₃	-OCH ₃	547.61
F-16		-H	-OCH ₃	-OCH ₃	489.53
F-17	-OCH ₂ CH ₂ NH ₂	-H	-OCH ₃	-OCH ₃	456.50
F-18	-OCH ₃		-H	-H	451.52
F-19	-OCH ₃		-H	-H	463.53
F-20	-OCH ₃		-H	-H	475.50
F-21	-OCH ₃		-H	-H	449.51
F-22		-H	-OCH ₃	-OCH ₃	439.51
F-23		-H	-OCH ₃	-OCH ₃	491.52

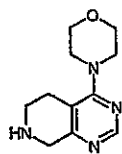
F-24	-CH ₃	-H	-OCH ₃	-OCH ₃	411.46
F-25	-OCH ₃		-H	-H	451.52
F-26	-CH ₃		-H	-H	447.54
F-27	-CH ₃		-H	-H	459.50
F-28	-CH ₃		-H	-H	435.53
F-29	-CH ₃		-H	-H	433.51
F-30	-CH ₃		-H	-H	461.56
F-31	-CH ₃		-H	-H	431.49
F-32	-CH ₃		-H	-H	477.56
F-33	-CH ₃		-H	-H	461.56
F-34	-CH ₃		-H	-H	447.54
F-35	-CH ₃	-H	-H		435.53
F-36	-F	-H	-OCH ₃	-OCH ₃	415.42
F-37	-Cl	-H	-OCH ₃	-OCH ₃	431.87

Additional compounds prepared according to the procedure of Example A-1 are shown in Table 9.

Example G-1: 5,6,7-Trimethoxy-2-(4-morpholin-4-yl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-1H-quinazolin-4-one

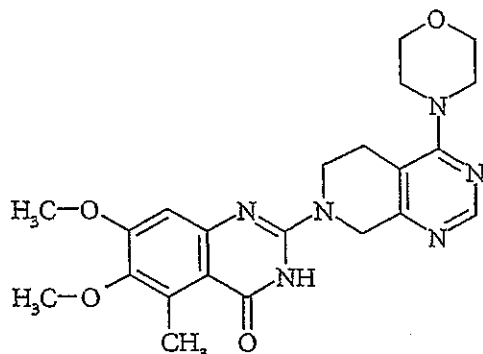


To a sample of 707 mg (2.5 mmol) of 2-methylthiol-5,6,7-trimethoxy-1H-quinazolin-4-one in 100 mL of DCE was added 1.3 g of 75% MCPBA (about 5.5 mmol). The mixture was stirred for 2-3 hrs, and then it was treated with 790 mg of 4-morpholin-4-yl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine



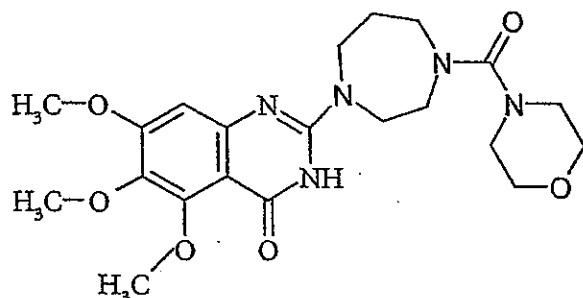
as the dihydrochloride salt (2.7 mmol) and 1.1 g (11 mmol) of TEA. The resulting mixture was stirred at ambient temperature for 4 days and then for an additional 3 h at 80 °C. The solvent was removed and the resulting solid was stirred with EtOAc, collected, stirred with diluted ammonium hydroxide, and extracted with EtOAc again. A hydrochloride salt was prepared as described in WO 02/053558 A1 to furnish 190 mg (13%) of Example G-1. Mp 190-192 °C; ms 455 (M+H).

Example G-2: 6,7-Dimethoxy-5-methyl-2-(4-morpholin-4-yl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-1H-quinazolin-4-one



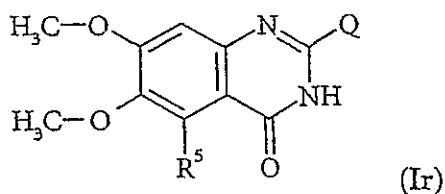
The above compound was prepared in the same fashion as Example G-1, except 6,7-dimethoxy-2-methylthiol-5-methyl-1*H*-quinazolin-4-one was used in place of 2-methylthiol-5,6,7-trimethoxy-1*H*-quinazolin-4-one. MW = 438.48

- 5 **Example H-1:** 6,7-Dimethoxy-5-methyl-2-[4-(morpholine-4-carbonyl)-[1,4]diazepan-1-yl]-1*H*-quinazolin-4-one



- 2-Chloro-6,7-dimethoxy-5-methyl-1*H*-quinazolin-4-one (254 mg, 1.0 mmol) and [1,4]diazepan-1-yl-morpholin-4-yl-methanone (256 mg, 1.2 mmol) were combined in 4 mL EtOH in a sealed tube and heated in an oil bath at 105°C for 2.5 hrs. The mixture was cooled in an ice bath. The product was filtered, washed with a little cold EtOH and dried to afford 319 mg (74%) as an off-white solid. Mp 236.6-237.7 °C; MS (ES+) *m/z* 432 (M + H); IR (KBr) $\nu_{\max}$ 1651, 1588, 1477, 1465, 1410; ¹H NMR (DMSO-*d*₆, 2.50) δ 1.86 (m, 2 H), 2.59 (s, 3 H), 2.95 (t, 2 H, *J* = 4.50), 3.28 (t, 2 H, *J* = 5.5), 3.51 (m, 4 H), 3.61 (s, 3 H), 3.68 (t, 2 H, *J* = 5.8), 3.80 (t, 2 H, *J* = 5.4), 3.85 (s, 3 H), 6.60 (s, 1 H), 10.71 (s, 1 H); ¹³C (DMSO-*d*₆, 39.89) δ 163.87, 157.59, 142.81, 131.88, 104.73, 66.22, 60.22, 55.90, 48.15, 47.93, 47.80, 46.97, 46.90, 26.98, 13.88; Anal. (C₂₁H₂₉N₅O₅·HCl) C: calcd. 53.90; found 53.90; H: calcd. 6.46; found 6.10; N: calcd. 14.97; found 14.87 The [1,4]diazepan-1-yl-morpholin-4-yl-methanone intermediate was synthesized as described in EP 9605609.

EXAMPLES H-2 to H-7



Compounds having the above formula (Ir), wherein R⁵ and Q have the values reported in Table 8, were prepared following the same or similar methods as described for examples detailed above.

5 **TABLE 8**

Ex.	R ⁵	Q	MW (M+H ⁺)
H-2	-OCH ₃		463.54
H-3	-OCH ₃		481.55
H-4	-OCH ₃		277.28
H-5	-CH ₃		329.40
H-6	-CH ₃		449.55
H-7	-OCH ₃		387.82

Representative compounds in accordance with the invention are shown in Table 9.

#	Systematic Name	Melting Point	MS (M+H)
1	2-{7-[(Ethyl-methyl-amino)-methyl]-3,4-dihydro-1H-isoquinolin-2-yl}-5,6,7-trimethoxy-1H-quinazolin-4-one	161.4-163.9	
2	2-{7-[(Ethyl-methyl-amino)-methyl]-3,4-dihydro-1H-isoquinolin-2-yl}-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one	189.4-204.6	
3	2-{5-[(Ethyl-methyl-amino)-methyl]-3,4-dihydro-1H-isoquinolin-2-yl}-5,6,7-trimethoxy-1H-quinazolin-4-one	214.0-216.9	
4	5,6,7-Trimethoxy-2-(7-methylaminomethyl-3,4-dihydro-1H-isoquinolin-2-yl)-1H-quinazolin-4-one	178.1-180.9	
5	2-[5-(1,3-Dimethyl-imidazolidin-2-ylideneamino)-3,4-dihydro-1H-isoquinolin-2-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one	215-217.5	
6	6,7-Dimethoxy-5-methyl-2-(5-methylaminomethyl-3,4-dihydro-1H-isoquinolin-2-yl)-1H-quinazolin-4-one	241.9-245.5	
7	6,7-Dichloro-2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1H-quinolin-4-one	266-271	
8	N-[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl]-N-methyl-2-methylamino-acetamide	208.8-212.0	
9	5-Isopropyl-6,7-dimethoxy-2-{5-[1-methyl-pyrrolidin-(2E)-ylideneamino]-3,4-dihydro-1H-isoquinolin-2-yl}-1H-quinazolin-4-one	196-200	
10	5,6,7-Trimethoxy-2-[4-(4-methyl-pentanoyl)-piperazin-1-yl]-1H-quinazolin-4-one hydrochloride	198-201	
11	2-[4-(Furan-2-carbonyl)-piperazin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one		415.5
12	4-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid ethyl		393.4

	ester		
13	[4-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazin-1-yl]-acetic acid ethyl ester		407.4
14	5,6,7-Trimethoxy-2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-1H-quinazolin-4-one		465.4
15	N,N-Dimethyl-2-[4-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazin-1-yl]-acetamide		406.4
16	4-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide		474.4
17	2-[4-(2-Cyclopentyl-acetyl)-piperazin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one		431.4
18	5,6,7-Trimethoxy-2-[4-(3-methyl-butyryl)-piperazin-1-yl]-1H-quinazolin-4-one		405.4
19	4-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid (3-fluoro-phenyl)-amide		458.3
20	4-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid (3,4-difluoro-phenyl)-amide		476.3
21	4-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid (3-cyano-phenyl)-amide		465.3
22	5,6,7-Trimethoxy-2-(4-pyridin-2-yl-piperazin-1-yl)-1H-quinazolin-4-one		398
23	2-[4-(1H-Imidazol-2-yl)-piperazin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one		387
24	5,6,7-Trimethoxy-2-[4-(6-methyl-pyridin-2-yl)-piperazin-1-yl]-1H-quinazolin-4-one	231.1-232.2	
25	5,6,7-Trimethoxy-2-[4-(4-methyl-pyridin-2-yl)-piperazin-1-yl]-1H-quinazolin-4-one	235.3-235.5	
26	5,6,7-Trimethoxy-2-[4-(1-oxy-pyridin-2-yl)-piperazin-1-yl]-1H-quinazolin-4-one	142.8-147.2	
27	5,6,7-Trimethoxy-2-[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-yl]-1H-quinazolin-4-	181.6-188.8 (HCl Salt)	

	one		
28	5,6,7-Trimethoxy-2-[4-(1-methyl-1 <i>H</i> -imidazol-2-yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one	227-229	
29	5,6,7-Trimethoxy-2-[4-(1,4,5-trimethyl-1 <i>H</i> -imidazol-2-yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one		429.2
30	5,6,7-Trimethoxy-2-[4-(4-methoxy-pyridin-2-yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one	229-231	
31	4-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid ethyl ester		377.4
32	[4-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazin-1-yl]-acetic acid ethyl ester		391.4
33	2-[4-(Furan-2-carbonyl)-piperazin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		399.4
34	6,7-Dimethoxy-5-methyl-2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one		449.4
35	6,7-Dimethoxy-5-methyl-2-[4-(4-methyl-pentanoyl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one		403.5
36	4-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide		458.4
37	2-[4-(2-Cyclopentyl-acetyl)-piperazin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		415.5
38	6,7-Dimethoxy-5-methyl-2-[4-(3-methyl-butyryl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one		389.4
39	2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		483.3
40	6,7-Dimethoxy-5-methyl-2-(4-pyridin-2-yl-piperazin-1-yl)-1 <i>H</i> -quinazolin-4-one	286.6-293.1 (HCl Salt)	
41	2-[4-(1 <i>H</i> -Imidazol-2-yl)-piperazin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		371
42	6,7-Dimethoxy-5-methyl-2-[4-(6-methyl-pyridin-2-yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one	284.5-285.5	
43	6,7-Dimethoxy-5-methyl-2-[4-(4-methyl-pyridin-2-	277.7-280	

	yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one	(HCl Salt)	
44	2-[4-[1-(3-Fluoro-phenyl)-4,5-dihydro-1 <i>H</i> -imidazol-2-yl]-piperazin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one	257.9-260	
45	2-[4-(1-Isopropyl-4,5-dihydro-1 <i>H</i> -imidazol-2-ylmethyl)-piperazin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		429
46	6,7-Dimethoxy-5-methyl-2-[4-(1-methyl-4,5-dihydro-1 <i>H</i> -imidazol-2-ylmethyl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one		401.2
47	6,7-Dimethoxy-5-methyl-2-[4-(1-methyl-1 <i>H</i> -imidazol-2-yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one	263-264	
48	6,7-Dimethoxy-5-methyl-2-[4-(1,4,5-trimethyl-1 <i>H</i> -imidazol-2-yl)-piperazin-1-yl]-1 <i>H</i> -quinazolin-4-one		413
49	6,7-Dimethoxy-2-[4-(4-methoxy-pyridin-2-yl)-piperazin-1-yl]-5-methyl-1 <i>H</i> -quinazolin-4-one	273-274	
50	2-(3-Cyclohexyl-5,6-dihydro-8 <i>H</i> -imidazo[1,5- <i>a</i>]-pyrazin-7-yl)-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one; compound with trifluoro-acetic acid		424.4
51	6,7-Dimethoxy-2-[4-[2-((<i>S</i>)-2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidin-1-yl]-5-methyl-1 <i>H</i> -quinazolin-4-one	83.1-110.9	445
52	6,7-Dimethoxy-5-methyl-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-piperidin-1-yl]-1 <i>H</i> -quinazolin-4-one		402.4
53	6,7-Dimethoxy-5-methyl-2-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-1 <i>H</i> -quinazolin-4-one		387.4
54	2-(4-Benzyl-piperidin-1-yl)-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		394.4
55	2-[4-(4-Chloro-benzoyl)-piperidin-1-yl]-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one		442.3
56	6,7-Dimethoxy-5-methyl-2-[4-(3-pyrrolidin-1-yl-benzylamino)-piperidin-1-yl]-1 <i>H</i> -quinazolin-4-one		478
57	6,7-Dimethoxy-2-[4-[2-((<i>R</i>)-2-methoxymethyl-	219.0-221.9	

	pyrrolidin-1-yl)-ethyl]-piperidin-1-yl}-5-methyl-1H-quinazolin-4-one		
58	2-{4-[2-(2-Amino-imidazol-1-yl)-ethyl]-piperidin-1-yl}-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one	130.9-133.3	
59	6,7-Dimethoxy-5-methyl-2-{4-[2-(2-methyl-4,5-dihydro-imidazol-1-yl)-ethyl]-piperidin-1-yl}-1H-quinazolin-4-one	266.1-269.5	
60	2-[4-(2-Imidazol-1-yl-ethyl)-piperidin-1-yl]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one		398.1
61	2-[1-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-yloxymethyl]-N,N-dimethyl-benzenesulfonamide	217.9-219.8	
62	2-{4-[(2-Fluoro-benzyl)-methyl-amino]-piperidin-1-yl}-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one		441
63	2-(4-Benzyl-piperidin-1-yl)-5,6,7-trimethoxy-1H-quinazolin-4-one	212-215	
64	5,6,7-Trimethoxy-2-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-1H-quinazolin-4-one		403.4
65	5,6,7-Trimethoxy-2-(4-propyl-piperidin-1-yl)-1H-quinazolin-4-one		362.4
66	2-[4-(4-Chloro-benzoyl)-piperidin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one		458.4
67	5,6,7-Trimethoxy-2-(4-pyridin-2-ylmethyl-piperidin-1-yl)-1H-quinazolin-4-one		411.1
68	5,6,7-Trimethoxy-2-[4-(3-pyrrolidin-1-yl-benzylamino)-piperidin-1-yl]-1H-quinazolin-4-one		494
69	5,6,7-Trimethoxy-2-{4-[2-((S)-2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidin-1-yl}-1H-quinazolin-4-one	78.8-91.6	
70	5,6,7-Trimethoxy-2-{4-[2-((R)-2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-piperidin-1-yl}-1H-quinazolin-4-one	65.0-79.1	
71	2-{4-[2-(2-Amino-imidazol-1-yl)-ethyl]-piperidin-1-yl}-5,6,7-trimethoxy-1H-quinazolin-4-one	252.4-253.2	
72	2-[4-(2-Fluoro-benzylamino)-piperidin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one		443

73	2-[4-(2-Chloro-benzylamino)-piperidin-1-yl]-5,6,7-trimethoxy-1 <i>H</i> -quinazolin-4-one		459
74	5,6,7-Trimethoxy-2-[4-(2-methoxy-benzylamino)-piperidin-1-yl]-1 <i>H</i> -quinazolin-4-one		455
75	2-[4-(2-Imidazol-1-yl-ethyl)-piperidin-1-yl]-5,6,7-trimethoxy-1 <i>H</i> -quinazolin-4-one		414.1
76	5,6,7-Trimethoxy-2-[4-(2-methyl-benzylamino)-piperidin-1-yl]-1 <i>H</i> -quinazolin-4-one		439
77	<i>N,N</i> -Dimethyl-2-[1-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-yloxymethyl]-benzenesulfonamide	186.0-188.2	
78	3-[1-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-ylmethyl]-benzoic acid methyl ester		468.2
79	3-[1-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-ylmethyl]-benzoic acid	245-249	
80	<i>N</i> -Methanesulfonyl- <i>N</i> '-{3-[1-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-yloxymethyl]-phenyl}-methanesulfonamide	100.7-160.4	
81	<i>N,N</i> -Dimethyl- <i>N</i> '-{3-[1-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-yloxy-methyl]-phenyl}-acetamidine	56.0-64.9	
82	<i>N</i> -{3-[1-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-piperidin-4-yloxymethyl]-phenyl}-methanesulfonamide	86.0-92.0	
83	2-(3,4-dihydro-1' <i>H</i> -spiro[chromene-2,4'-piperidin]-1'-yl)-6,7-dimethoxy-5-methylquinazolin-4(1 <i>H</i>)-one		422.4
84	2-(3,4-dihydro-1' <i>H</i> -spiro[chromene-2,4'-piperidin]-1'-yl)-5,6,7-trimethoxyquinazolin-4(1 <i>H</i>)-one		438.4
85	6,7-Dimethoxy-5-methyl-2-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl)-1 <i>H</i> -quinazolin-4-one		450.4
86	8-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-(2-methoxy-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione; compound with trifluoro-acetic acid		494.4

87	9-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-4-(4-fluoro-phenyl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one		483.4
88	4-(4-Fluoro-phenyl)-9-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one		499.4
89	1-(2-Methoxy-phenyl)-8-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione		510.4
90	1-(3-Methoxy-phenyl)-8-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione		510.5
91	9-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one		405.4
92	5-Phenyl-9-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one		481.4
93	5,6,7-Trimethoxy-2-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl)-1 <i>H</i> -quinazolin-4-one		466.4
94	8-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-(3-methoxy-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione		494.4
95	8-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-(3-dimethylamino-propyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione		473.5
96	9-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one		389.4
97	9-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-5-phenyl-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one		465.4
98	<i>N'</i> -[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]- <i>N,N</i> -dimethyl-acetamidine	270.9-273.5	436
99	2-[5-(1,3-Dimethyl-imidazolidin-2-ylideneamino)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-6,7-dimethoxy-5-		463.3

	methyl-1 <i>H</i> -quinazolin-4-one		
100	5,6,7-Trimethoxy-2-{5-[1-methyl-pyrrolidin-(2 <i>E</i>)-ylideneamino]-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-1 <i>H</i> -quinazolin-4-one		464.1
101	2-{5-[2-(4,5-Dihydro-1 <i>H</i> -imidazol-2-yl)-ethyl]-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl}-5,6,7-trimethoxy-1 <i>H</i> -quinazolin-4-one		464.1
102	2-[5-(4,5-Dihydro-1 <i>H</i> -imidazol-2-yl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-5,6,7-trimethoxy-1 <i>H</i> -quinazolin-4-one		436
103	<i>N,N</i> -Dimethyl- <i>N'</i> -[2-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-acetamidine	115.8-120.1	
104	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5,6,7-trimethoxy-1 <i>H</i> -quinazolin-4-one	267-270 (HCl Salt)	
105	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-6,7-dimethoxy-5-(2-methoxy-ethoxy)-1 <i>H</i> -quinazolin-4-one	202.4-204.4	
106	2-[5-(Imino-morpholin-4-yl-methyl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-5,6,7-trimethoxy-1 <i>H</i> -quinazolin-4-one		480.1
107	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5-isopropoxy-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	253.3-261.9 (HCl Salt)	
108	5-Cyclopropylmethoxy-2-(6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	214-215.8	
109	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5-ethoxy-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	218.5-221 (HCl Salt)	
110	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5-hydroxy-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	255-259 (HCl Salt)	
111	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5-(2-hydroxy-ethoxy)-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	224-229	
112	5-(2-Benzoyloxy-ethoxy)-2-(6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-6,7-dimethoxy-1 <i>H</i> -	197.0-201.9	

	quinazolin-4-one		
113	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-6,7-dimethoxy-5-phenoxy-1 <i>H</i> -quinazolin-4-one	238.7-241.9	
114	5-(2-Amino-ethoxy)-2-(6,7-dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one		457.1
115	<i>N</i> -[2-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-butyramidine	192.2-193.5	
116	<i>N</i> -[2-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-cyclobutanecarboxamide	199.5-200.8	
117	<i>N</i> -[2-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-furan-2-carboxamide	223.9-225.9	
118	5,6,7-Trimethoxy-2-[5-(1-methyl-4,5-dihydro-1 <i>H</i> -imidazol-2-yl)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-1 <i>H</i> -quinazolin-4-one		450
119	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5-isopropyl-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	243-244 (HCl Salt)	
120	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-5-(4-fluoro-phenyl)-6,7-dimethoxy-1 <i>H</i> -quinazolin-4-one	220-225	
121	2-(6,7-Dimethoxy-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl)-6,7-dimethoxy-5-methyl-1 <i>H</i> -quinazolin-4-one	260-268 (HCl Salt)	
122	<i>N,N</i> -Dimethyl- <i>N'</i> -[2-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide	223.5-226.6	
123	<i>N</i> -[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-cyclobutanecarboxamide	252.1-256.1	
124	<i>N</i> -[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-furan-2-carboxamide	279.0-282.0	
125	<i>N</i> -[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-	254.3-257.1	

	quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-butyramidine		
126	6,7-Dimethoxy-5-methyl-2-[5-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-1H-quinazolin-4-one	246-250	
127	6,7-Dimethoxy-5-methyl-2-[5-(2,4,4-trimethyl-4,5-dihydro-imidazol-1-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-1H-quinazolin-4-one		462
128	6,7-Dimethoxy-5-methyl-2-[5-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-1H-quinazolin-4-one		432
129	6,7-Dimethoxy-2-[5-[1-(2-methoxy-ethyl)-4,5-dihydro-1H-imidazol-2-yl]-3,4-dihydro-1H-isoquinolin-2-yl]-5-methyl-1H-quinazolin-4-one		478
130	2-[5-(1-Isopropyl-4,5-dihydro-1H-imidazol-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one		462.2
131	2-[5-(2,4-Dimethyl-4,5-dihydro-imidazol-1-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one		448
132	N'-[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-N,N-dimethyl-acetamide	176-177.1	
133	2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-5-fluoro-6,7-dimethoxy-1H-quinazolin-4-one	260.8-269	
134	5-Chloro-2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxy-1H-quinazolin-4-one	255.4-259.9	
135	5,6,7-Trimethoxy-2-(4-morpholin-4-yl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-1H-quinazolin-4-one	190-192 (HCl Salt)	455
136	6,7-Dimethoxy-5-methyl-2-(4-morpholin-4-yl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-1H-quinazolin-4-one	>300	
137	6,7-Dimethoxy-5-methyl-2-[4-(morpholine-4-carbonyl)-[1,4]diazepan-1-yl]-1H-quinazolin-4-one	236.6-237.7 (HCl Salt)	432
138	5,6,7-Trimethoxy-2-[2-[3-(2-methyl-4,5-dihydro-	205.1-209.1	

	imidazol-1-yl)-phenyl]-pyrrolidin-1-yl]-1H-quinazolin-4-one		
139	N-(2-{3-[1-(5,6,7-Trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-pyrrolidin-2-yl]-phenylamino}-ethyl)-acetamide	188.6-191	
140	2-Aziridin-1-yl-5,6,7-trimethoxy-1H-quinazolin-4-one	>300. (HCl Salt)	
141	2-(8-Aza-bicyclo[3.2.1]oct-8-yl)-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one		330.3
142	N'-{3-[1-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-pyrrolidin-3-yl]-phenyl}-N,N-dimethyl-acetamidine	152.2-154.4	
143	2-(5-Chloro-1,3-dihydro-isoindol-2-yl)-5,6,7-trimethoxy-1H-quinazolin-4-one hydrochloride	289-291	

Assay Examples

EXAMPLE I-1

- The potency and selectivity of the inventive compounds as α 1A/B antagonists was
- 5 determined with CHO-K1 cells expressing adrenoceptor subtype α 1A-215, α 1B or α 1D by measuring cAMP accumulation using AlphaScreen.
- Cell preparation was accomplished by culturing CHO- α 1 cloned cells in Ham's F12 nutrient media supplemented with 10% FBS and G418 (25mg/ml), harvested at 80% confluence, washed with warmed PBS x2, and detached with versene for 5 min. at 37°C.
- 10 The cultured cells were then resuspended in 40 ml of stimulation buffer (HBSS with 5 mM hepes, 0.1% BSA) and centrifuged at 500-100 rpm for 5 min. The obtained pellet was resuspended in stimulation buffer (with 0.5M IBMX), and the cells were counted. Cells were diluted to the desired number of cells/ml (α 1A at 3×10^6 /ml, α 1B 15×10^6 /ml, and α 1D 20×10^6 /ml).
 - 15 The compounds being tested were diluted in stimulation buffer (with 0.5M IBMX), from 10^{-5} to 10^{-11} (final) dilution, 11 points. 5 μ l of each compound was dispensed to 96 well $\frac{1}{2}$ area plates in triplicate. 5 μ l of stimulation buffer was dispensed to a norepinephrine (NE) plate. 10 μ l of cells were added with anti-cAMP Acceptor beads in stimulation buffer

to each plate and incubated for 15 min. at RT (in dark or covered with black plate). Then 5 μ l of NE was added to the antagonist plates, at 1 μ M for α 1A and 1B and at 100nM for α 1D, and then 5 μ l serial dilution of NE was added to NE plate. Plates were incubated for 30 min. at RT (in dark or covered with black plate) and 10 μ l Donor beads + biotin-cAMP in lysis buffer (5mM Hepes, 0.54% Tween-20, 0.1% BSA) was added. Plates were incubated for 3h. at RT with gentle shaking (in dark or covered with black plate). Plates were read on an AlphaScreen Fusion analyzer, using reagent pursuant to AlphaScreen cAMP detection kit (PerkinElmer Cat#6760600).

Reference compounds norepinephrine, prazosin and vehicle were run in every experiment. In each plate, on column 12, A-D were loaded with only cells to define total count and E-H were loaded with NE 1 μ M, (total - NE 1 μ M), to define 100% NE activity. The values determined for each experimental well on the plate were divided by (total count - NE 1 μ M), to determine % of NE activity. All data was plotted using non-linear curve fitting by GraphPad Prism to get pEC₅₀ (pEC₅₀ being the negative logarithm of EC₅₀, i.e., the molar concentration of an agonist which produces 50% of the maximum possible response for that agonist) for norepinephrine and pK_b (wherein K_b is the equilibrium dissociation for a competitive antagonist, determined in a functional assay, and being equal to the concentration of antagonist which would occupy 50% of the receptors at equilibrium, units=mol l⁻¹, and pK_b is the negative logarithm of K_b) for prazosin and tested compounds. (AlphaScreen cAMP Detection Kit from PerkinElmer Life Sciences).

Proceeding as in Example I-1, compounds of Formula I were tested and found to be selective α 1A/B-adrenoceptor antagonists.

Example I-2: [³H]prazosin Binding (α 1-Adrenoceptor) Assay

α 1A, α 1B, and α 1D adrenoceptor transfected CHO-K1 cells, prepared using the methods described by Chang *et al.*, *FEBS Lett.* 1998, 422:279-283, were grown to confluence in T-162 tissue culture flasks in Ham's F-12 culture medium supplemented with 10% fetal bovine serum, geneticin (150 μ g/mL) and streptomycin/penicillin (30 μ g/mL/30 μ g/mL) at 37° C in 7% CO₂. Cells were harvested by incubating with phosphate-buffered saline (PBS) containing 30 μ M EDTA for 5-10 min at 37° C. Cells were pelleted by centrifuging at 500 x g for 5min, and the pelleted cells were homogenized (Polytron homogenizer) in 10 vols (w/v) of 50 mM Tris, 1 mM EDTA, (homogenisation buffer, pH 7.4 at 4° C). The homogenate was centrifuged at 45,000 x g for 20 min. The pellet was resuspended in the homogenizing buffer and rehomogenized.

The resulting homogenate was centrifuged at 45,000 x g for 20 min. The pellet was resuspended in 50 mM Tris buffer (pH 7.4 at 4° C), aliquoted, frozen, and stored at -80° C for further use.

The membranes were thawed at rt and diluted in assay buffer (50 mM Tris buffer at pH 4) at 37°C and homogenized using the Polytron tissue disrupter. The membranes were incubated with the radioligand ([³H]prazosin, NEN, 0.1 – 0.5 nM) and test compound at 37°C for 30 min. The membranes were then filtered over polyethyleneimine-treated GF/B unfilter plates using a Packard Filtermate Harvester and washed with ice-cold 50 mM Tris-HCl, 1 mM EDTA buffer (3 x 3 sec. washes). Scintillation cocktail was added to the filter plates and bound radioligand determined by liquid scintillation spectrophotometry.

For each experiment, total binding (in the absence of any test or reference compounds) and non-specific binding (10 µM phentolamine) were determined. For each sample tested, the concentration producing 50% inhibition of binding (IC₅₀) and Hill Slope (n_H) was determined using iterative non-linear curve fitting techniques with Kaleidagraph (Synergy Software) or other appropriate software. If the radioligand K_D was known, the inhibition dissociation constant (K_I) of each ligand was determined according to the method of Cheng and Prusoff (Cheng and Prusoff, *Biochem.Pharmacol.*, 1973, 22, 3099-3108).

Proceeding as in Example I-2, compounds of Formula I were tested and found to be selective alpha1A/B-adrenoceptor antagonists.

Example I-3: Dog *In Vivo* Intraurethral and Blood Pressure Assay

The following describes an *in vivo* assay for measuring the relative effect of test compounds on hypogastric nerve stimulation-induced increases in intraurethral pressure and phenylephrine-induced increases in diastolic blood pressure in anesthetized dog. Male Mongrel dogs (10 to 20 kg) were fasted for 12 to 18 hours and anesthetized with phenobarbital sodium (36 mg/kg, *i.v.*). An endotracheal tube was inserted and thereafter the lungs were mechanically ventilated with room air. The right femoral vein was isolated and cannulated with two polyethylene cannulae, one for the administration of a continuous infusion of phenobarbital sodium (5 to 10 mg/kg/hr) and the other for bolus administration of test substances. The right femoral artery was isolated and cannulated to the abdominal aorta with a fluid filled polyethylene cannula connected to an external pressure transducer for monitoring diastolic aortic pressure (DAP). The bladder was exposed via a ventral midline abdominal incision and emptied of urine through a 22 gauge needle. The bladder was cannulated through a stab incision with a water filled

balloon catheter connected to an external pressure transducer for monitoring prostatic intraurethral pressure (IUP). The right hypogastric nerve (HGN) was carefully isolated and attached to a Dastre's electrode for nerve stimulation.

The preparation was allowed to stabilize for at least 20-30 minutes and must have had a stable basal IUP for not less than 15 minutes prior to commencement of the assay protocol. The HGN was stimulated (20-50V, 10Hz, 10 msec pulse train for 10 sec) to induce a measurable increase in IUP and then phenylephrine (PE) was administered by bolus injection (6 µg/kg, *i.v.*) to induce a measurable increase in DAP. The HGN stimulation and PE bolus injection were repeated every 5 minutes until three consecutive reproducible increases in IUP and DAP were achieved. Test compound was administered and 10 minutes later the HGN stimulation and PE bolus injection were repeated. Test compound was administered approximately every 20 minutes, increasing the dose until maximal or near maximal inhibition of the increases in IUP and DAP is attained.

Proceeding as in Example I-3, compounds of Formula I were tested and found to selectively inhibit the HGN stimulation-induced increases in IUP. In contrast, prazosin inhibited increases in IUP and DAP in similar fashion.

Compounds of formula I are active in the above assays. For some exemplary compounds the following table shows corresponding data.

Compound	pKi		
	alpha 1A	alpha 1B	alpha 1D
2-[4-(1H-Imidazol-2-yl)-piperazin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one	8.95	8.60	6.34
2-[4-(2-Imidazol-1-yl-ethyl)-piperidin-1-yl]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one	8.28	8.66	7.06
4-(4-Fluoro-phenyl)-9-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-oxa-4,9-diazaspiro[5.5]undecan-3-one	8.21	7.86	6.59
N-[2-(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl]-N-methyl-2-methylamino-acetamide	8.8	8.8	7.1

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the

true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

1. A compound of the Formula I



wherein

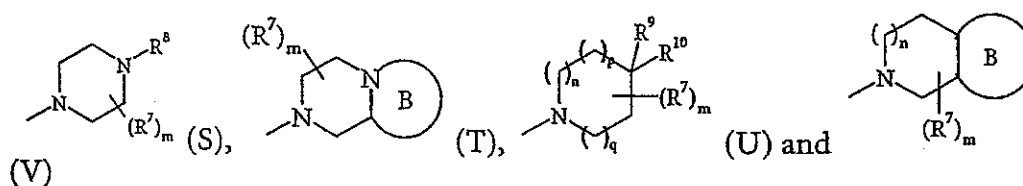
5 Z is $-\text{C}(=\text{O})-$ or $-\text{S}(=\text{O})_2-$;

R and R' are lower alkoxy;

R⁵ is selected from halogen, cyano, hydroxy, optionally substituted phenyl, $-\text{R}^6$, and $-\text{OR}^6$;

10 R⁶ is alkyl, alkoxyalkyl, hydroxyalkyl, optionally substituted benzyloxyalkoxy, optionally substituted phenoxy, aminoalkyl, optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, or cycloalkyloxy; and

Q is a monocyclic or bicyclic heterocyclic ring selected from (S), (T), (U), and (V)



15 wherein

B is an optionally-substituted fused aryl or heteroaryl ring;

20 R⁷ is attached to any available carbon atom of the piperidinyl or piperazinyl ring and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, cyano, hydroxy, alkoxy, haloalkoxy, amino, and alkylamino; or alternatively, wherein Q is ring (T), two R⁷ groups attached to different carbon atoms may be taken together to form a carbon-carbon bridge of one to two bridgehead carbon atoms;

R⁸ is $-\text{K}-\text{R}^{14}$;

25 R⁹ and R¹⁰ are (i) independently selected from $-\text{L}-\text{R}^{15}$, or alternatively, (ii) R⁹ and R¹⁰ are taken together to form an optionally-substituted spirocyclic ring;

K and L are independently selected from a bond, optionally-substituted C₁-

alkylene, $-\text{M}_1-\text{O}-\text{M}_2-$, $-\text{M}_1-\text{C}(=\text{O})-\text{M}_2-$, $-\text{M}_1-\text{C}(\text{O})_2-\text{M}_2-$, $-\text{M}_1-$

$\text{C}(=\text{O})\text{NR}^{16}-\text{M}_2-$, and $-\text{M}_1-\text{NR}^{16}-\text{M}_2-$, wherein M₁ and M₂ are selected from a bond and optionally-substituted C₁-alkylene;

R^{14} and R^{15} are independently selected from hydrogen, optionally-substituted alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclo, provided that if K or L is a bond or $-NR^{16}-$, then R^{14} and R^{15} are not selected from phenyl, pyridyl, or pyrimidinyl having a para substituent that is CO_2R^{22} , wherein R^{22} is selected from hydrogen, alkyl, aryl, arylalkyl, guanidinyl, hydroxy, alkoxy, aryloxy, and arylalkyloxy; R^{16} is selected from hydrogen and alkyl;

m is 0, 1, 2, 3, or 4;

n is 0 or 1;

p is 0, 1 or 2; and

q is 0 or 1; or

an isomer or pharmaceutically-acceptable salt, hydrate, or prodrug thereof.

2. The compound of claim 1 selected from

2-[4-(1H-imidazol-2-yl)-piperazin-1-yl]-5,6,7-trimethoxy-1H-quinazolin-4-one;

2-[4-(2-imidazol-1-yl-ethyl)-piperidin-1-yl]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one;

4-(4-fluoro-phenyl)-9-(5,6,7-trimethoxy-4-oxo-1,4-dihydro-quinazolin-2-yl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one; and

N-[2-(6,7-dimethoxy-5-methyl-4-oxo-1,4-dihydro-quinazolin-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl]-*N*-methyl-2-methylamino-acetamide.

3. The compound of claim 1 for use as therapeutic active substance.

4. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

5. Use of a compound of claim 1 for the manufacture of a medicament comprising a compound according to claim 1 for treating a disease state in a patient modulated via an α -1A/B adrenoceptor.

6. The use of claim 5 wherein the disease state is selected from disorders and symptoms of the urinary tract, sexual dysfunction, benign prostatic hypertrophy, and pain.

7. A process for the preparation of a compound of claim 1.