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(54) Title: THERAPEUTIC PYRAZOLOQUINOLINE DERIVATIVES

(57) Abstract: The invention provides a novel chemical series of formula (I), as well as methods of use thereof for binding to the benzodiazepine site of the GABA_A receptor and modulating GABA_A, and use of the compound of formula (I) in the manufacture of a medicament for the treatment of GABA_A receptor associated disorders. The invention further provides a method of modulation of one or more GABA_A subtypes in an animal comprising administering to the animal an effective amount of a compound of formula (I).

THERAPEUTIC PYRAZOLOQUINOLINE DERIVATIVES

RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/943,005, filed June 8, 2007 which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention is related to the use of novel derivatives of pyrazoloquinolines as modulators of GABA_A α 5 for the intended use of therapy for enhancing cognition.

Description of the Related Art

[0003] The inhibitory neurotransmitter γ -aminobutyric acid (GABA), serves as a ligand for two distinct classes of receptors, GABA_A and GABA_B. The GABA_A class is a ligand-gated ion channel while GABA_B is a canonical seven transmembrane G-protein coupled receptor. The GABA_A receptor is comprised of a number of subunits, including α , β , γ , and δ . Cloning of the individual subunits of the GABA_A receptor has confirmed the existence, so far, of six α subunits, three β subunits, three γ subunits, and one δ subunit. The overall structure of the receptor is a pentamer with a minimum subunit requirement of at least one α subunit, one β subunit, and one γ subunit.

[0004] Due to afore mentioned diversity of subunits, there are more than 10,000 possible combinations of the subunits that comprise the GABA_A receptor, though not all appear in nature. Specific combinations that have been identified to have biological relevance (and their relative abundance in rat brains, include α 1 β 2 γ 2 (43%), α 2 β 2/3 γ 2 (18%), α 3 β γ 2/3 (17%), α 2 β γ 1 (8%), α 5 β 3 γ 2/3 (4%), α 6 β γ 2 (2%), α 6 β δ (2%), and α 4 β δ (3%) (Barnard, E.A., *et al.* (1998) *Pharmacol. Rev.* 50: 291-313 incorporated herein in its entirety).

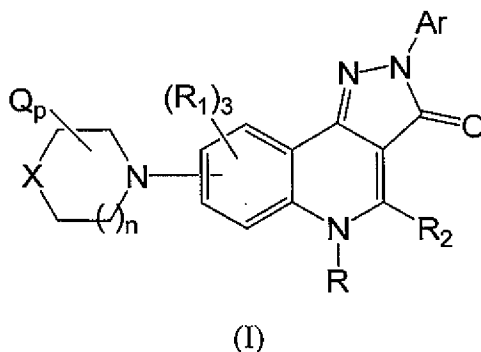
[0005] There are a number of distinct, small molecule binding sites on the GABA_A receptor that modulate the activity of the receptor including sites for benzodiazepines, steroids, barbiturates, ethanol, and convulsants (e.g. picrotoxin). The GABA binding site is located at the α/β interface. A tremendous amount of pharmaceutical research has been invested in identifying compounds that bind to the benzodiazepine binding site (BZ-site), which is located at the α/γ interface. Binding of GABA is greatly modulated by binding of drugs to the BZ-site, which can cause a number of different pharmacological responses. Drugs such as diazepam and zolpidem, agonists of GABA_A function, have shown historic success as anxiolytic agents (Muller, W.E. (1988) *Drugs of Today* 24: 649-663 incorporated herein in its entirety). More recent work has suggested that the sedative and hypnotic effects of these drugs are primarily due to interaction with the $\alpha 1$ -containing receptors, therefore much effort has been focused on finding drugs that have preferential activity towards $\alpha 2\beta 2\gamma 2$ and $\alpha 3\beta \gamma 2$ over $\alpha 1\beta \gamma 2$ to maintain the anxiolytic activity but reduce the sedative side effects (Rudolph, U. F., *et al.* (1999) *Nature* 401: 796-800 incorporated herein in its entirety; Löw, K.F., *et al.* (2000) *Science* 290: 131-134 incorporated herein in its entirety; McKernan, R.M., *et al.* (2000) *Nat. Neurosci.* 3: 587-592 incorporated herein in its entirety).

[0006] The $\alpha 5$ -subunit is predominantly found in the hippocampus, a part of brain that plays a part in memory and spatial navigation. As a result, much research has been focused on identifying links between $\alpha 5$ -containing GABA receptor function and cognition. Results from a number of laboratories have indicated that selective inverse agonism of the $\alpha 5\beta \gamma 2/3$ GABA_A receptor can show marked improvement of memory function in a number of animal models. There have been a growing number of examples of inverse agonists in both the patent and scientific literature (Yokoyama, N., *et al.* (1982) *J. Med. Chem.* 25: 337-339 incorporated herein in its entirety; Takada, S., *et al.* (1988) *J. Med. Chem.* 31: 1738-1745 incorporated herein in its entirety; Atack, J.R., *et al.* (2006) *European Journal of Pharmacology* 548: 77-82 incorporated herein in its entirety). A preferable profile for a cognitive enhancer is one that shows negative modulation at $\alpha 5$, but with less modulation of $\alpha 1$, $\alpha 2$, or $\alpha 3$ to minimize side effects such as convulsion or

sedation. As yet, no $\alpha 5$ selective GABA_A negative modulator has been brought to market, and only a limited number have been investigated in human clinical trials.

SUMMARY OF THE INVENTION

[0007] The invention provides a novel chemical series of formula I, and methods of use thereof for binding to the benzodiazepine site of the GABA_A receptor and negatively modulating the $\alpha 5$ subtype of GABA_A. The general structure of formula I is shown below:



[0008] The compounds of Formula I encompass all possible tautomers of the chemical structures and mixtures thereof.

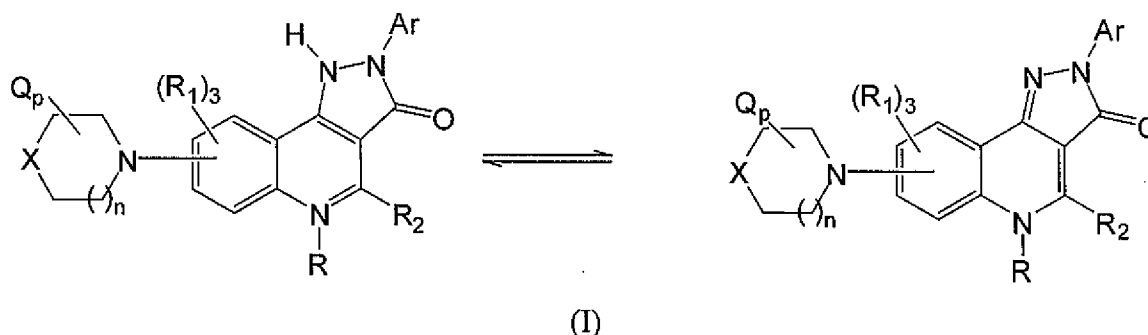
Embodiments, Aspects and Variations of the Invention

[0009] It is recognized in the following structures, when a formula is depicted as a mixture of two tautomeric structures, that the definitions of "R" can be different in the structure on the left than in the structure on the right. For example, in a compound of formula (I), in the structure on the left the definition of "R" can be absent and in the structure on the right the definition of "R" can be hydrogen. Compounds represented by the tautomeric structures can exist in all possible tautomeric forms and mixtures thereof. Additionally, compounds need not exist in both drawn tautomeric forms. A compound that can be represented by either drawn structure, whether in equilibrium or not in equilibrium, falls within the present disclosure.

[0010] It is recognized, that two tautomeric forms are drawn for some formulas. For simplicity, in some places (including the claims), only the tautomeric form on the right is drawn for an indicated formula, this is not to exclude the other tautomeric form. In

places where only one tautomeric form is drawn for a formula the other tautomeric form is also contemplated.

[0011] One embodiment of the invention provides a compound of formula (I):



or tautomer thereof, or their pharmaceutically acceptable salts,
wherein

[0012] R is absent, hydrogen, or oxide;

[0013] each R₁ is selected from the group consisting of hydrogen, hydroxy, halo, cyano, -CONR_aR_b, -NR_aR_b, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, amino(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

[0014] R₂ is selected from the group consisting of hydrogen, hydroxy, halo, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

[0015] each R_a and R_b is independently hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, (C₁-C₆)alkylaryl, -S(O)_z(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)(C₁-C₆)alkyl, -C(O)NR_g(C₁-C₆)alkyl, -C(O)NR_garyl, -C(O)O(C₁-C₆)alkyl, arylOC(O)- or arylC(O)-, or R_a together with R_b form a heterocycle group optionally substituted with one or more R_d; wherein the heterocycle group optionally include one or more groups selected from O (oxygen), S (sulfur), and NR_c;

[0016] each R_c is independently hydrogen, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -C(O)O(C₁-C₆)alkyl, -C(O)Oaryl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, arylO(C₁-C₆)alkyl, -C(O)NR_g(C₁-C₆)alkyl, -C(O)NR_garyl, -S(O)_z(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)(C₁-C₆)alkyl, arylC(O)-, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, or (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

[0017] each R_d is independently selected from the group consisting of hydrogen, halo, oxo, hydroxy, $-C(O)NR_aR_b$, $-NR_aR_b$, hydroxy(C_1-C_6)alkyl, aryl aryl(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with up to 5 fluoro, and (C_1-C_6)alkoxy optionally substituted with up to 5 fluoro;

[0018] each R_e and R_f is independently selected from hydrogen, (C_1-C_6)alkyl, aryl, heteroaryl, heterocycle, (C_1-C_6)alkylaryl, aryl(C_1-C_6)alkyl, $-C(O)(C_1-C_6)alkyl$, $-S(O)_z(C_1-C_6)alkyl$, $-S(O)_zNR_g(C_1-C_6)alkyl$, $-S(O)_zaryl$, $-C(O)NR_g(C_1-C_6)alkyl$, $-C(O)(C_1-C_6)alkyl$, arylC(O)-, arylOC(O)-, or $-C(O)O(C_1-C_6)alkyl$;

[0019] R_g is hydrogen, aryl, heteroaryl, heterocycle or (C_1-C_6)alkyl optionally substituted with up to 5 fluoro;

[0020] Ar is aryl optionally substituted with one or more M or heteroaryl optionally substituted with one or more M;

[0021] each Q is independently hydrogen, halo, oxo, hydroxy, $-C(O)NR_aR_b$, $-NR_aR_b$, (C_1-C_6)alkyl optionally substituted with up to 5 fluoro, (C_1-C_6)alkoxy optionally substituted with up to 5 fluoro, (C_1-C_6)alkyl optionally substituted with one or more R_d , hydroxy(C_1-C_6)alkyl optionally substituted with one or more R_d , aryl optionally substituted with one or more R_d , or aryl(C_1-C_6)alkyl optionally substituted with one or more R_d ;

[0022] each M is independently hydrogen, halo, CF_3 , CF_2H , hydroxy, cyano, nitro, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, $-NR_aR_b$, aryl, heteroaryl or heterocycle;

[0023] each X is independently NL, oxygen, $C(Q)_2$, or $S(O)_z$;

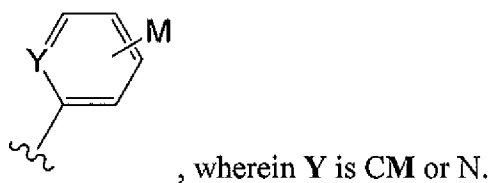
[0024] each L is independently hydrogen, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-C(O)O(C_1-C_6)alkyl$, $-C(O)Oaryl$, (C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, aryl, heteroaryl, heterocycle, arylO(C_1-C_6)alkyl, $-CONR_eR_f$, $-S(O)_z(C_1-C_6)alkyl$, $-S(O)_zaryl$, $-C(O)(C_1-C_6)alkyl$, arylC(O)-, $-C(O)NR_g(C_1-C_6)alkyl$, (C_1-C_6)alkyl optionally substituted with up to 5 fluoro, or (C_1-C_6)alkoxy optionally substituted with up to 5 fluoro;

[0025] p is an integer selected from 0, 1, 2 and 3,

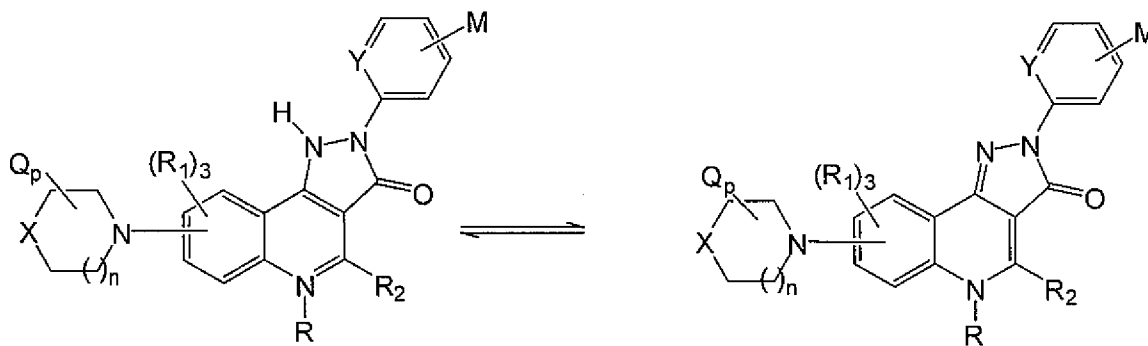
[0026] z is an integer selected from 0, 1, and 2; and

[0027] n is an integer selected from 0, 1, and 2.

[0028] In some embodiments, Ar can be:



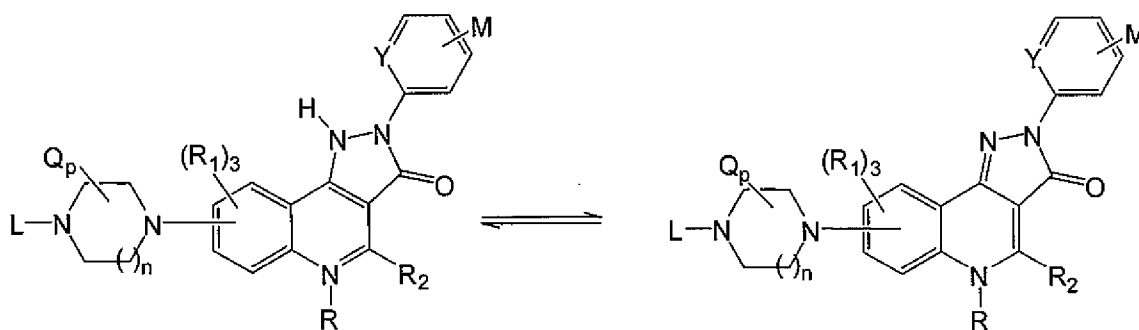
[0029] In another embodiment the compound has the formula **Ia**:



(Ia)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

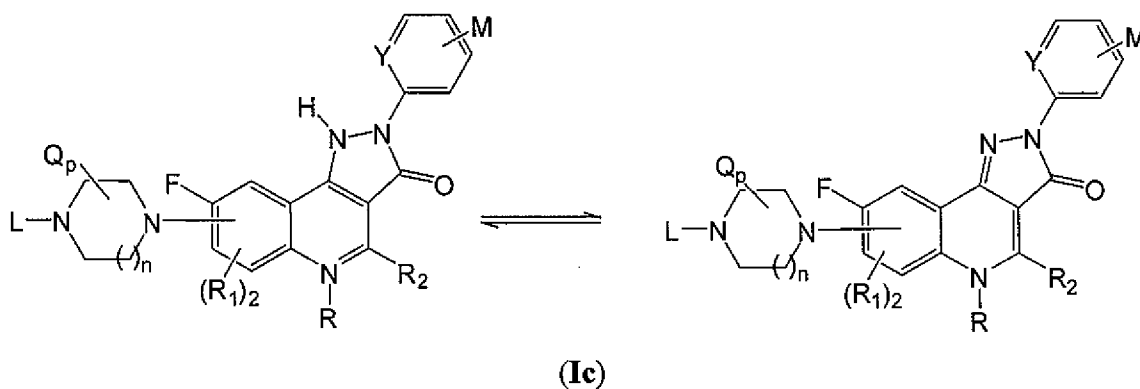
[0030] In another embodiment, the compound has the formula **Ib**:



(Ib)

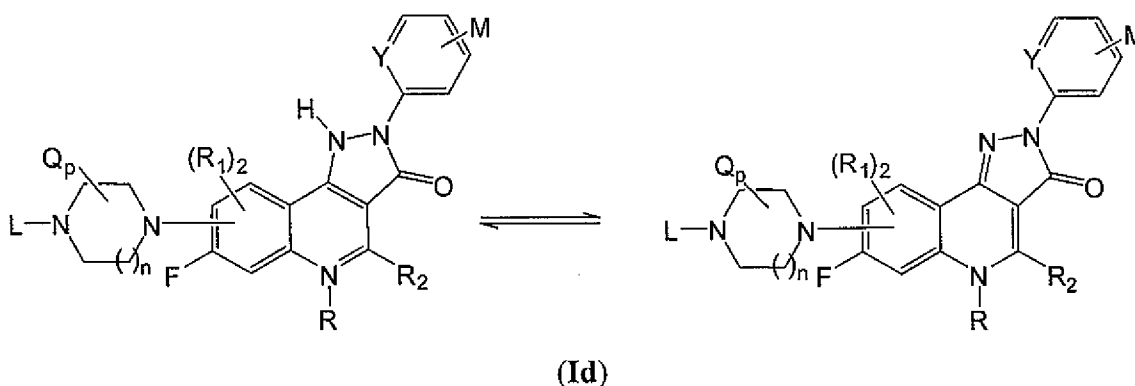
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0031] In another embodiment, the compound has the formula **Ic**:



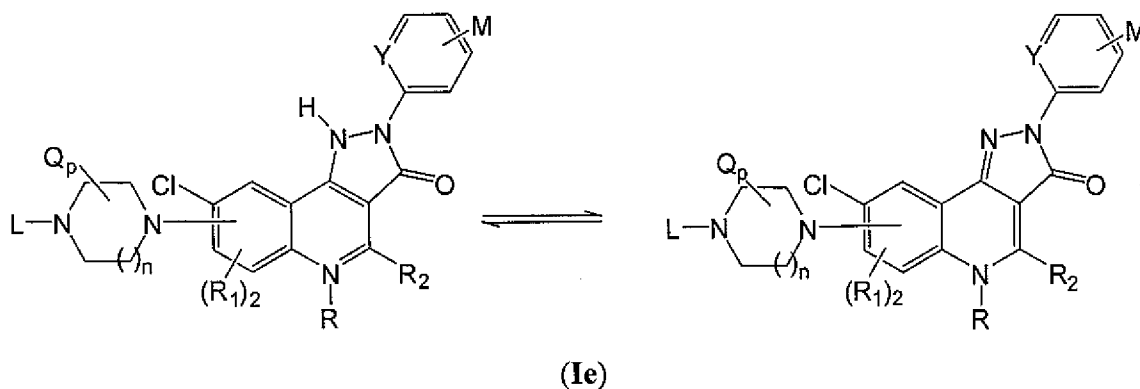
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0032] In another embodiment, the compound has the formula **Id**:



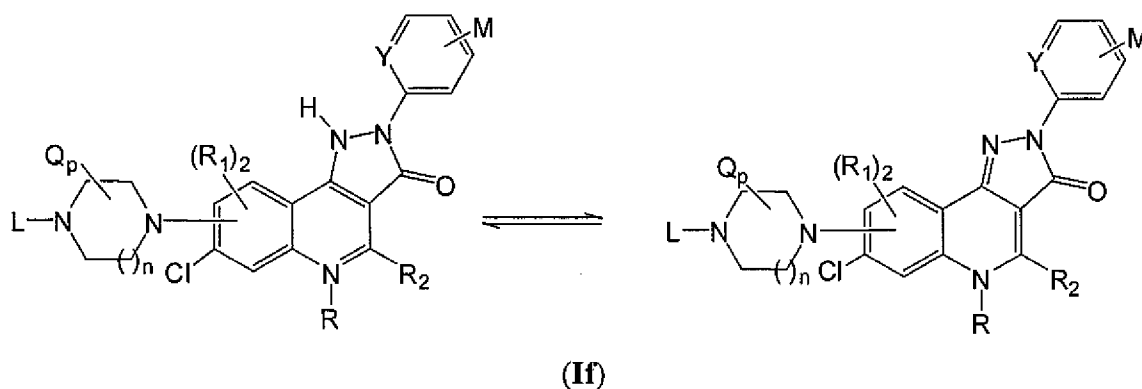
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0033] In another embodiment, the compound has the formula **Ie**:



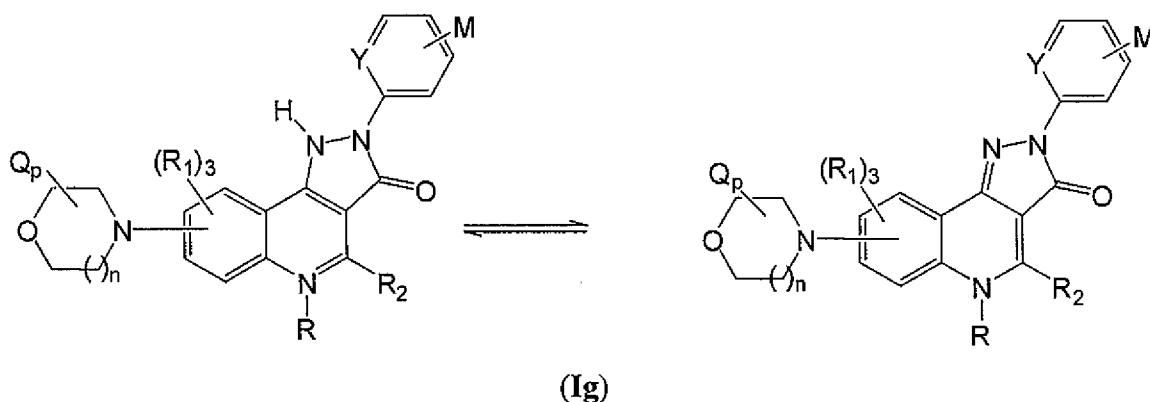
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0034] In another embodiment, the compound has the formula **If**:



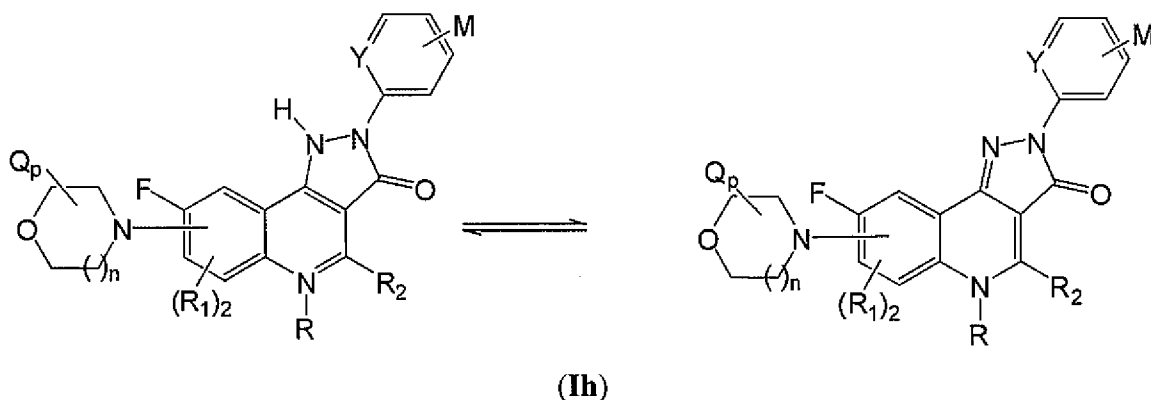
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0035] In another embodiment, the compound has the formula **Ig**:



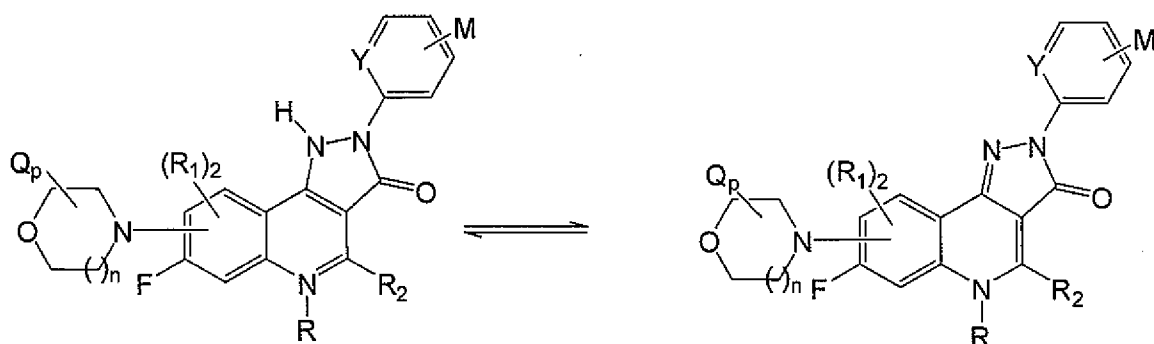
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0036] In another embodiment, the compound has the formula **Ih**:



or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

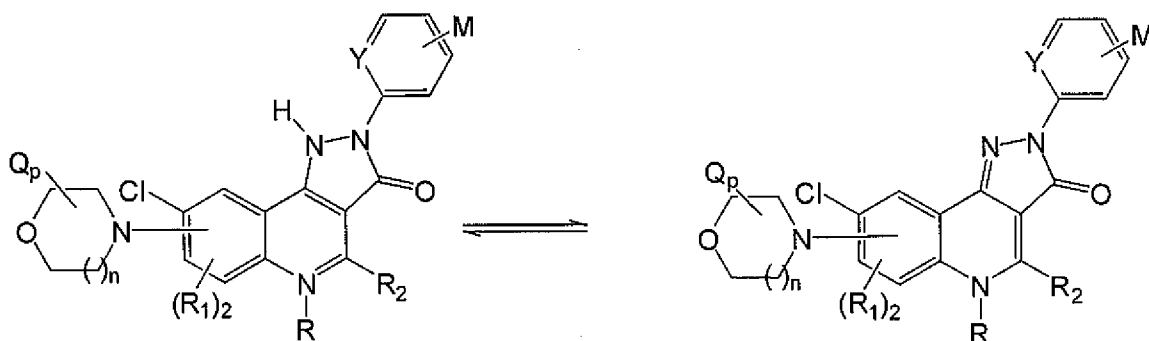
[0037] In another embodiment, the compound has the formula **Ii**:



(Ii)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

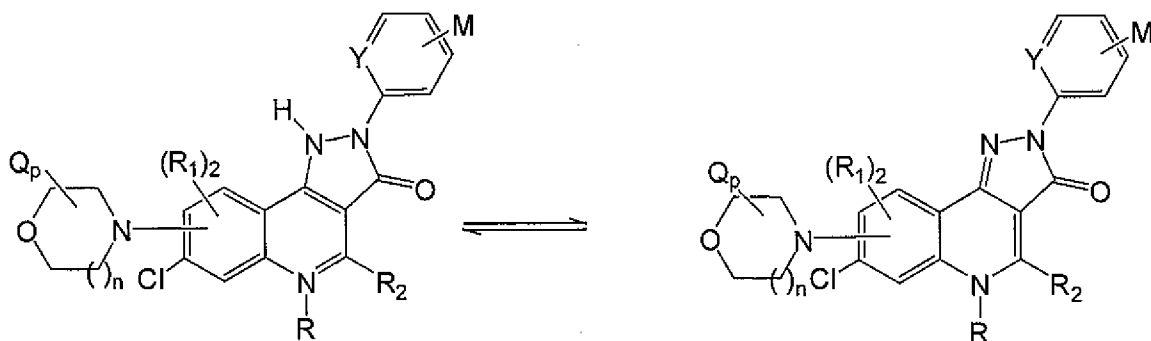
[0038] In another embodiment, the compound has the formula Ij:



(Ij)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

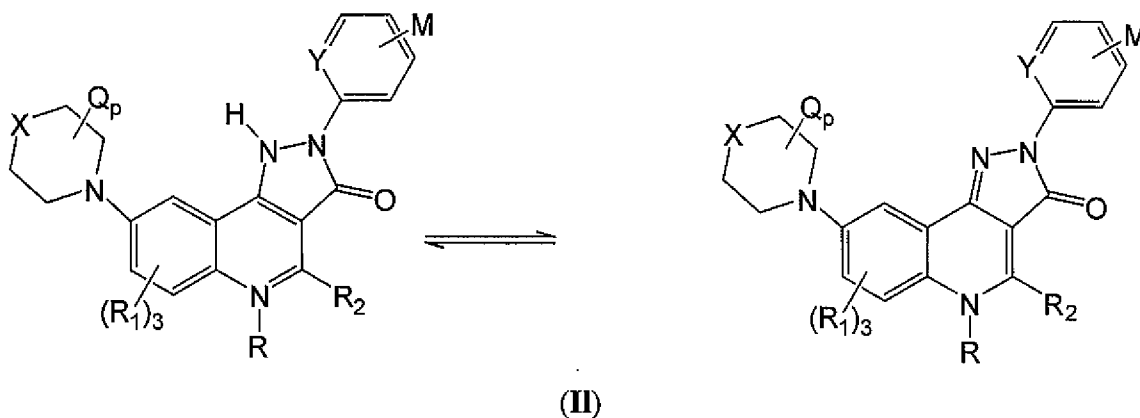
[0039] In another embodiment, the compound has the formula Ik:



(Ik)

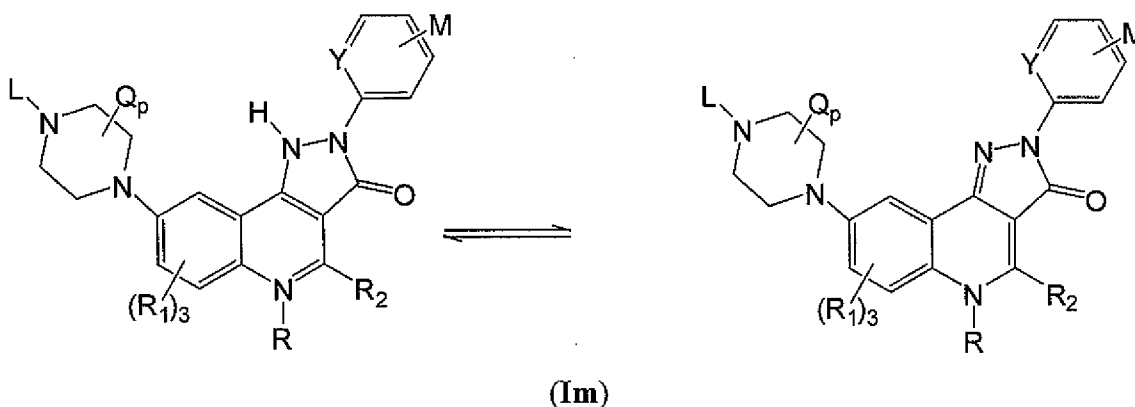
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0040] In another embodiment, the compound has the formula II:



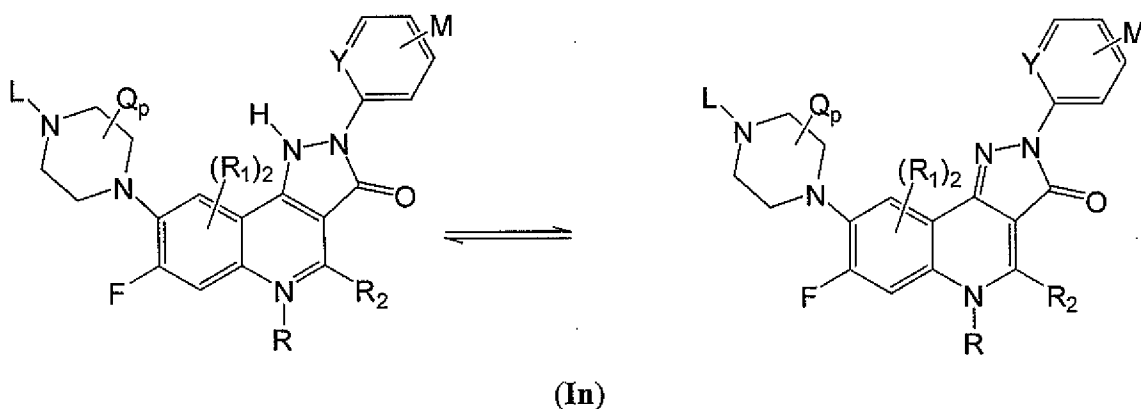
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0041] In another embodiment, the compound has the formula **Im**:



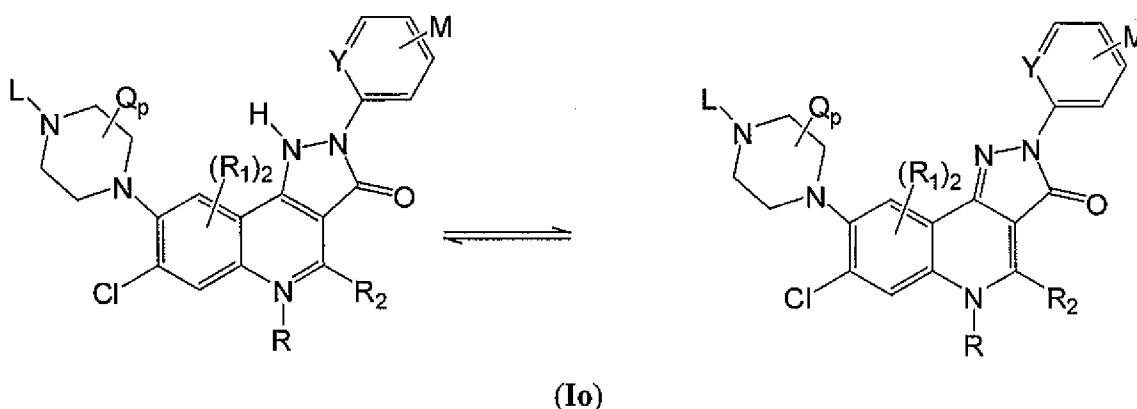
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0042] In another embodiment, the compound has the formula **In**:



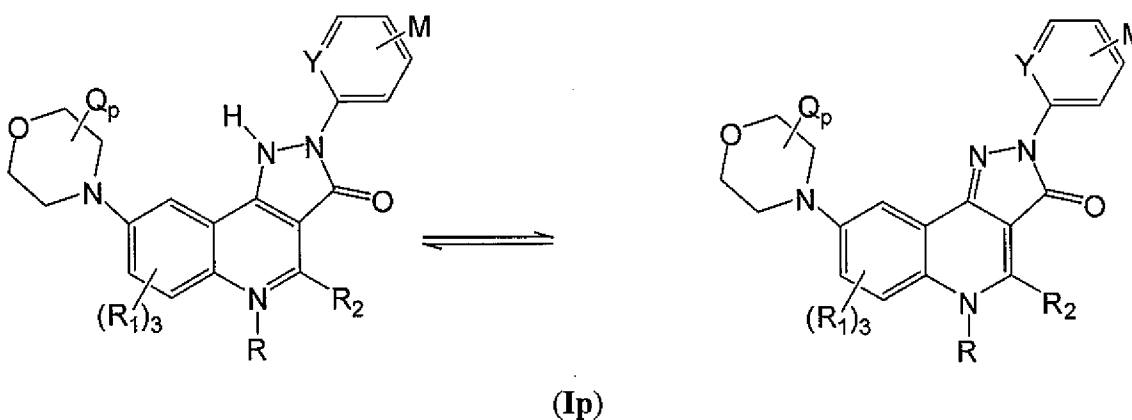
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0043] In another embodiment, the compound has the formula **Io**:



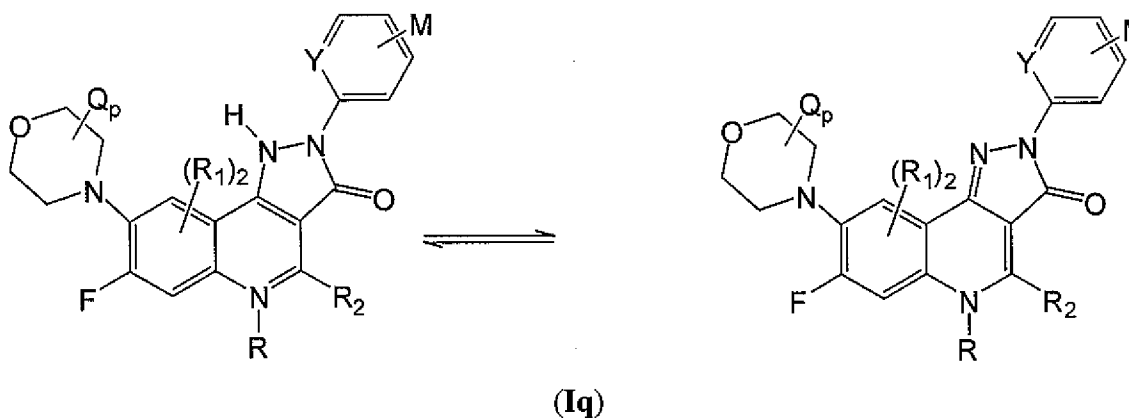
or tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

[0044] In another embodiment, the compound has the formula **Ip**:



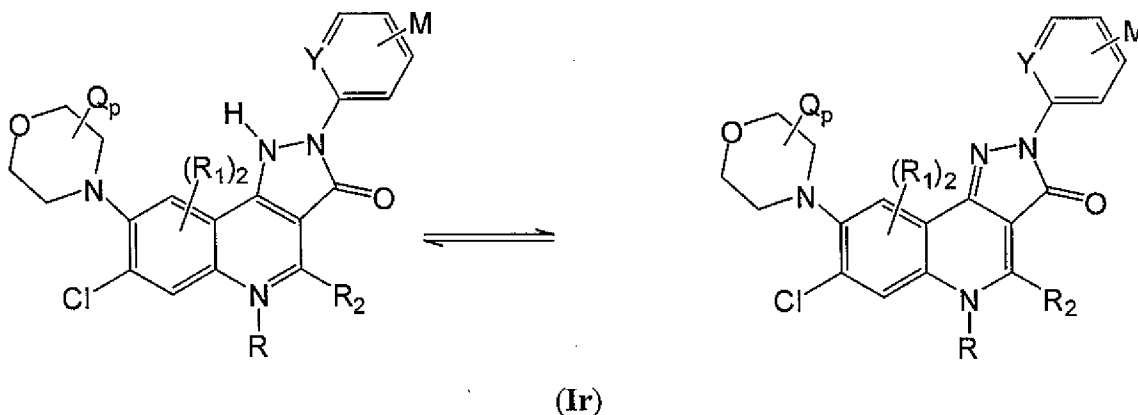
or tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

[0045] In another embodiment, the compound has the formula **Iq**:



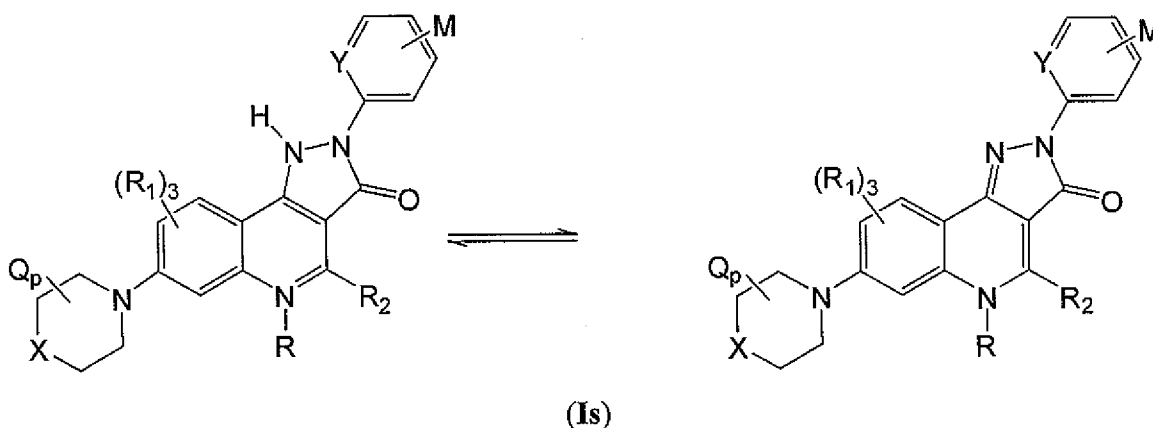
or tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

[0046] In another embodiment, the compound has the formula Ir:



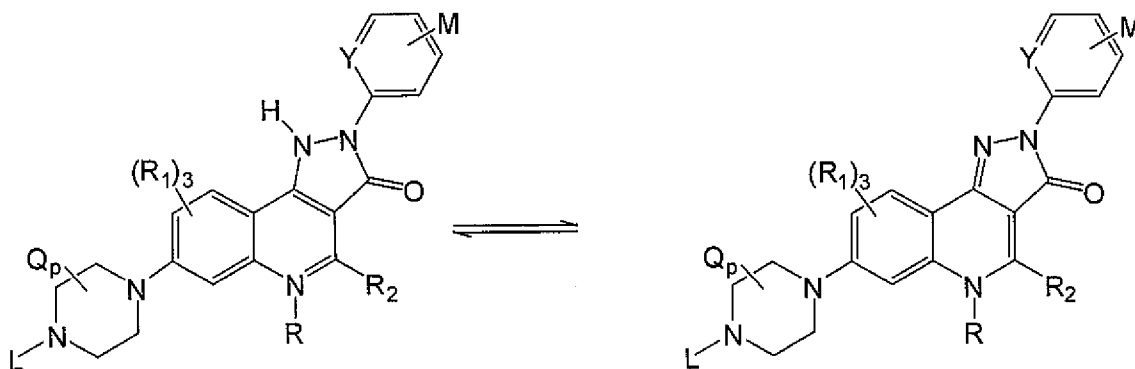
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0047] In another embodiment, the compound has the formula Is:



or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

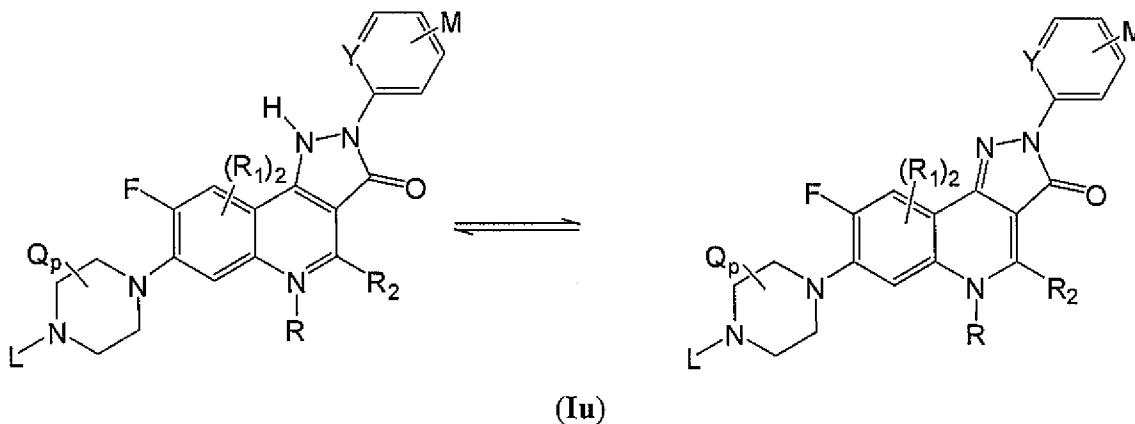
[0048] In another embodiment, the compound has the formula It:



(It)

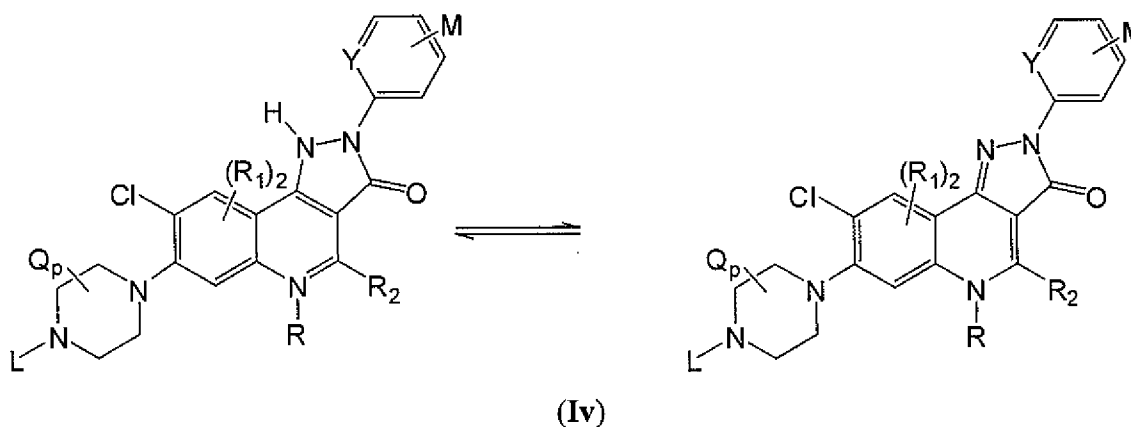
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0049] In another embodiment, the compound has the formula **Iu**:



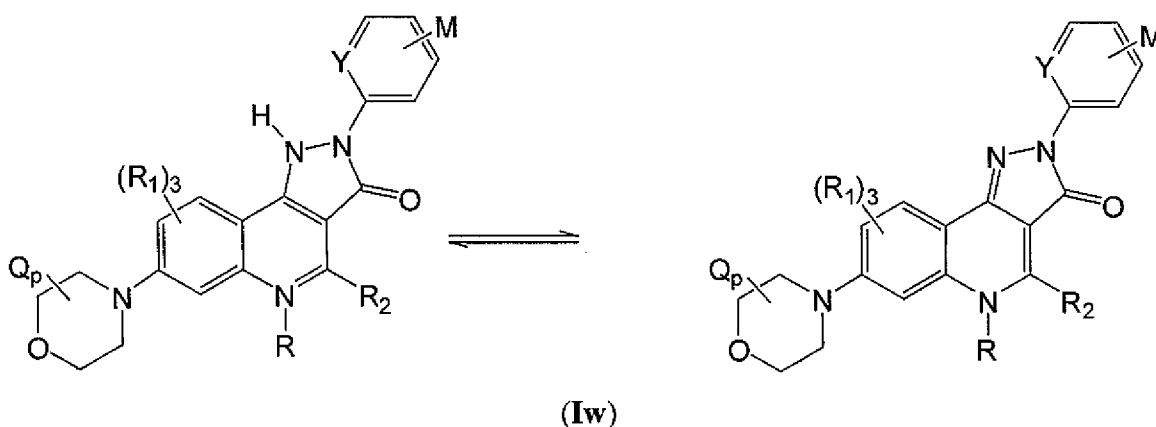
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0050] In another embodiment, the compound has the formula **Iv**:



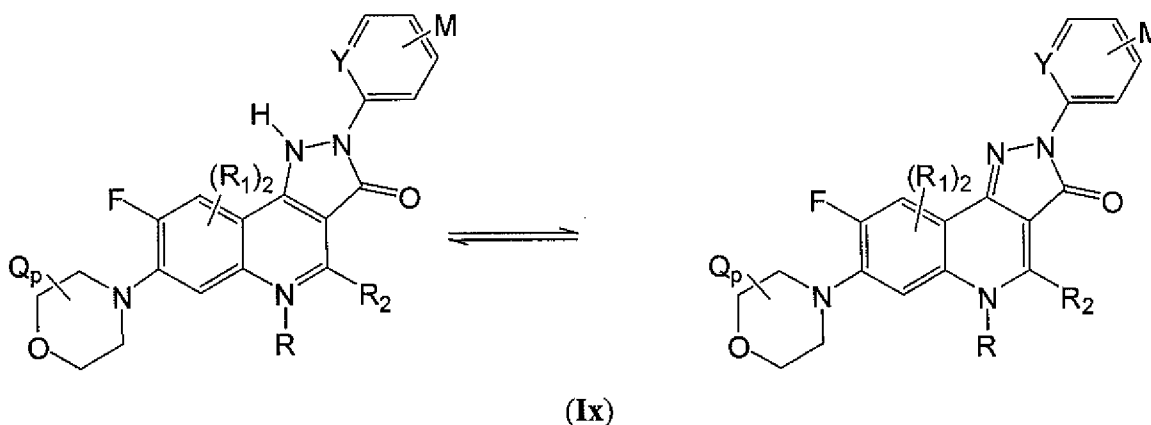
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0051] In another embodiment, the compound has the formula **Iw**:



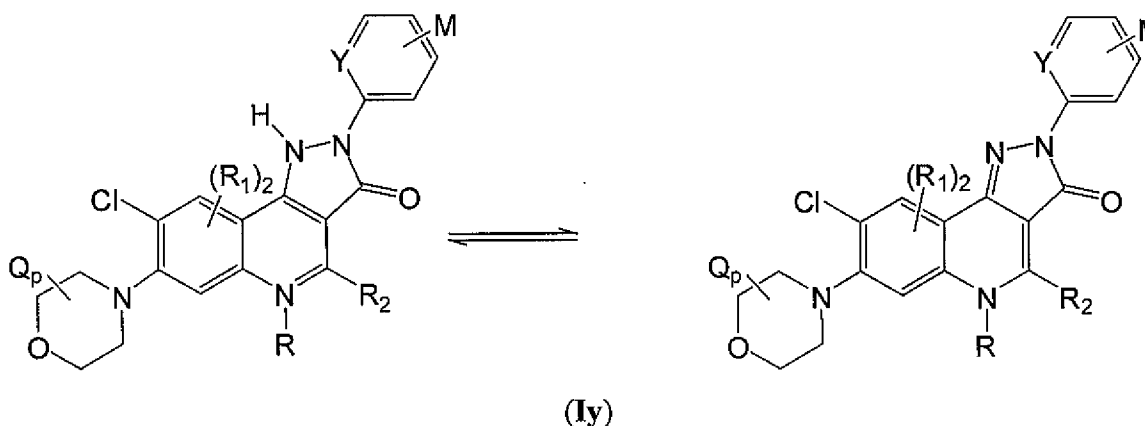
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0052] In another embodiment, the compound has the formula Ix:



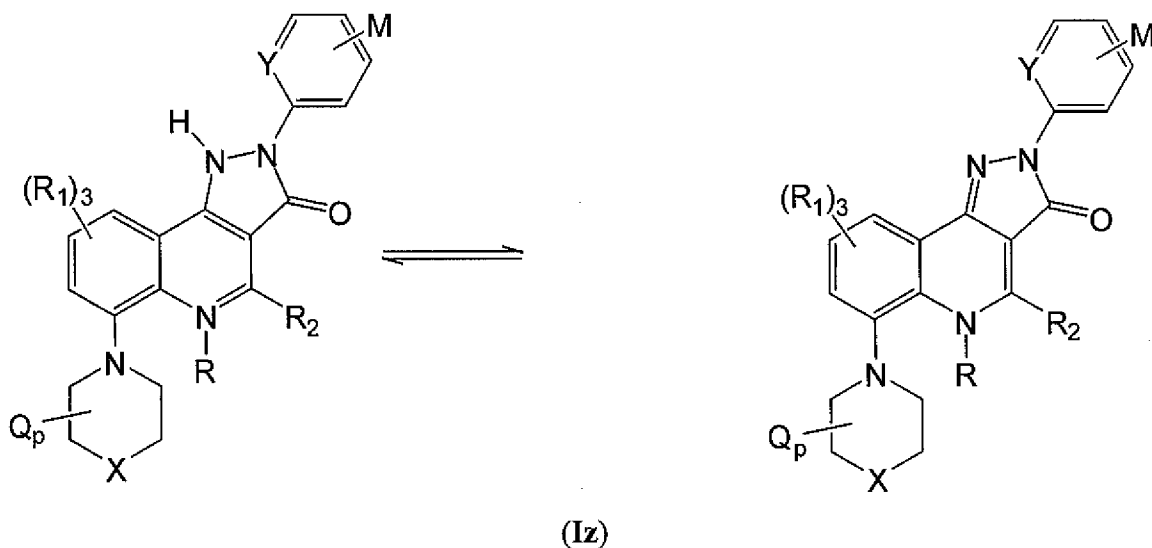
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0053] In another embodiment, the compound has the formula Iy:



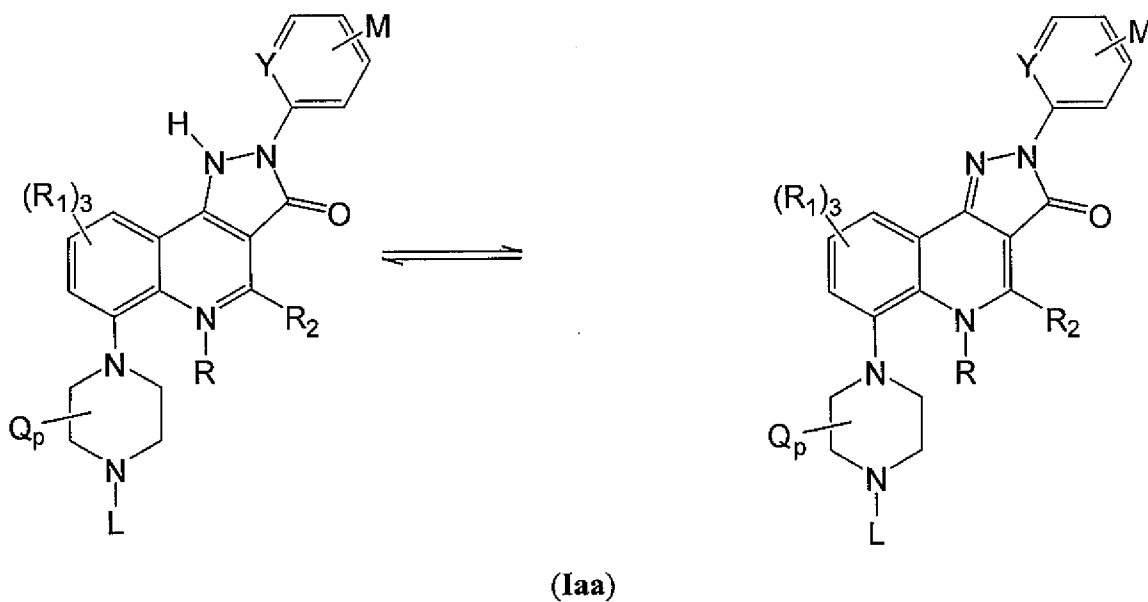
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

[0054] In another embodiment, the compound has the formula **Iz**:



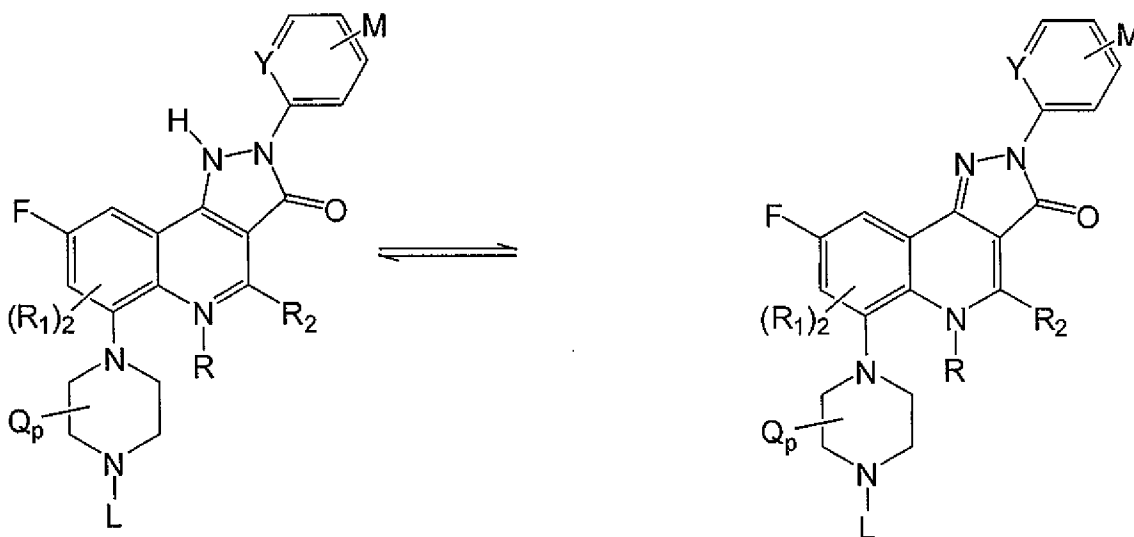
or tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

[0055] In another embodiment, the compound has the formula **Iaa**:



or tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

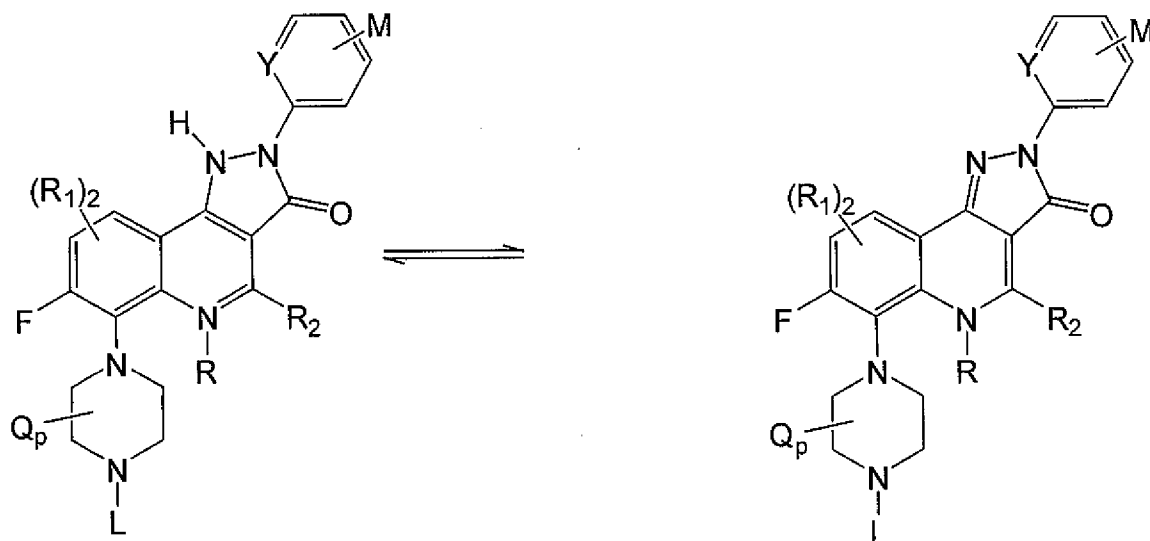
[0056] In another embodiment, the compound has the formula **Iab**:



(Iab)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

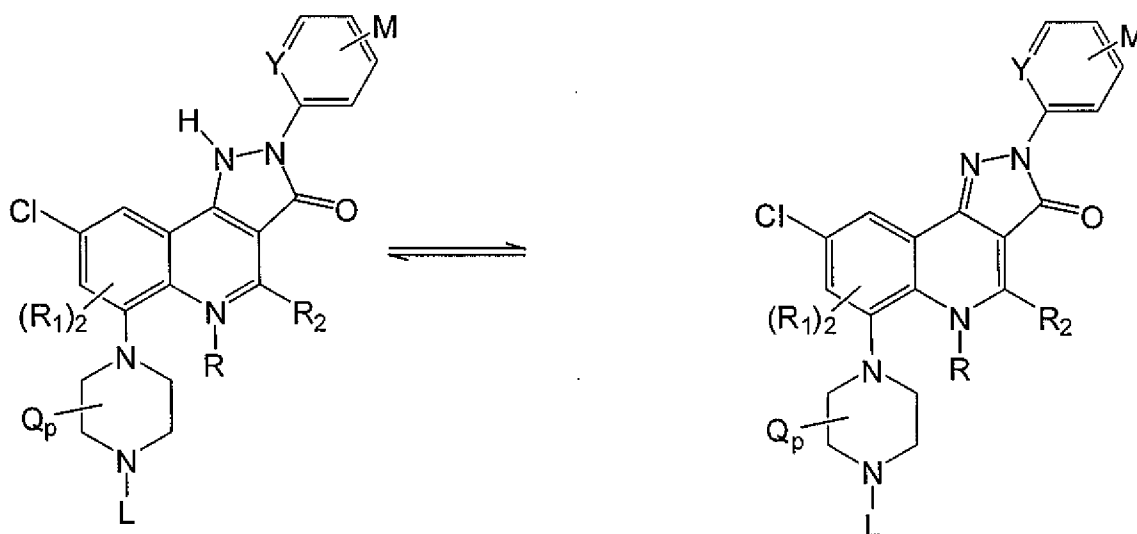
[0057] In another embodiment, the compound has the formula Iac:



(Iac)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

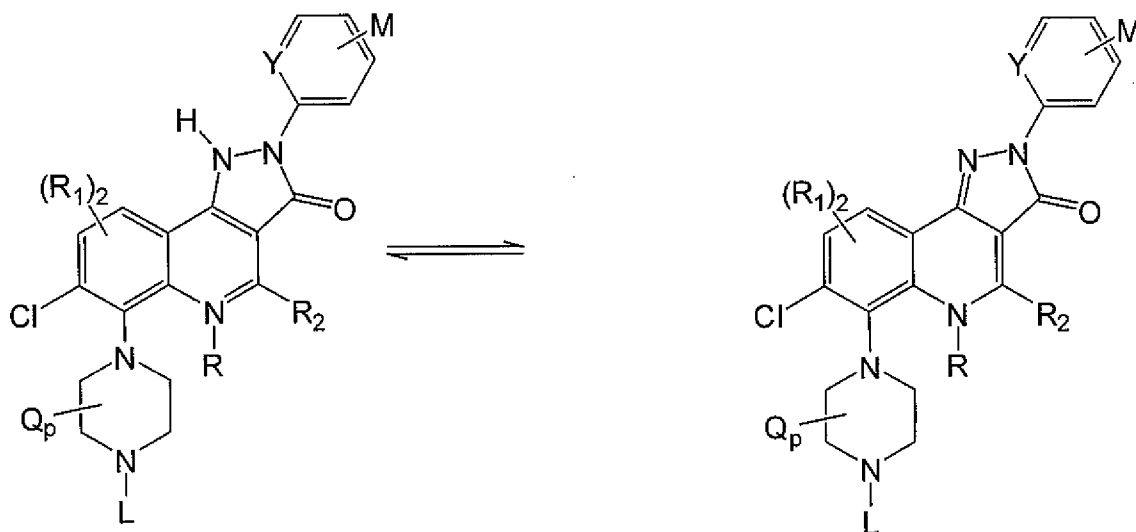
[0058] In another embodiment, the compound has the formula Iad:



(Iad)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

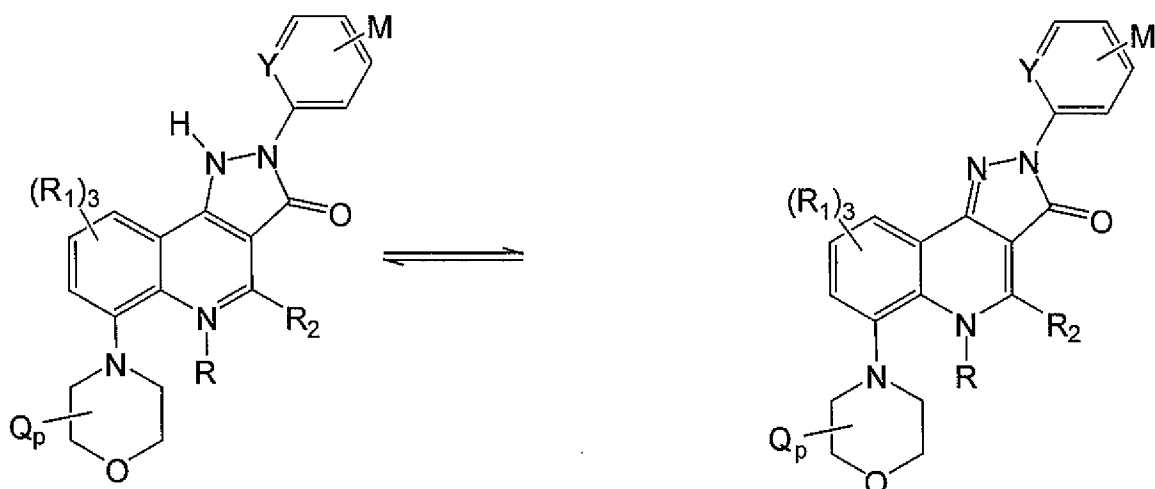
[0059] In another embodiment, the compound has the formula Iae:



(Iae)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

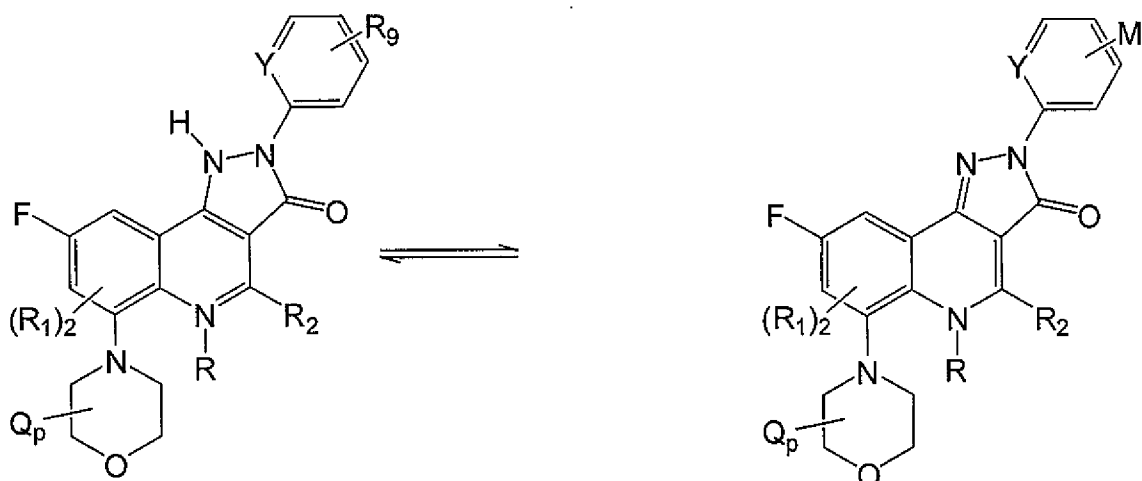
[0060] In another embodiment, the compound has the formula Iaf:



(Iaf)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

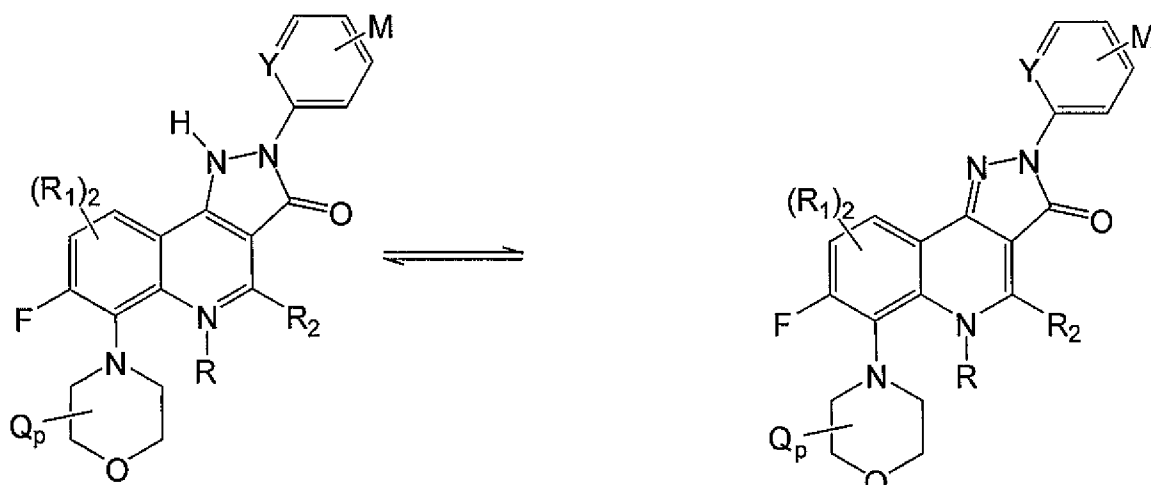
[0061] In another embodiment, the compound has the formula **Iag**:



(Iag)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

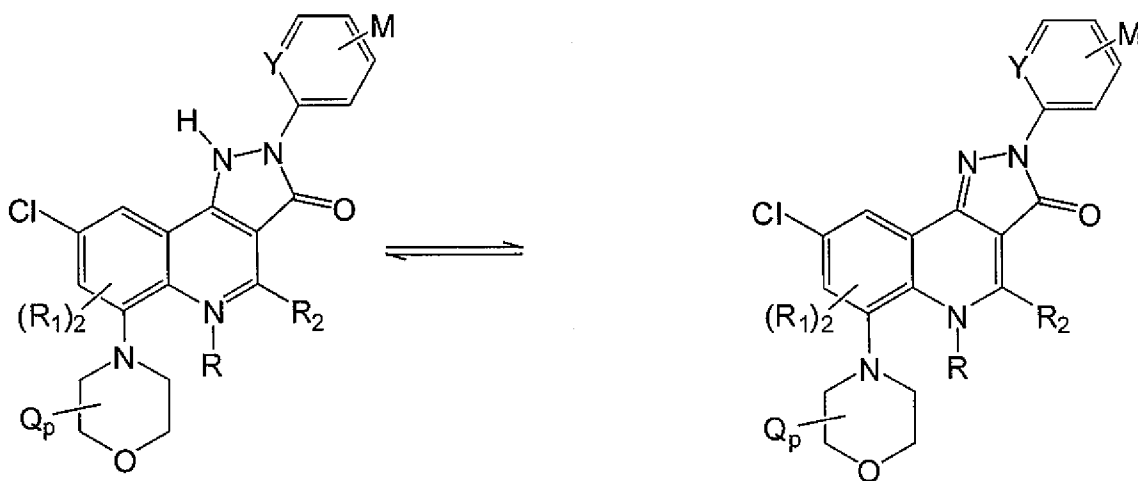
[0062] In another embodiment, the compound has the formula **Iah**:



(Iah)

or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

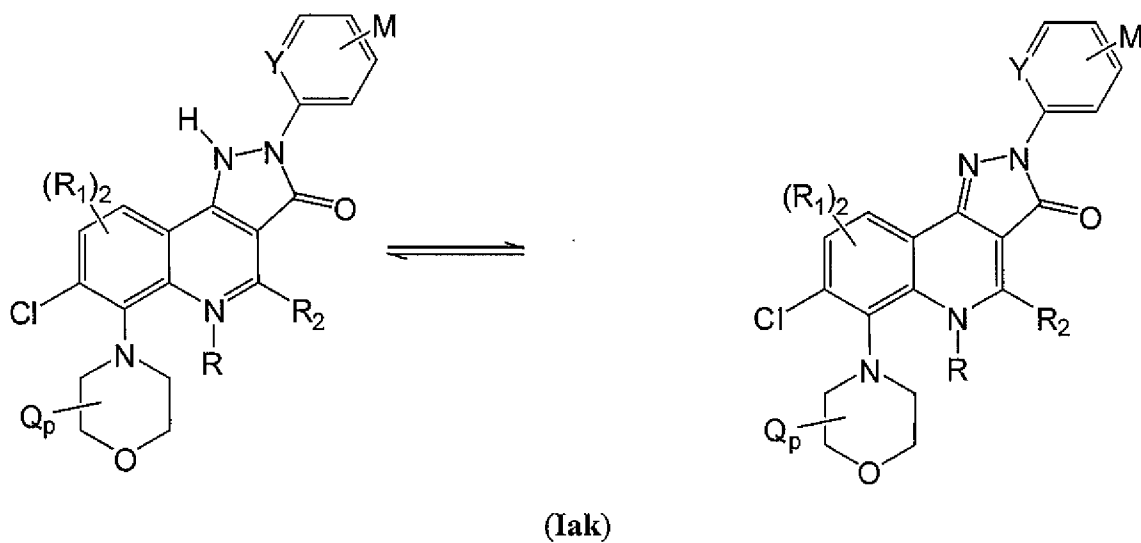
[0063] In another embodiment, the compound has the formula Iaj:



(Iaj)

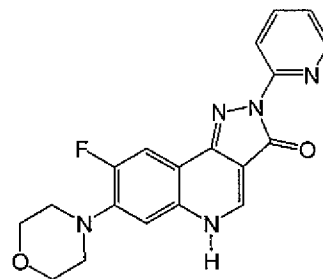
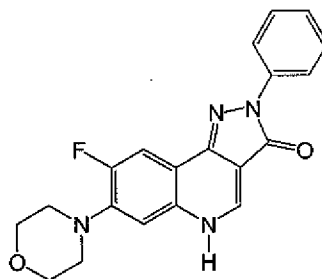
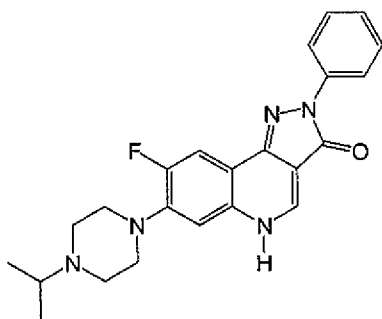
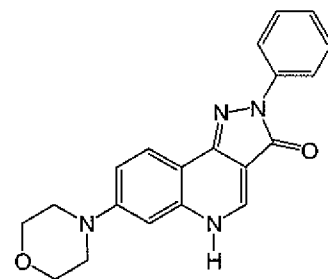
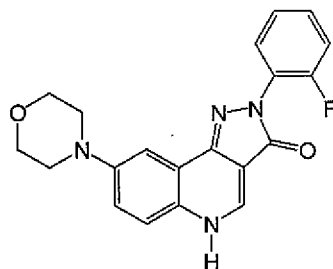
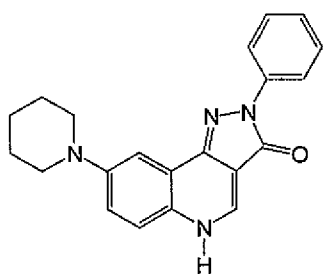
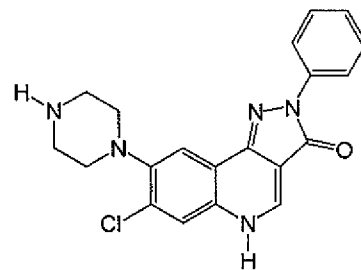
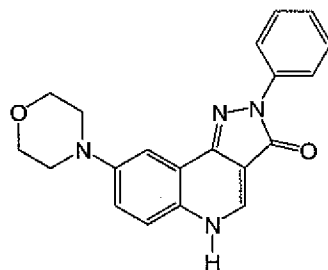
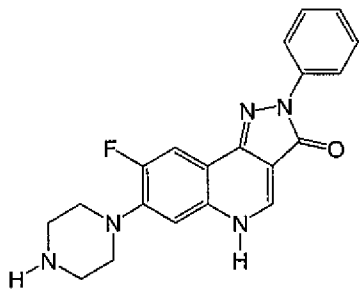
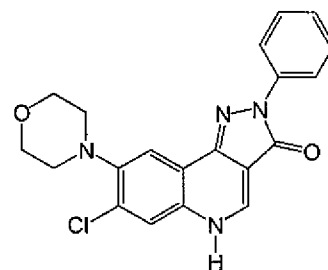
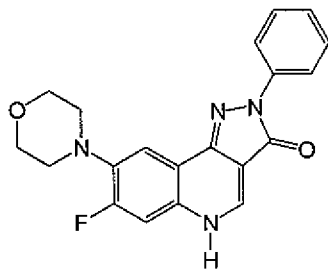
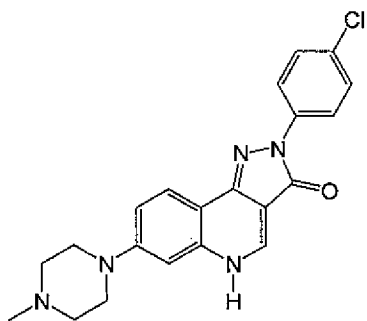
or tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

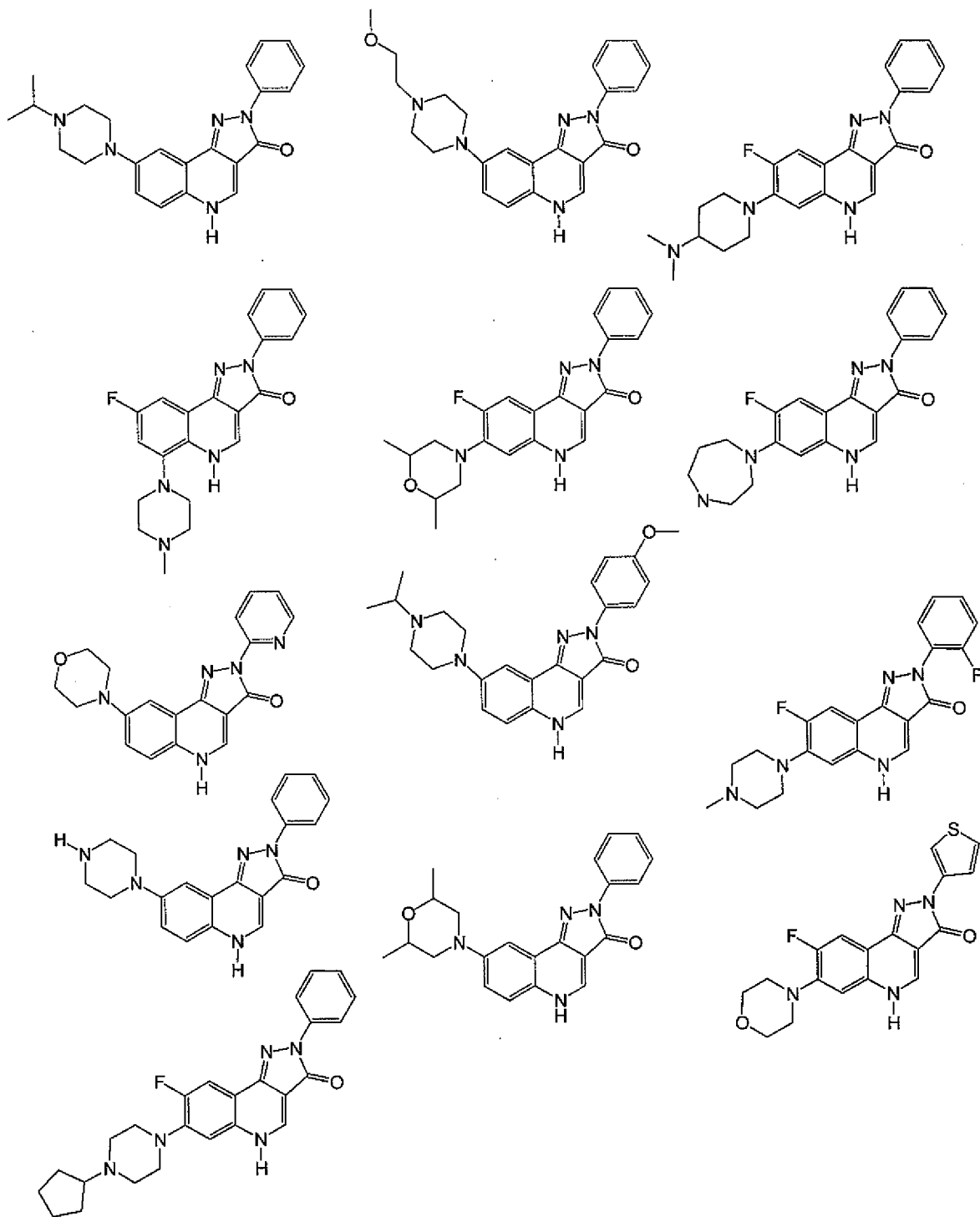
[0064] In another embodiment, the compound has the formula Iak:

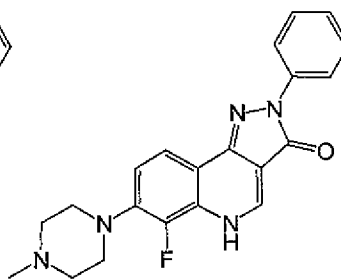
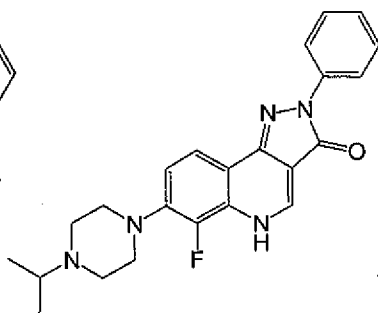
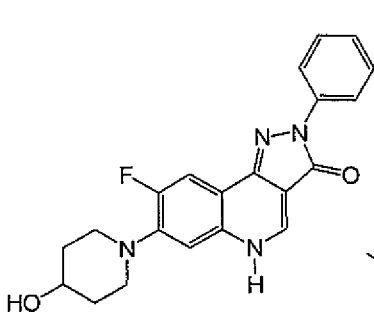
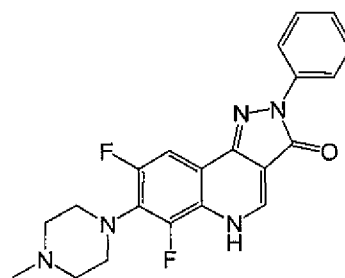
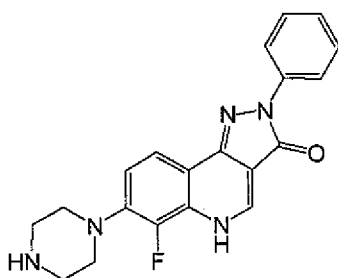
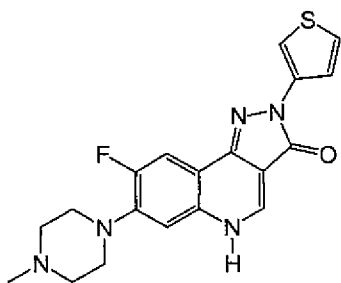
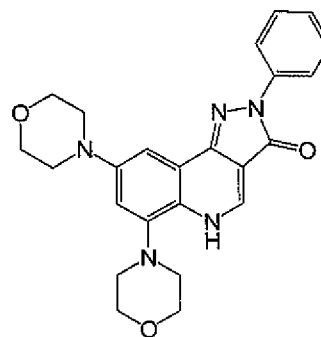
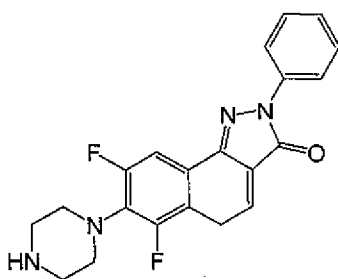
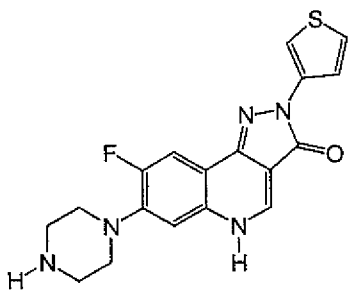
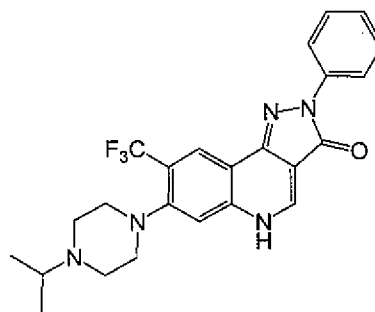
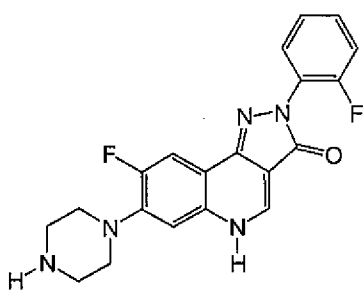
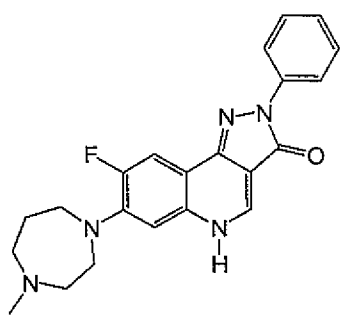


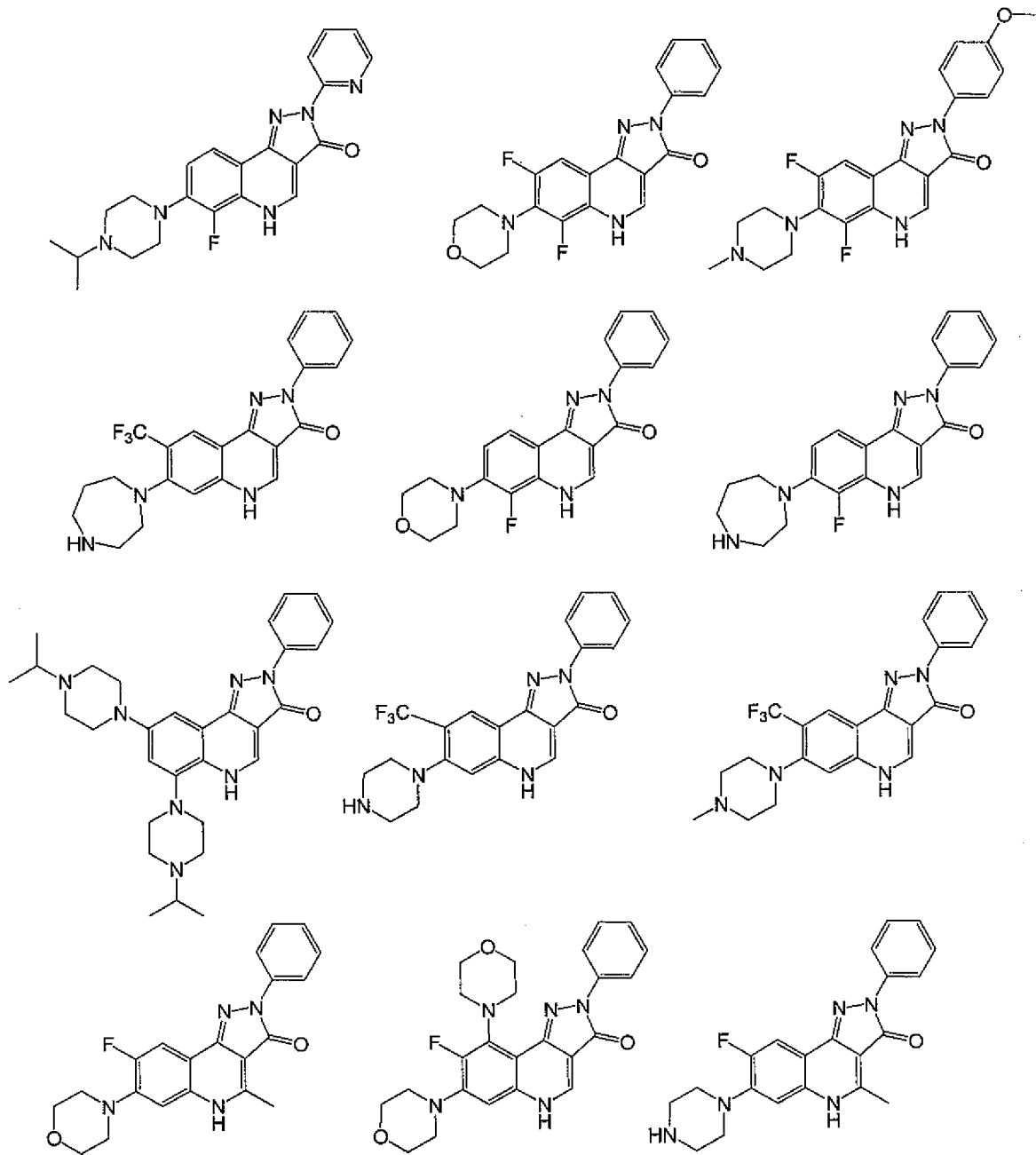
or tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

[0065] In another embodiment, the compound is selected from the group consisting of







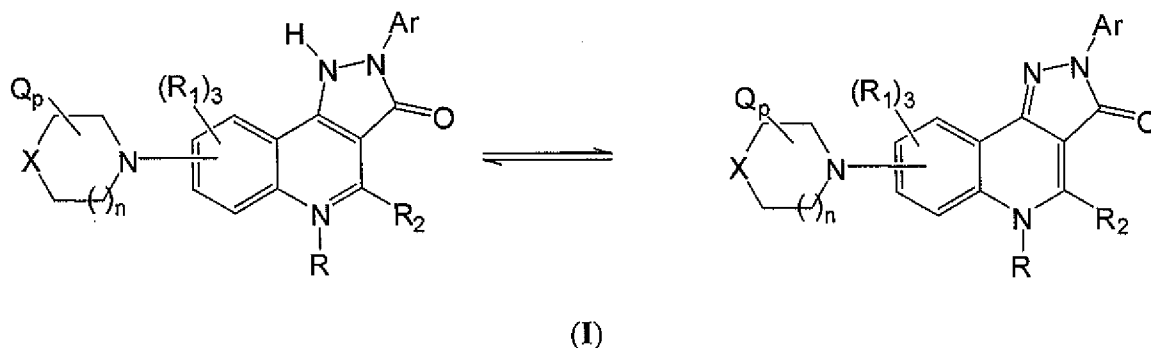


or tautomer thereof, or their pharmaceutically acceptable salts.

[0066] One embodiment of the invention provides a pharmaceutical composition comprising:

- a) the compound of any of the embodiments and examples disclosed herein; and
- b) a pharmaceutically acceptable carrier.

[0067] The present embodiments provide for a method of modulating one or more GABA_A subtypes in an animal comprising administering to the animal an effective amount of a compound, including enantiomers or diastereomers thereof, of formula (I):



or tautomer thereof, or their pharmaceutically acceptable salts,

[0068] **R** is absent, hydrogen, or oxide;

[0069] each **R**₁ is selected from the group consisting of hydrogen, hydroxy, halo, cyano, -CONR_aR_b, -NR_aR_b, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, amino(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

[0070] **R**₂ is selected from the group consisting of hydrogen, hydroxy, halo, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

[0071] each **R**_a and **R**_b is independently hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, (C₁-C₆)alkylaryl, -S(O)_z(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)(C₁-C₆)alkyl, -C(O)NR_g(C₁-C₆)alkyl, -C(O)NR_garyl, -C(O)O(C₁-C₆)alkyl, arylOC(O)- or arylC(O)-, or **R**_a together with **R**_b form a heterocycle group optionally substituted with one or more **R**_d; wherein the heterocycle group optionally include one or more groups selected from O (oxygen), S (sulfur), and NR_c;

[0072] each **R**_c is independently hydrogen, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -C(O)O(C₁-C₆)alkyl, -C(O)Oaryl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, arylO(C₁-C₆)alkyl, -C(O)NR_g(C₁-C₆)alkyl, -C(O)NR_garyl, -S(O)_z(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)(C₁-C₆)alkyl, arylC(O)-, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, or (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

[0073] each **R**_d is independently selected from the group consisting of hydrogen, halo, oxo, hydroxy, -C(O)NR_aR_b, -NR_aR_b, hydroxy(C₁-C₆)alkyl, aryl aryl(C₁-

C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro,;

[0074] each R_e and R_f is independently selected from hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, (C₁-C₆)alkylaryl, aryl(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl, -S(O)_z(C₁-C₆)alkyl, -S(O)_zNR_g(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)NR_g(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl, arylC(O)-, arylOC(O)-, or -C(O)O(C₁-C₆)alkyl;

[0075] R_g is hydrogen, aryl, heteroaryl, heterocycle or (C₁-C₆)alkyl optionally substituted with up to 5 fluoro;

[0076] Ar is aryl optionally substituted with one or more M or heteroaryl optionally substituted with one or more M;

[0077] each Q is independently hydrogen, halo, oxo, hydroxy, -C(O)NR_aR_b, -NR_aR_b, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro, (C₁-C₆)alkyl optionally substituted with one or more R_d, hydroxy(C₁-C₆)alkyl optionally substituted with one or more R_d, aryl optionally substituted with one or more R_d, or aryl(C₁-C₆)alkyl optionally substituted with one or more R_d;

[0078] each M is independently hydrogen, halo, CF₃, CF₂H, hydroxy, cyano, nitro, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy, -NR_aR_b, aryl, heteroaryl or heterocycle;

[0079] each X is independently NL, oxygen, C(Q)₂, or S(O)_z;

[0080] each L is independently hydrogen, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -C(O)O(C₁-C₆)alkyl, -C(O)Oaryl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, arylO(C₁-C₆)alkyl, -CONR_eR_f, -S(O)_z(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)(C₁-C₆)alkyl, arylC(O)-, -C(O)NR_g(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, or (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro,;

[0081] p is an integer selected from 0, 1, 2 and 3,

[0082] z is an integer selected from 0, 1, and 2; and

[0083] n is an integer selected from 0, 1, and 2.

[0084] In one embodiment of the method, the modulation is negative. In another embodiment, the modulation is positive. In one embodiment of the method, the GABA_A subtypes is GABA_A α5. In one embodiment of the method, the modulation is negative. In another embodiment, the modulation is positive.

[0085] Some embodiments disclosed herein relate to a method of treatment of a cognitive dysfunction in an animal comprising administering to the animal an effective amount of a compound of formula (I), and tautomers thereof, or their pharmaceutically acceptable salts, under conditions wherein the cognitive dysfunction is treated. In one embodiment, the animal is an aged animal. In another embodiment, the cognitive dysfunction is Alzheimer's disease, dementia or another neurodegenerative disease.

[0086] Some embodiments disclosed herein relate to a method of treatment of a psychiatric disorder in an animal comprising administering to the animal an effective amount of a compound of formula (I), and tautomers thereof, or their pharmaceutically acceptable salts, under conditions wherein the psychiatric disorder is treated.

[0087] Some embodiments disclosed herein relate to the use of a compound of formula (I), and tautomers thereof, or their pharmaceutically acceptable salts, for the manufacture of a medicament useful for modulation of one or more GABA_A subtypes in an animal. In one embodiment of the method, the modulation is negative. In another embodiment, the modulation is positive. In one embodiment of the method, the GABA_A subtypes is GABA_A α 5. In one embodiment of the method, the modulation is negative. In another embodiment, the modulation is positive.

[0088] Some embodiments disclosed herein relate to the use of a compound of formula (I), and tautomers thereof, or their pharmaceutically acceptable salts, for the manufacture of a medicament useful for treatment of a cognitive dysfunction in an animal. In one embodiment, the animal is a healthy animal. In another embodiment, the animal is an aged animal. In another embodiment, the cognitive dysfunction is Alzheimer's disease, dementia or another neurodegenerative disease.

[0089] Some embodiments disclosed herein relate to the use of a compound of formula (I), and tautomers thereof, or their pharmaceutically acceptable salts, for the manufacture of a medicament useful for treatment of psychiatric disorders in an animal. In one embodiment the psychiatric disorder is an anxiety disorder, sleep disorder, depression, or schizophrenia.

[0090] Some embodiments disclosed herein relate to the use of a compound of formula (I), and tautomers thereof, or their pharmaceutically acceptable salts, for the manufacture of a medicament useful for treatment of disorders ameliorated by modulation

of GABA_A α subunits other than α 5 in an animal. In one embodiment, the modulation is positive. In another embodiment, the modulation is negative.

[0091] Some embodiments disclosed herein relate to a method for treating cognitive impairment resulting from diseases such as schizophrenia, Alzheimer's, Parkinson's, Pick's, Huntington's, and Creutzfeld-Jakob along with other forms of dementia, MCI, AAMI, and delirium.

[0092] One embodiment provides the use of compounds not specifically inverse agonists of α 5 for other CNS disorders, such as anxiety.

[0093] Some embodiments disclosed herein relate to a method of increasing cognitive function in an animal comprising administering to the animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, under conditions wherein memory is increased. In one embodiment, the animal is healthy. In one embodiment, the memory is long term memory. In one embodiment, the memory is short term memory.

[0094] Some embodiments disclosed herein relate to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for increasing cognitive function in an animal wherein the GABA_A α 5 subtype in the animal is negatively modulated. In one embodiment, the animal is healthy. In one embodiment, the memory is long term memory. In one embodiment, the memory is short term memory.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0095]	As used herein, common organic abbreviations are defined as follows:	
[0096]	Ac	Acetyl
[0097]	aq.	Aqueous
[0098]	Bu	n-Butyl
[0099]	cat.	Catalytic
[0100]	CDI	1,1'-carbonyldiimidazole
[0101]	°C	Temperature in degrees Centigrade

[0102]	Dowtherm®	eutectic mixture of diphenyl ether and biphenyl
[0103]	DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
[0104]	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
[0105]	DIEA	Diisopropylethylamine
[0106]	DMA	Dimethylacetamide
[0107]	DMF	N,N'-Dimethylformamide
[0108]	DMSO	Dimethylsulfoxide
[0109]	Et	Ethyl
[0110]	g	Gram(s)
[0111]	h	Hour (hours)
[0112]	HPLC	High performance liquid chromatography
[0113]	iPr or isopr	Isopropyl
[0114]	LCMS	Liquid chromatography-mass spectrometry
[0115]	Me	Methyl
[0116]	MeOH	Methanol
[0117]	mL	Milliliter(s)
[0118]	Pd/C	Palladium on activated carbon
[0119]	ppt	Precipitate
[0120]	rt	Room temperature
[0121]	TEA	Triethylamine
[0122]	Tert, t	tertiary
[0123]	μL	Microliter(s)

[0124] The term “halo” used herein refers to fluoro, chloro, bromo, or iodo.

[0125] As used herein, the term “alkyl” refers to an aliphatic hydrocarbon group. The alkyl moiety may be a “saturated alkyl” group, which means that it does not contain any alkene or alkyne moieties. An “alkene” moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an “alkyne” moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety may be branched, straight chain, or cyclic. Examples of branched alkyl groups include, but are not limited to, isopropyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to,

methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and the like. Examples of cyclic alkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

[0126] The term “alkoxy” used herein refers to straight or branched chain alkyl radical covalently bonded to the parent molecule through an --O-- linkage. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, n-butoxy, sec-butoxy, t-butoxy and the like.

[0127] The term “alkenyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon double bond including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

[0128] The term “alkynyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond including, but not limited to, 1-propynyl, 1-butyne, 2-butyne, and the like.

[0129] The term “aryl” used herein refers to homocyclic aromatic radical whether one ring or multiple fused rings. Moreover, the term “aryl” includes fused ring systems wherein at least two aryl rings, or at least one aryl and an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic share at least one chemical bond. Examples of “aryl” rings include, but are not limited to, optionally substituted phenyl, biphenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl.

[0130] The term, “heterocycle” or “heterocycle group” used herein refers to an optionally substituted monocyclic, bicyclic, or tricyclic ring system comprising at least one heteroatom in the ring system backbone. The heteroatoms are independently selected from oxygen, sulfur, and nitrogen. The term, “heterocycle” includes multiple fused ring systems. Moreover, the term “heterocycle” includes fused ring systems that may have any degree of saturation provided that at least one ring in the ring system is not aromatic. The monocyclic, bicyclic, or tricyclic ring system may be substituted or unsubstituted, and can be attached to other groups via any available valence, preferably any available carbon or nitrogen. Preferred monocyclic ring systems are of 4, 5, 6, 7, or 8 members. Six membered monocyclic rings contain from up to three heteroatoms wherein each heteroatom is

individually selected from oxygen, sulfur, and nitrogen, and wherein when the ring is five membered, preferably it has one or two heteroatoms wherein each heteroatom is individually selected from oxygen, sulfur, and nitrogen. Preferred bicyclic cyclic ring systems are of 8 to 12 members and include spirocycles.

[0131] The term “heteroaryl” used herein refers to an aromatic heterocyclic group, whether one ring or multiple fused rings. In fused ring systems, the one or more heteroatoms may be present in only one of the rings. Examples of heteroaryl groups include, but are not limited to, benzothiazyl, benzoxazolyl, quinazoliny, quinoliny, isoquinoliny, quinoxaliny, pyridyl, pyrrolyl, oxazolyl, indolyl, thienyl and the like. The term “heterocycle” encompasses heteroaryl fused to a non-aromatic ring system.

[0132] The term “heteroatom” used herein refers to, for example, oxygen, sulfur and nitrogen.

[0133] The term “amino” used herein refers to a nitrogen radical substituted with hydrogen, alkyl, aryl, or combinations thereof. Examples of amino groups include, but are not limited to, -NHMethyl, -NH₂, -NMethyl₂, -NPhenylMethyl, -NHPhenyl, -NEthylMethyl, and the like.

[0134] The term “arylalkyl” used herein refers to one or more aryl groups appended to an alkyl radical. Examples of arylalkyl groups include, but are not limited to, benzyl, phenethyl, phenpropyl, phenbutyl, and the like.

[0135] The term “heteroarylalkyl” used herein refers to one or more heteroaryl groups appended to an alkyl radical. Examples of heteroarylalkyl include, but are not limited to, pyridylmethyl, furanylmethyl, thiophenylethyl, and the like.

[0136] The term “aryloxy” used herein refers to an aryl radical covalently bonded to the parent molecule through an --O-- linkage.

[0137] The term “alkylthio” used herein refers to straight or branched chain alkyl radical covalently bonded to the parent molecule through an --S-- linkage. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, n-butoxy, sec-butoxy, t-butoxy and the like.

[0138] The term “carbonyl” used herein refers to C=O (i.e. carbon double bonded to oxygen).

[0139] The term “oxo” used herein refers to =O (i.e. double bond to oxygen). For example, cyclohexane substituted with “oxo” is cyclohexanone.

[0140] The term “alkanoyl” used herein refers to a “carbonyl” substituted with an “alkyl” group, the “alkanoyl” group is covalently bonded to the parent molecule through the carbon of the “carbonyl” group. Examples of alkanoyl groups include, but are not limited to, methanoyl, ethanoyl, propanoyl, and the like. Methanoyl is commonly known as acetyl.

[0141] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term “radical” can be used interchangeably with the term “group.”

[0142] As used herein, a substituted group is derived from the unsubstituted parent structure in which there has been an exchange of one or more hydrogen atoms for another atom or group.

[0143] Asymmetric carbon atoms may be present in the compounds described. All such isomers, including diastereomers and enantiomers, as well as the mixtures thereof are intended to be included in the scope of the recited compound. In certain cases, compounds can exist in tautomeric forms. All tautomeric forms are intended to be included in the scope. Likewise, when compounds contain an alkenyl or alkenylene group, there exists the possibility of cis- and trans- isomeric forms of the compounds. Both cis- and trans- isomers, as well as the mixtures of cis- and trans- isomers, are contemplated. Thus, reference herein to a compound includes all of the aforementioned isomeric forms unless the context clearly dictates otherwise.

[0144] Various forms are included in the embodiments, including polymorphs, solvates, hydrates, conformers, salts, and prodrug derivatives. A polymorph is a composition having the same chemical formula, but a different structure. A solvate is a composition formed by solvation (the combination of solvent molecules with molecules or ions of the solute). A hydrate is a compound formed by an incorporation of water. A conformer is a structure that is a conformational isomer. Conformational isomerism is the phenomenon of molecules with the same structural formula but different conformations

(conformers) of atoms about a rotating bond. Salts of compounds can be prepared by methods known to those skilled in the art. For example, salts of compounds can be prepared by reacting the appropriate base or acid with a stoichiometric equivalent of the compound.

[0145] The term "animal" as used herein includes birds, reptiles, and mammals (e.g. domesticated mammals and humans).

[0146] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, murines, simians, humans, mammalian farm animals, mammalian sport animals, and mammalian pets.

Exemplified Embodiments

[0147] In an exemplified embodiment of the invention, the compound of formula (I) is a compound of any of the formulae **Ia-Iak**.

[0148] Exemplified values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

[0149] An exemplified value for **Ar** is phenyl, 4-chlorophenyl, 4-methoxyphenyl, 2-fluorophenyl, or 2-pyridyl.

[0150] An exemplified value for **X** is carbon, oxygen, or nitrogen.

[0151] An exemplified value of **n** is 1.

[0152] An exemplified value for **L** is hydrogen, methyl, isopropyl, or 2-methoxyethyl.

[0153] An exemplified value for **Q** is hydrogen, and methyl.

Process of Preparation

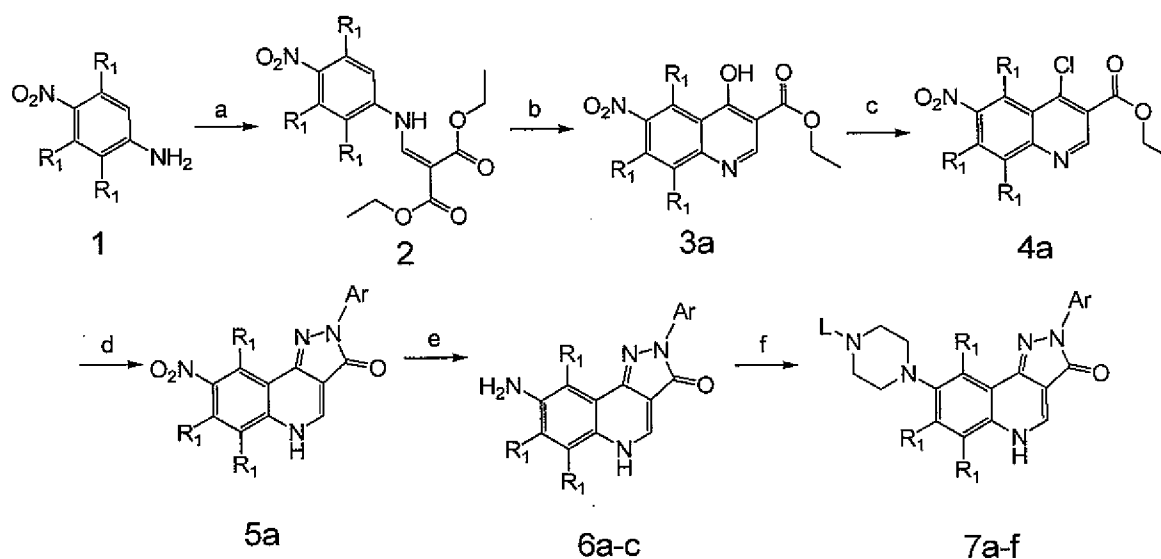
[0154] Processes for preparing compounds of formula (I) are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified.

[0155] Compounds of the general formula (I) can be prepared using a number of general synthetic approaches, as illustrated below in Schemes 1-7. In one example,

shown in Scheme 1, a 4-hydroxy-6-nitroquinoline of formula 3 is prepared by reacting aniline 1 with diethyl 2-(ethoxymethylene)malonate. Compound 3 is converted to the 4-chloro-6-nitroquinoline 4 by reaction with oxalyl chloride. The pyrazoloquinoline 5 is formed by reaction of 4 with aryl hydrazines. Conversion to the final product is accomplished by reduction of the 8-nitro group and reaction of resulting free amine with an appropriately N-substituted bis(chloroethyl)amine. The other approaches, shown in schemes 2-14, use methods common to those skilled in the art.

[0156] It will be understood by those of skill in the art that depicted structures that can exist in other isomeric forms, either by tautomerization or via sigmatropic rearrangements, encompass said isomeric forms.

Scheme 1: General Reaction Scheme to 8-(Piperazin-1-yl)-pyrazoloquinoline

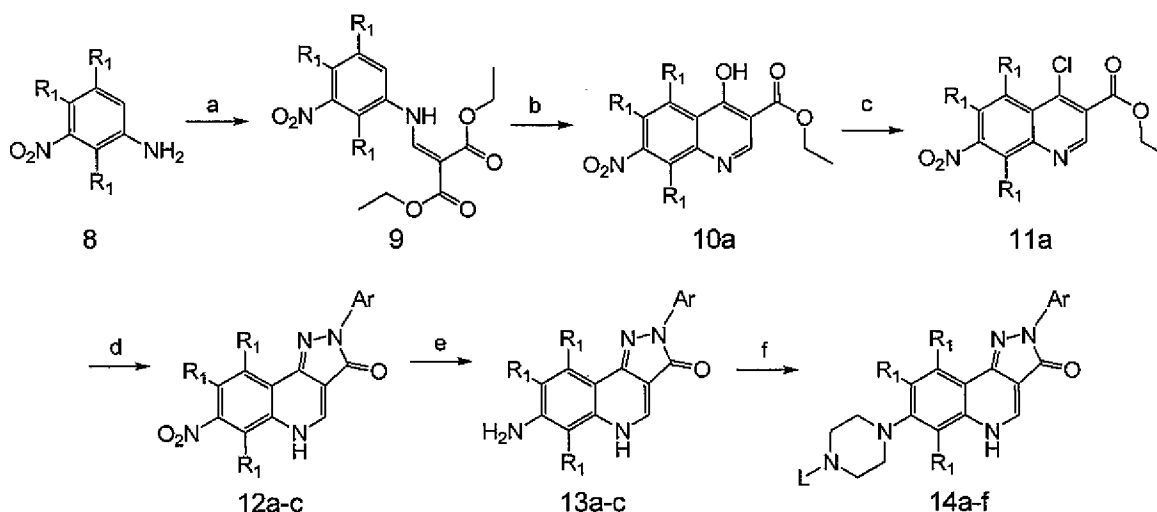


a) 1 equiv. diethyl 2-(ethoxymethylene)malonate, 125 °C, 3 hrs, b) Ph₂O, reflux, 30 min-3 hrs, c) 4 equiv. oxalyl chloride, cat. DMF, CHCl₃, reflux, 3 hrs, d) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs. e) SnCl₂, methanol, reflux, 12 hrs. f) bis(chloroethyl)NL·HCl, chlorobenzene, reflux, 72 hrs.

[0157] General Reaction Scheme 1 shows a representative synthetic method for the synthesis of 8-(Piperazin-1-yl)-pyrazoloquinoline. The 4-nitro-aniline of Formula 1 can be reacted with diethyl 2-(ethoxymethylene)malonate under heating to afford, in an addition-elimination type reaction, the 4-nitro-enamine of Formula 2. Thermal cyclization of the compound of Formula 2 provides the hydroxyquinoline of formula 3a. Solvents that

can be used in step (b) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the hydroxyquinoline of formula 3 to the chloro-quinoline of formula 4a can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (c) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (c) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane and similar solvents. The chloro-quinoline of formula 4a can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula 5a. Organic bases that can be used in step (d) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (d) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Reduction of the nitro group of the compound of formula 5a provides the compound of formula 6a-c. The nitro group can be reduced to an amine using reducing agent such as SnCl₂ in methanol, Fe/H₂, Raney Nickel, Pt/H₂, PtO₂/H₂, and the like. The amine of the compound of formula 6a-c can be reacted with bis(chloroalkyl)amines to provide the compound of formula 7a-f. Solvents that can be used in step (f) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Bis(chloroalkyl)amines that can be used in step (f) include but are not limited to optionally substituted bis(chloroethyl)amine, and the like.

Scheme 2: General Reaction Scheme to 7-(Piperazin-1-yl)-pyrazoloquinoline

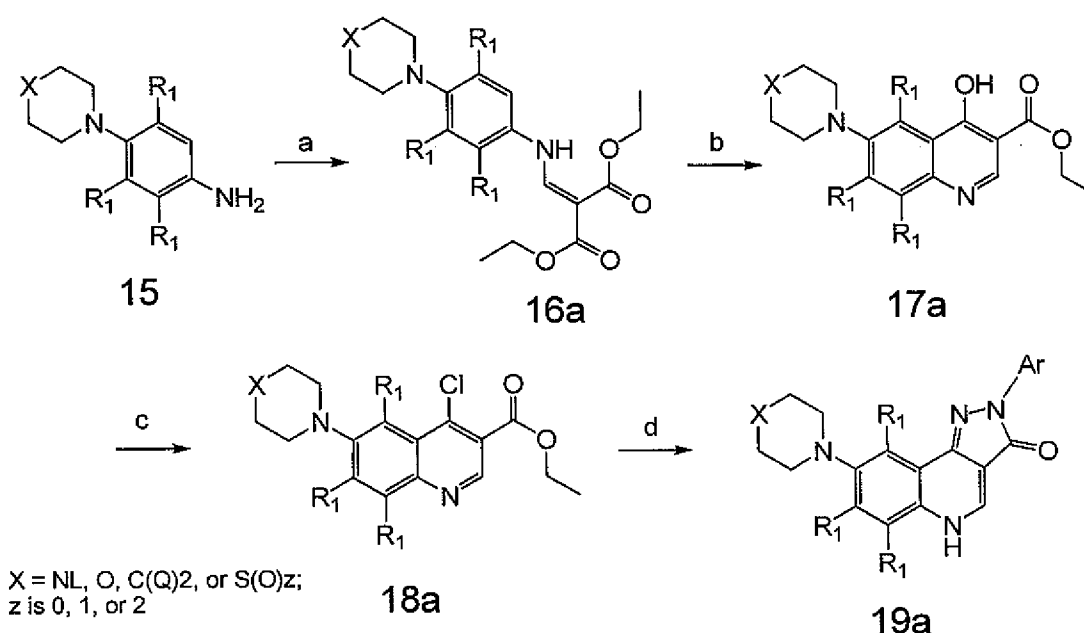


a) 1 equiv. diethyl 2-(ethoxymethylene)malonate, 125 °C, 3 hrs; b) Ph₂O, reflux, 30 min - 3 hrs; c) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; d) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, *o*-xylene, reflux, 12 hrs; e) SnCl₂, methanol, reflux, 12 hrs; f) bis(chloroethyl)NL·HCl, chlorobenzene, reflux, 72 hrs.

[0158] General Reaction Scheme 2 shows a representative synthetic method for the synthesis of 7-(Piperazin-1-yl)-pyrazoloquinoline. The 3-nitro-aniline of formula 8 can be reacted with diethyl 2-(ethoxymethylene)malonate under heating to afford, in an addition-elimination type reaction, the 3-nitro-enamine of formula 9. Thermal cyclization of the compound of formula 9 provides the hydroxyquinoline of formula 10a. Solvents that can be used in step (b) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the hydroxyquinoline of formula 10a to the chloro-quinoline of formula 11a can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (c) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (c) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula 11a can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula 12a-c. Organic bases that can be used in step (d) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (d) include but are not limited to *o*-xylene, xylenes, chlorobenzene,

toluene, and the like. Reduction of the nitro group of the compound of formula **12a-c** provides the compound of formula **13a-c**. The nitro group can be reduced to an amine using reducing agent such as SnCl_2 in methanol, Fe/H_2 , Raney Nickel, Pt/H_2 , PtO_2/H_2 , and the like. The amine of the compound of formula **13a-c** can be reacted with bis(chloroalkyl)amines to provide the compound of formula **14a-f**. Solvents that can be used in step (f) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Bis(chloroalkyl)amines that can be used in step (f) include optionally substituted bis(chloroethyl)amine, and the like.

Scheme 3: Alternative Method to Synthesize 8-(morpholin-1-yl)-pyrazoloquinoline or 8-(piperidin-1-yl)-pyrazoloquinoline

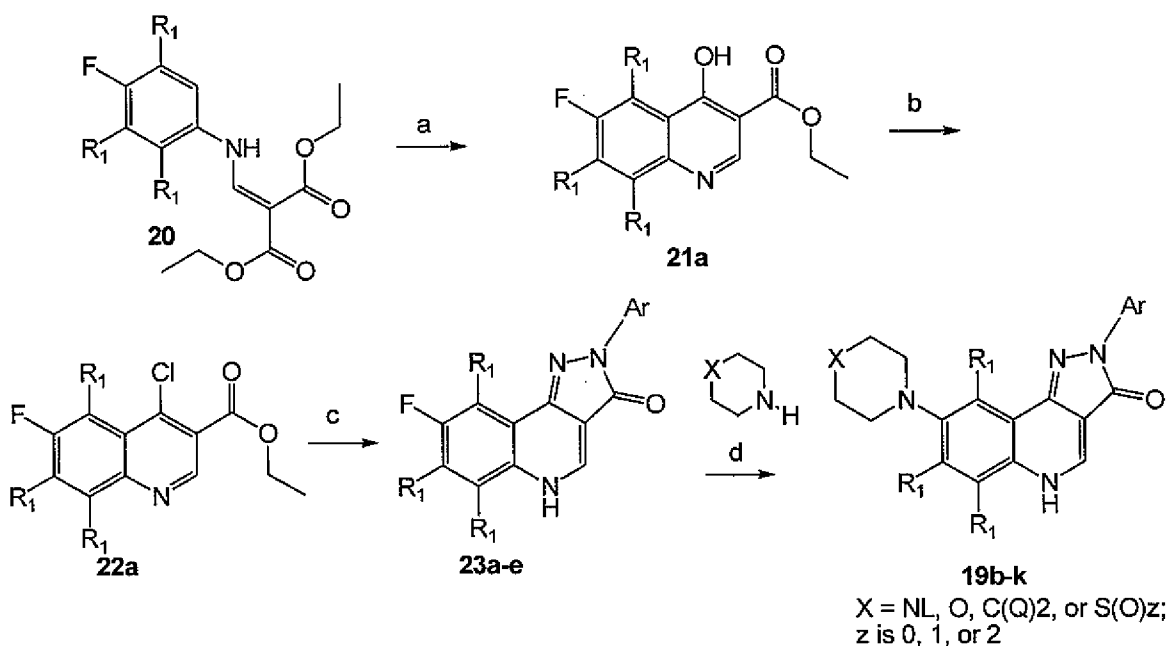


a) 1 equiv. diethyl 2-(ethoxymethylene)malonate, 125 °C, 3 hrs; b) Ph_2O , reflux, 30 min – 3 hrs; c) 4 equiv. oxalyl chloride, cat. DMF, CH_2Cl_2 , reflux, 3 hrs; d) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs.

[0159] General Reaction Scheme 3 shows a representative synthetic method for the synthesis of 8-(morpholin-1-yl)-pyrazoloquinoline or 8-(piperidin-1-yl)-pyrazoloquinoline. The 4-morpholine- or piperidine-aniline of formula **15** can be reacted with diethyl 2-(ethoxymethylene)malonate under heating to afford, in an addition-elimination type reaction, the 4-morpholine- or piperidine-enamine of formula **16a**.

Thermal cyclization of the compound of formula **16a** provides the morpholine- or piperidine-hydroxyquinoline of formula **17a**. Solvents that can be used in step (b) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the compound of formula **17a** to the chloro-quinoline of formula **18a** can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (c) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (c) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula **18a** can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula **19a**. Organic bases that can be used in step (d) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (d) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like.

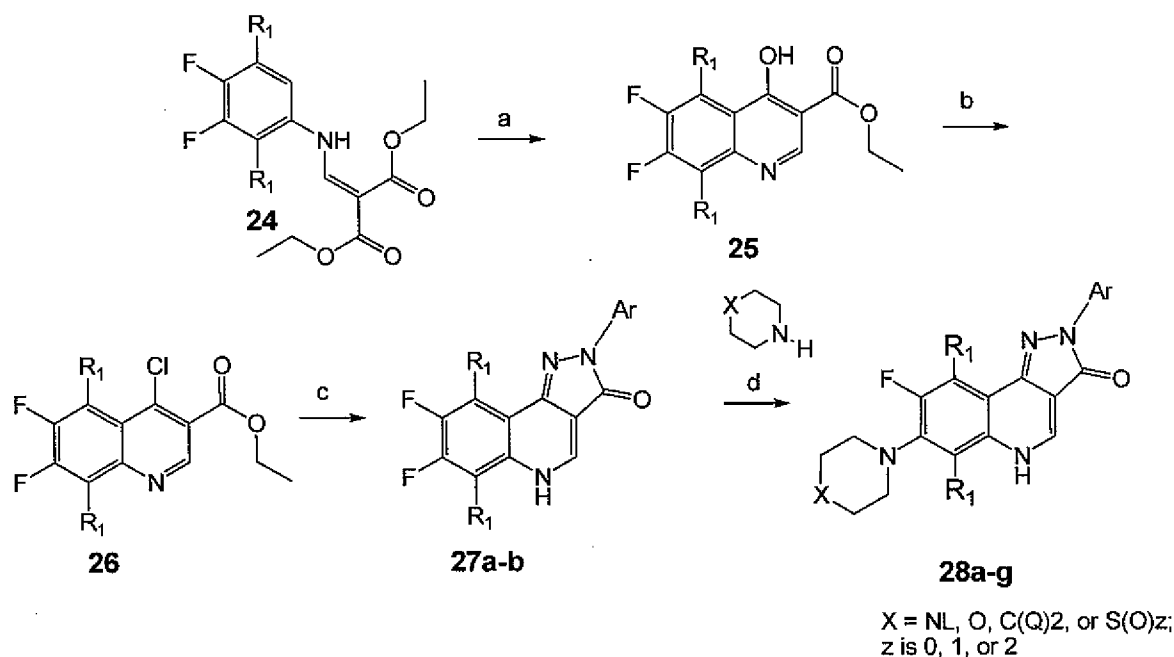
Scheme 4: Alternative Method to Synthesize 8-(piperazin-1-yl), 8-(piperidin-1-yl), or 8-(morpholin-1-yl)-pyrazoloquinoline



a) Ph₂O, reflux, 30 min – 3 hrs; b) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; c) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs., 175°C, 12 hrs; d) 175°C, 72 hrs

[0160] General Reaction Scheme 4 shows a representative synthetic method for the synthesis of 8-(piperazin-1-yl), 8-(piperidin-1-yl), or 8-(morpholin-1-yl)-pyrazoloquinoline. Thermal cyclization of the enamine of formula 20 provides the fluoro-hydroxyquinoline of formula 17a. Solvents that can be used in step (a) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the compound of formula 21a to the fluoro-chloro-quinoline of formula 22a can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (b) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (b) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula 22a can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula 23a-e. Organic bases that can be used in step (c) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (c) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of the fluoro of the compound of formula 23a-e with a cyclic amine under heating provides the compound of formula 19b-k. Step (d) can be performed with solvent or neat.

Scheme 5: Alternative Method to Synthesize 7-(piperazin-1-yl), 8-(piperidin-1-yl), or 8-(morpholin-1-yl)-pyrazoloquinoline

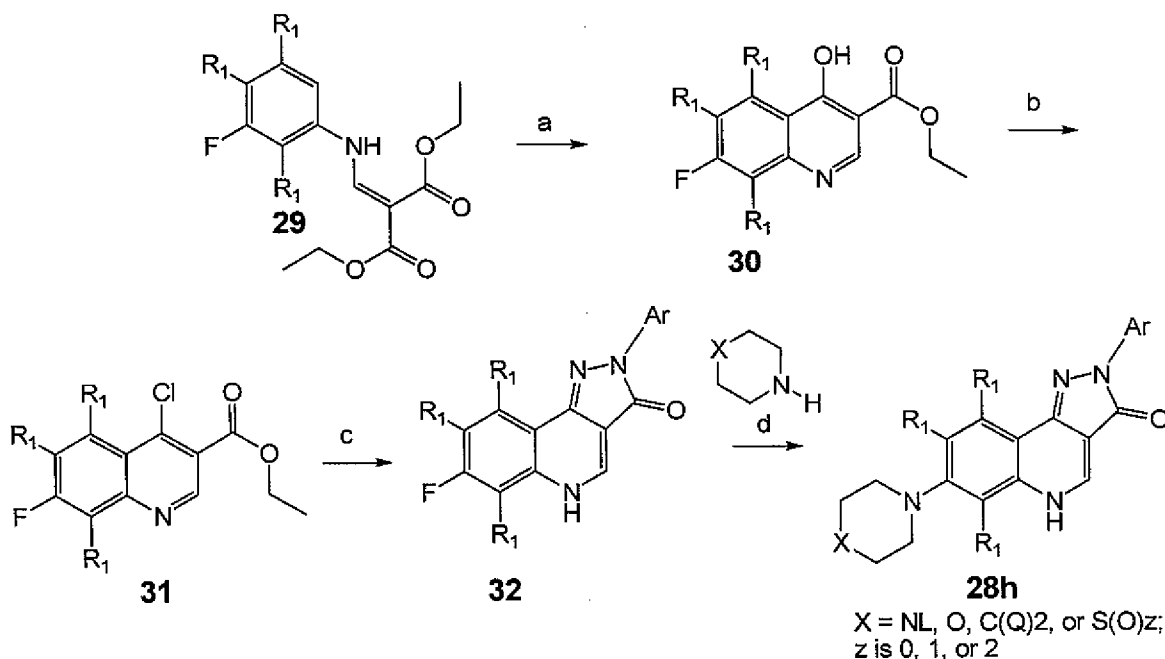


a) Ph₂O, reflux, 30 min – 3 hrs; b) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; c) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs., 175 °C, 12 hrs; d) 175 °C, 72 hrs

[0161] General Reaction Scheme 5 shows a representative synthetic method for the synthesis of 7-(piperazin-1-yl), 8-(piperidin-1-yl), or 8-(morpholin-1-yl)-pyrazoloquinoline. Thermal cyclization of the enamine of formula 24 provides the difluoro-hydroxyquinoline of formula 25. Solvents that can be used in step (a) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the compound of formula 25 to the difluoro-chloro-quinoline of formula 26 can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (b) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (b) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula 26 can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula 27a-b. Organic bases that can be used in step (c) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (c) include but are not

limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of the fluoro of the compound of formula **27a-b** with a cyclic amine under heating provides the compound of formula **28a-g**. Step (d) can be performed with solvent or neat.

Scheme 6: Alternative Method to Synthesize 7-(piperazin-1-yl), 8-(piperidin-1-yl), or 8-(morpholin-1-yl)-pyrazoloquinoline

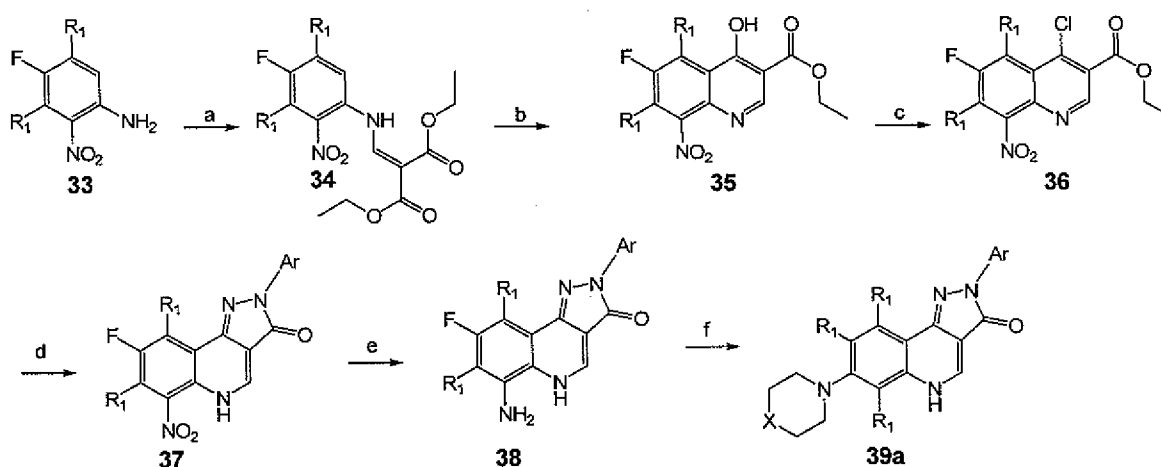


a) Ph₂O, reflux, 30 min – 3 hrs; b) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; c) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs. 175°C, 12 hrs; d) 175 °C, 72 hrs

[0162] General Reaction Scheme 6 shows a representative synthetic method for the synthesis of 7-(piperazin-1-yl), 8-(piperidin-1-yl), or 8-(morpholin-1-yl)-pyrazoloquinoline. Thermal cyclization of the enamine of formula **29** provides the fluoro-hydroxyquinoline of formula **30**. Solvents that can be used in step (a) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the compound of formula **30** to the fluoro-chloro-quinoline of formula **31** can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (b) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (b) include but are not limited to

chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula **31** can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula **32**. Organic bases that can be used in step (c) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (c) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of the fluoro of the compound of formula **32** with a cyclic amine under heating provides the compound of formula **28h**. Step (d) can be performed with solvent or neat.

Scheme 7: Method to Synthesize 6-Substituted Pyrazoloquinoline

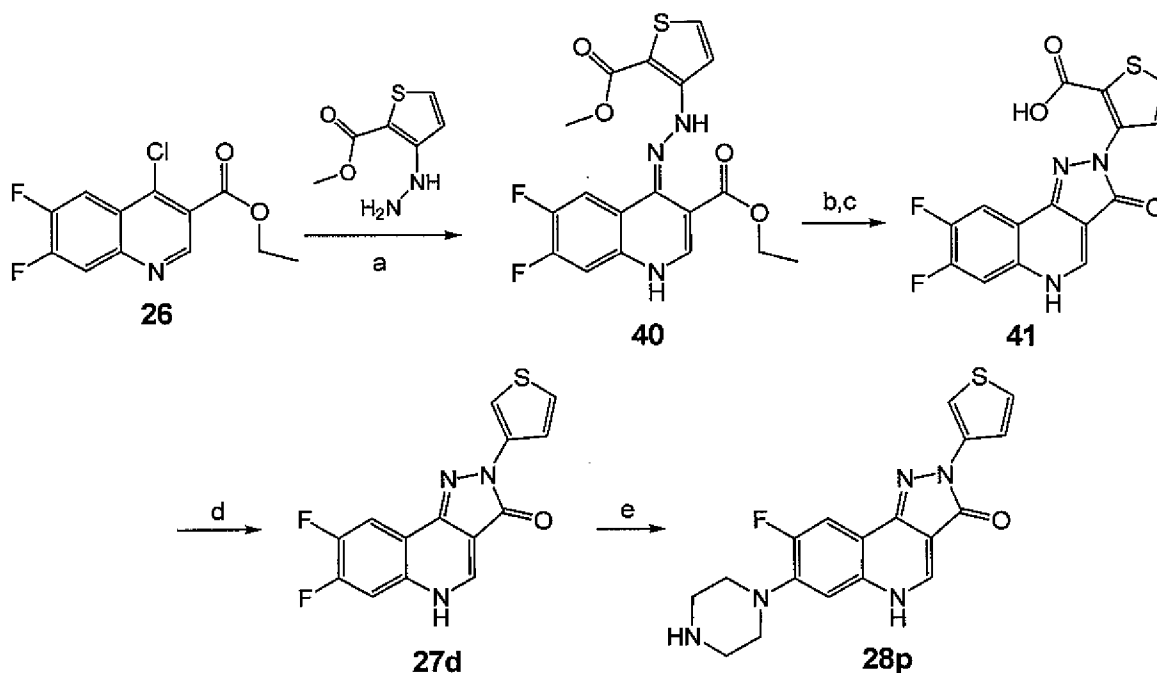


a) 1 equiv. diethyl 2-(ethoxymethylene)malonate, 125°C, 3 hrs, b) Ph₂O, reflux, 30 min-3 hrs, c) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs, d) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs. e) SnCl₂, methanol, reflux, 12 hrs. f) bis(chloroethyl)N-L·HCl, chlorobenzene, reflux, 72 hrs.

[0163] General Reaction Scheme 7 shows a representative synthetic method for the synthesis of 6-Substituted Pyrazoloquinoline. The 2-nitro-aniline of formula **33** can be reacted with diethyl 2-(ethoxymethylene)malonate under heating to afford, in an addition-elimination type reaction, the 2-nitro-enamine of formula **34**. Thermal cyclization of the compound of formula **34** provides the hydroxyquinoline of formula **35**. Solvents that can be used in step (b) include but are not limited to diphenyl ether, Dowtherm® and similar high boiling point stable solvents. Conversion of the hydroxyquinoline of formula **35** to

the chloro-quinoline of formula **36** can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (c) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (c) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula **36** can be reacted with aryl or heteroaryl hydrazine to form the tricyclic oxo-pyrazole of formula **37**. Organic bases that can be used in step (d) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (d) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Reduction of the nitro group of the compound of formula **37** provides the compound of formula **38**. The nitro group can be reduced to an amine using reducing agent such as SnCl₂ in methanol, Fe/H₂, Raney Nickel, Pt/H₂, PtO₂/H₂, and the like. The amine of the compound of formula **38** can be reacted with bis(chloroalkyl)amines to provide the compound of formula **39a**. Solvents that can be used in step (f) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Bis(chloroalkyl)amines that can be used in step (f) include but are not limited to optionally substituted bis(chloroethyl)amine, and the like.

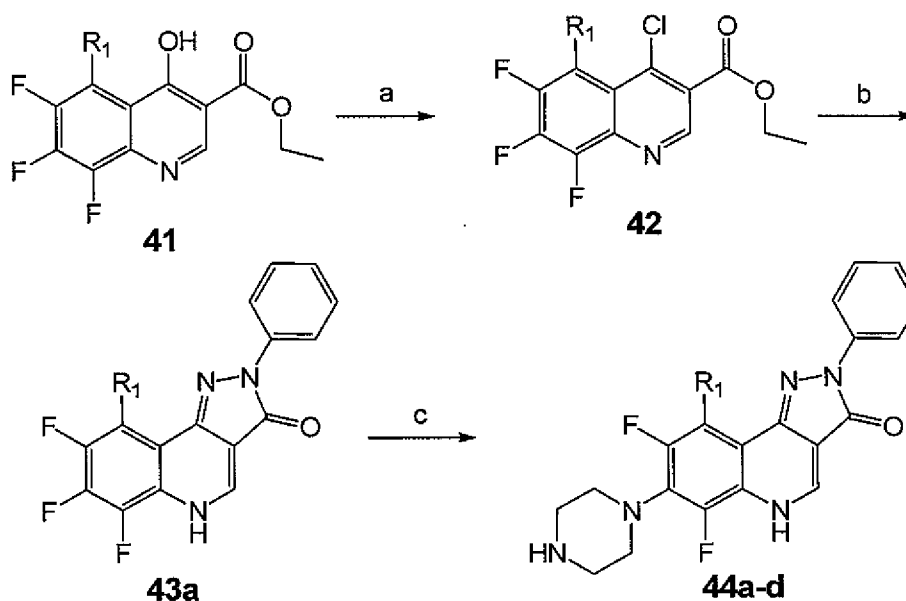
Scheme 8: Method to Synthesize 2-thiopheno-Pyrazoloquinoline



a) NaOH/Ethanol, b) NaOH, Ethanol, c) NaOH, Ethanol, d) Cu, Quinoline, e) piperazine, 175 °C, 72 hrs

[0164] Reaction Scheme 8 shows a representative synthetic method for the synthesis of 2-thiopheno-pyrazoloquinoline. Reaction of the chloro-quinoline of formula 26 with methyl 3-hydrazinylthiophene-2-carboxylate under basic conditions can provide a compound of formula 40. Conditions that can be used in step (a) include but are not limited to NaOH in ethanol, NaOH in MeOH, and the like. The compound of formula 40 can be converted to the compound of formula 41 under basic conditions. Conditions that can be used for the conversion of the compound of formula 40 to the carboxylic acid of formula 41 include but are not limited to NaOH in ethanol, NaOH in MeOH, and the like. The compound of formula 41 can be converted to the compound of formula 27d by decarboxylation using Copper in the presence of quinoline. Displacement of a fluoro group of the compound of formula 27d with piperazine under heating provides the compound of formula 28p. Step (e) can be performed with solvent or neat.

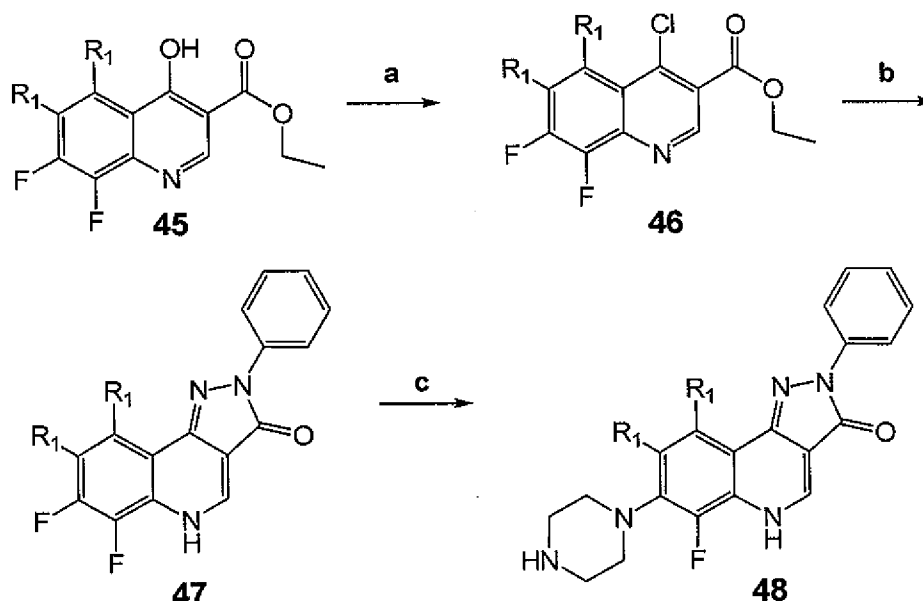
Scheme 9: Alternative Method to Synthesize 6,8-difluoro-7-(piperazin-1-yl)-pyrazoloquinoline



a) 4 equiv. oxalyl chloride, cat. DMF, CH_2Cl_2 , reflux, 3 hrs; b) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs. 175°C, 12 hrs; c) 175 °C, 72 hrs

[0165] Reaction Scheme 9 shows a representative synthetic method for the synthesis of 6,8-difluoro-7-(piperazin-1-yl)-pyrazoloquinoline. Conversion of the compound of formula 41 to the trifluoro-chloro-quinoline of formula 42 can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (a) include but are not limited to oxalyl chloride, $\text{P}(\text{O})\text{Cl}_3$, PCl_5 , thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (a) include chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The chloro-quinoline of formula 42 can be reacted with phenylhydrazine to form the tricyclic oxo-pyrazole of formula 43a. Organic bases that can be used in step (b) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (b) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of a fluoro of the compound of formula 43a with a cyclic amine under heating provides the compound of formula 44a-d. Step (c) can be performed with solvent or neat.

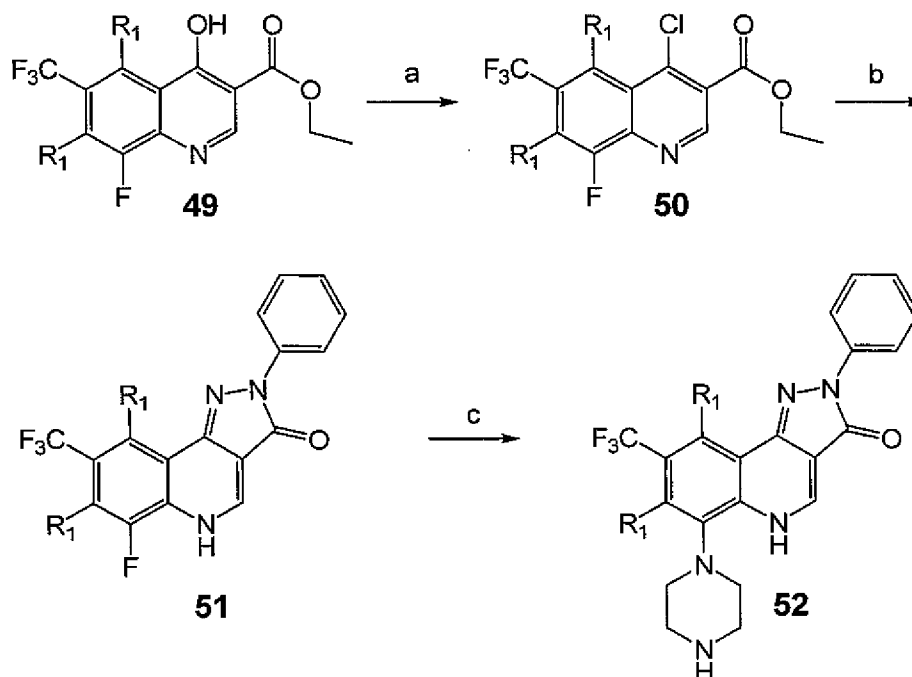
Scheme 10: Method to Synthesize 6-fluoro-7-(piperazin-1-yl)- pyrazoloquinoline



a) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; b) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs. 175°C, 12 hrs; c) 175 °C, 72 hrs

[0166] Reaction Scheme 10 shows a representative synthetic method for the synthesis of 6-fluoro-7-(piperazin-1-yl)pyrazoloquinoline. Conversion of the compound of formula 45 to the difluoro-chloro-quinoline of formula 46 can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (a) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (a) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The difluoro-chloro-quinoline of formula 46 can be reacted with phenylhydrazine to form the tricyclic oxo-pyrazole of formula 43a. Organic bases that can be used in step (b) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (b) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of a fluoro of the compound of formula 43a with piperazine under heating provides the compound of formula 44a-d. Step (c) can be performed with solvent or neat.

Scheme 11: Method to Synthesize 6-(piperazin-1-yl)-8-trifluoromethyl-pyrazoloquinoline

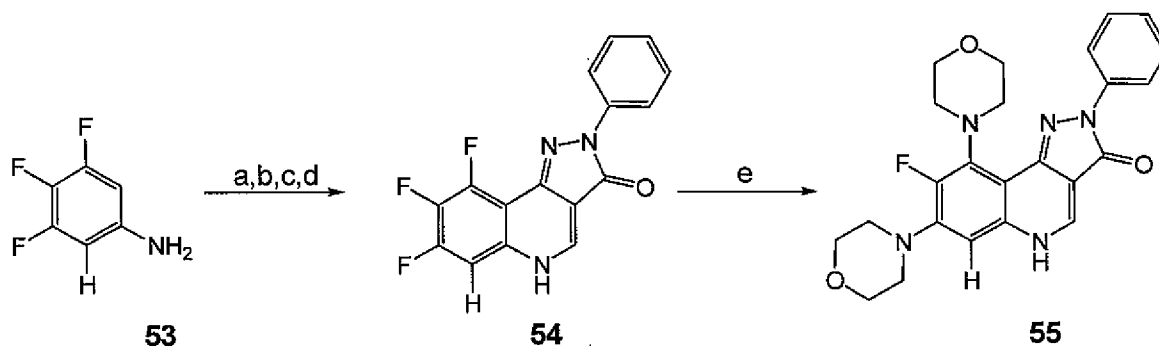


a) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; b) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs. 175 °C, 12 hrs; c) 175 °C, 72 hrs

[0167] Reaction Scheme 11 shows a representative synthetic method for the synthesis of 6-(piperazin-1-yl)-8-trifluoromethyl-pyrazoloquinoline. Conversion of the compound of formula 49 to the fluoro-chloro-quinoline of formula 50 can be accomplished using a chlorinating agent in a halogenated solvent and optionally catalytic DMF. Chlorinating agents that can be used in step (a) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. Solvents that can be used in step (a) include but are not limited to chlorobenzene, methylene chloride, 1,2-dichloroethane, chloroform and similar solvents. The fluoro-chloro-quinoline of formula 50 can be reacted with phenylhydrazine to form the tricyclic oxo-pyrazole of formula 51. Organic bases that can be used in step (b) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (b) include but are not

limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of a fluoro of the compound of formula **51** with piperazine under heating provides the compound of formula **52**. Step (c) can be performed with solvent or neat.

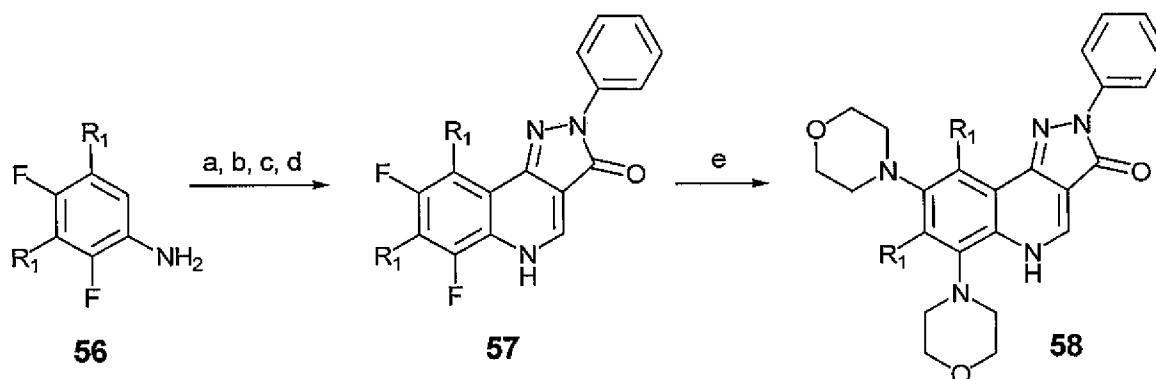
Scheme 12: Method to Synthesize 7,9-bis(morpholin-1-yl)-8-fluoro-pyrazoloquinoline



a) 1 equiv. diethyl 2-(ethoxymethylene)malonate, 125 °C, 3 hrs; b) Ph₂O, reflux, 30 min – 3 hrs; c) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; d) 2 equiv. aryl hydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs; e) 5 equiv. morpholine, 175 °C.

[0168] Reaction Scheme 12 shows a representative synthetic method for the synthesis of 7,9-bis(morpholin-1-yl)-8-fluoro-pyrazoloquinoline. Conversion of the compound of formula **53** to the tricyclic trifluoro-oxo-pyrazole-quinoline of formula **54** can be accomplished using the protocol disclosed in steps **a**, **b**, **c**, and **d**. Displacement of a fluoro of the compound of formula **54** with morpholine under heating provides the tricyclic trifluoro-oxo-pyrazole of formula **55**. Step (e) can be performed with solvent or neat.

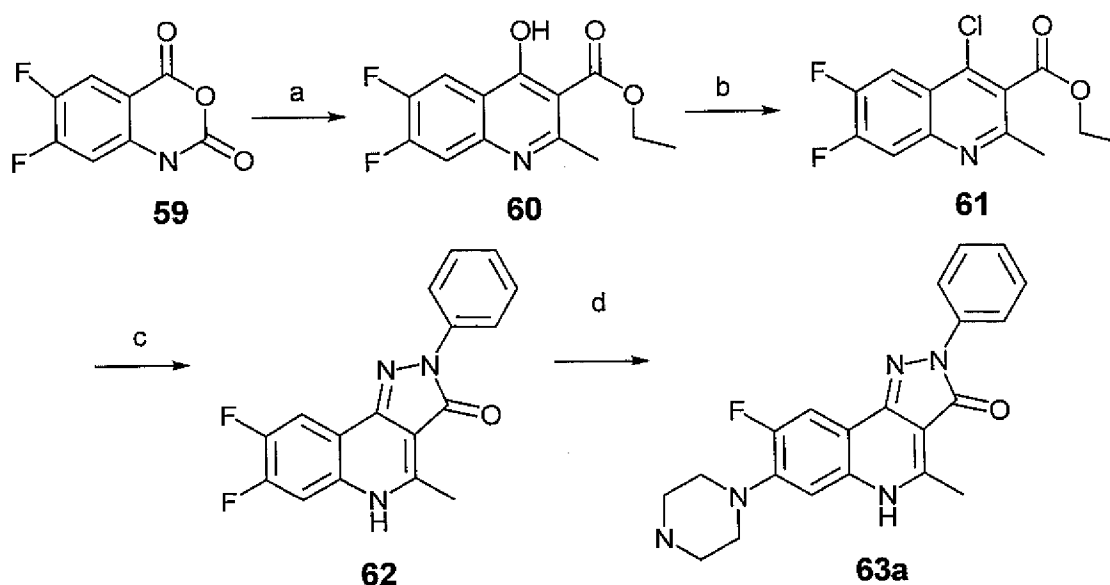
Scheme 13: Method to Synthesize 6,8-bis(morpholin-1-yl)-pyrazoloquinoline



a) 1 equiv. diethyl 2-(ethoxymethylene)malonate, 125 °C, 3 hrs; b) Ph₂O, reflux, 30 min – 3 hrs; c) 4 equiv. oxalyl chloride, cat. DMF, CH₂Cl₂, reflux, 3 hrs; d) 2 equiv. phenylhydrazine, 2 equiv. triethylamine, o-xylene, reflux, 12 hrs; e) 5 equiv. morpholine, 175 °C.

[0169] General Reaction Scheme 13 shows a representative synthetic method for the synthesis of 6,8-bis(morpholin-1-yl)-pyrazoloquinoline. Conversion of the compound of formula 53 to the tricyclic trifluoro-oxo-pyrazole-quinoline of formula 57 can be accomplished using the protocol disclosed in steps a, b, c, and d. Displacement of a fluoro of the compound of formula 57 with morpholine under heating provides the tricyclic trifluoro-oxo-pyrazole of formula 58. Step (e) can be performed with solvent or neat.

Scheme 14: Method to Synthesize 8-fluoro-4-methyl-7-piperazin-1-yl-pyrazoloquinoline

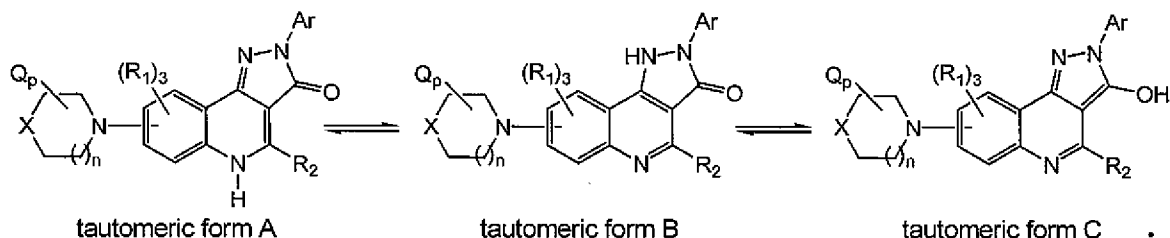


a) 10 equiv. ethyl acetoacetate, 1.1 equiv. NaH, DMA, 125°C, 10 min ; b) POCl₃, 0.5 hr; c) 2 equiv. phenyl hydrazine, 2 equiv. triethylamine, o-xylene, reflux , 12 hrs; d) 5 equiv. piperazine, 125°C, 72 hours.

[0170] Reaction Scheme 14 shows a representative synthetic method for the synthesis of 8-fluoro-4-methyl-7-piperazin-1-yl-pyrazoloquinoline. Reaction of the difluoro-isatoic anhydride of formula 59 with ethyl acetoacetate in the presence of a base provides the hydroxymethylquinoline of formula 60. Solvents that can be used in step (a) include but are not limited to DMA, DMF, NMP and similar solvents. Bases that can be used in step (a) include but are not limited to sodium hydride, potassium hydride, lithium hydride and the like. Conversion of the compound of formula 60 to the difluoro-chloro-methylquinoline of formula 61 can be accomplished using a chlorinating agent. Chlorinating agents that can be used in step (b) include but are not limited to oxalyl chloride, P(O)Cl₃, PCl₅, thionyl chloride, phosgene triphosgene, and similar chlorinating agents. The difluoro-chloro-methylquinoline of formula 61 can be reacted with phenylhydrazine to form the tricyclic oxo-pyrazole of formula 62. Organic bases that can be used in step (c) include but are not limited to triethyl amine (TEA), diisopropylethyl amine (DIEA), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpiperidine, and the like. Solvents that can be used in step (c) include but are not limited to o-xylene, xylenes, chlorobenzene, toluene, and the like. Displacement of a fluoro of the compound of formula 62 with piperazine under heating provides the compound of formula 63a. Step (d) can be performed with solvent or neat.

[0171] It is understood that compounds of formula (I) may be single components or mixtures of diastereomers or enantiomers if the substitutions on (I) contain chiral centers.

[0172] It is understood that compounds of formula (I) can exist in different tautomeric forms or mixtures thereof depending on the environment encompassing the compound, that is, an equilibrium can exist between the different tautomeric forms of the compounds and the equilibrium between said forms can be influenced by outside factors. For example, compounds of formula (I) can exist as tautomers as shown below:



The embodiments of the invention include all possible tautomers of the compounds of formula (I). One of skill in the art will understand that depending on the definitions of the radicals of formula (I), additional tautomeric forms are anticipated and encompassed.

[0173] In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, besylate, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

[0174] Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium), or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

[0175] The compounds of formula (I) can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

[0176] Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such

compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[0177] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

[0178] The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0179] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture

and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0180] Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[0181] For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

[0182] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

[0183] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[0184] Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the those practiced in the art.

[0185] The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[0186] In general, however, a suitable dose will be in the range of from about 0.15 to about 100 mg/kg, e.g., from about 1 to about 75 mg/kg of body weight per day, such as 0.75 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 1 to 90 mg/kg/day, most preferably in the range of 1 to 60 mg/kg/day.

[0187] The compound is conveniently administered in unit dosage form; for example, containing 1 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 5 to 500 mg of active ingredient per unit dosage form.

[0188] Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μ M, preferably, about 1 to 50 μ M, most preferably, about 2 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

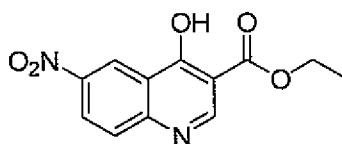
[0189] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or

more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

[0190] The compounds of the invention can optionally be administered alone or in combination with one or more other therapeutic agents that are effective to treat disorders of the CNS, including, but not limited to, AAMI (Age Associated Memory Impairment), MCI (Mild Cognitive Impairment), Alzheimer's disease, schizophrenia, dementia (due to HIV disease, Parkinson's disease, head trauma, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease), and delirium.

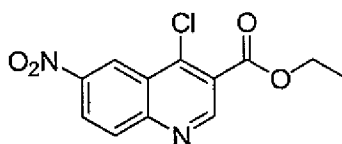
[0191] The routes used to synthesize the compounds of the invention are shown in Schemes 1-7 and the general methods used are detailed below

SYNTHETIC EXAMPLES



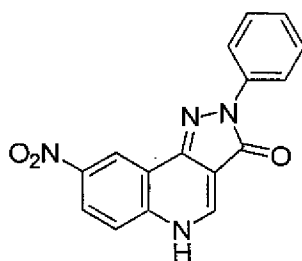
3a

[0192] Step 1: *Ethyl 4-hydroxy-6-nitro-quinoline-3-carboxylate (3a)*: Equimolar quantities of 4-nitroaniline and diethylethoxymethylene malonate were combined and refluxed for 3 hours at 120 °C, Ethanol was removed *in vacuo* to afford the 2-(4-nitrophenyl)-aminomethylene-malonic acid diethyl ester in quantitative yield. The resulting solid was added to refluxing Dowtherm A® and maintained at that temperature for 1 hour. The mixture was cooled to 80°C and added to ligroin. The solid formed was collected by filtration and washed with hexane to afford product in 30-80% yield. ¹H-NMR (DMSO-d₆) δ (ppm): 1.24 (3H, t, J = 7.14 Hz), 4.21 (2H, q, J = 7.14 Hz), 7.79 (1H, d, J = 9.06, Hz), 8.47 (1H, dd, J = 9.06, 2.47 Hz), 8.65 (1H, br), 8.85 (1H, d, J = 2.47 Hz). m/z 263.3 (MH⁺).



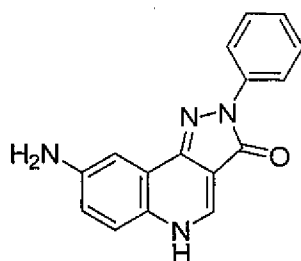
4a

[0193] Step 2: *Ethyl 4-chloro-6-nitro-quinoline-3-carboxylate (4a)*: To a suspension of **3a** in chloroform were added 4 equivalents of oxalyl chloride followed by 0.1 equiv. of dimethylformamide. The solution was refluxed for 3 hours and was quenched with 5 M sodium hydroxide solution at 4°C. The chloroform layer was collected, washed with 100 mL water and brine solution, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Product was obtained by recrystallization using acetone. ¹H-NMR (CDCl₃) δ (ppm): 1.48 (3H, t, J = 7.08 Hz), 4.55 (2H, q, J = 7.08 Hz), 8.31 (1H, d, J = 9.27 Hz), 8.62 (1H, m), 9.36 (2H, m). m/z 281.7 (MH⁺).



5a

[0194] Step 3: *8-Nitro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (5a)*: In a vial were added **4a**, phenyl hydrazine and triethylamine. The vial was sealed and heated to 135 °C for 12 hours. The product was collected by filtration and was washed with methanol in 85% yield. ¹H-NMR (DMSO-d₆) δ (ppm): 7.19 (1H, tt, J = 7.32, 1.22 Hz), 7.42 (2H, t, J = 7.56 Hz), 7.84 (1H, d, J = 9.03 Hz), 8.16 (2H, dd, J = 8.30, 1.22 Hz), 8.82 (1H, s), 8.89 (1H, d, J = 2.44 Hz). m/z 307.3 (MH⁺).

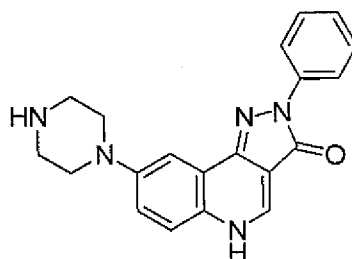


6a

[0195] Step 4: *8-Amino-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (6a)*: To a solution of **5a** in methanol were added catalytic amounts of Pd on carbon.

Reaction mixture was stirred at 20 psi of hydrogen overnight. Solid was filtered off and methanol was removed in vacuo to afford 8-amino-2-phenyl-2,5-dihydro-pyrazolo-(4,3-c)quinolin-3-one in 87% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 6.92 (1H, dd, $J = 8.79, 2.47$ Hz), 7.13 (1H, m), 7.28 (1H, d, $J = 2.47$ Hz), 7.43 (3H, m), 8.20 (2H, dd, $J = 7.69, 1.10$ Hz), 8.44 (1H, d, $J = 6.59$ Hz). m/z 277.3 (MH^+).

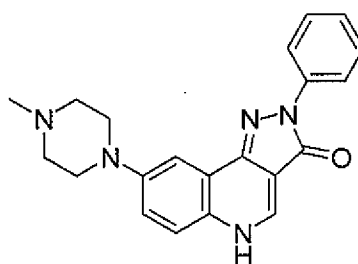
Example 1



7a

[0196] Step 5: *2-Phenyl-8-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (7a)*: Equimolar quantities of **6a** and bis(chloroethyl)amine hydrochloride were suspended in chlorobenzene and stirred at 175°C for 60 hours. The solid was collected by filtration and washed with methanol, acetonitrile and diethylether in 75% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.25 (4H, br), 3.52 (4H, br), 7.12 (1H, t, $J = 7.47$ Hz), 7.39 (3H, m), 7.45 (1H, m), 7.68 (1H, m), 8.22 (2H, dd, $J = 8.55, 0.98$ Hz), 8.60 (1H, d, $J = 5.86$ Hz), 9.12 (1H, br). m/z 346.4 (MH^+).

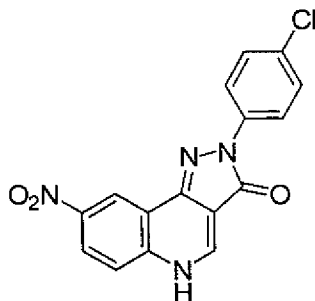
Example 2



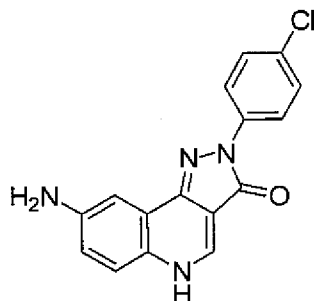
7b

[0197] *8-(4-Methylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (7b)*: The title compound was prepared following the procedure described for **7a** using 1-methylpiperazine instead of piperazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.25

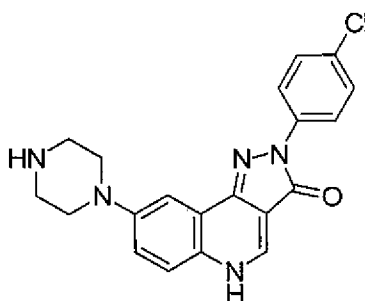
(4H, br), 3.41 (3H, s), 3.52 (4H, br), 7.12 (1H, t, $J = 7.47$ Hz), 7.39 (3H, m), 7.45 (1H, m), 7.68 (1H, m), 8.22 (2H, dd, $J = 8.55, 0.98$ Hz), 8.60 (1H, d, $J = 5.86$ Hz), 9.12 (1H, br). m/z 346.4 (MH^+). m/z 360.4 (MH^+).

**5b**

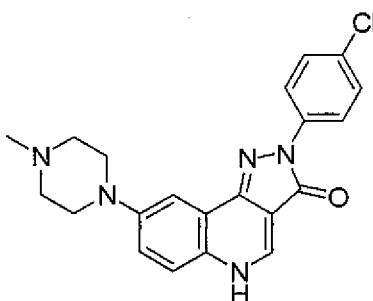
[0198] *2-(4'-Chlorophenyl)-8-nitro-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (5b)*: The title compound was prepared following the procedure described for **5a** using 4-chlorophenylhydrazine instead of phenylhydrazine. 1H -NMR (DMSO- d_6) δ (ppm): 7.50 (2H, d, $J = 8.91$ Hz), 7.90 (1H, d, $J = 8.91$ Hz), 8.29 (2H, d, $J = 8.91$ Hz), 8.48 (1H, dd, $J = 8.91, 2.38$ Hz), 8.88 (1H, s), 8.91 (1H, d, $J = 2.67$ Hz). m/z 341.8 (MH^+).

**6b**

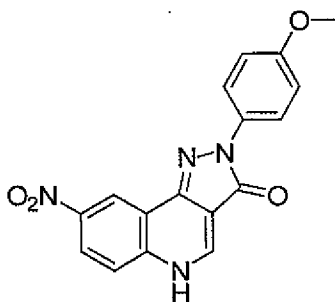
[0199] *8-Amino-2-(4-chlorophenyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (6b)*: The title compound was prepared following the procedure described for **6a** using **5b**. 1H -NMR (DMSO- d_6) δ (ppm): 7.19 (1H, tt, $J = 7.32, 1.22$ Hz), 7.44 (4H, m), 8.22 (4H, m), 8.48 (1H, d, $J = 6.59$ Hz). m/z 311.8 (MH^+).

Example 3**7c**

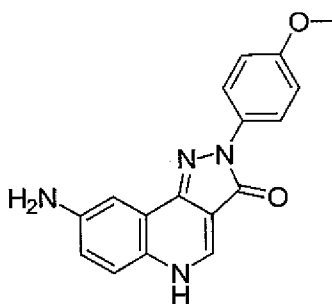
[0200] *2-(4'-Chlorophenyl)-8-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (7c)*: The title compound was prepared following the procedure described for **7a** using **6b**. ¹H-NMR (DMSO-d₆) δ (ppm): 3.25 (4H, br), 3.50 (4H, br), 3.75 (3H, s), 7.00 (1H, d, J = 9.06 Hz), 7.40 (1H, m), 7.48 (1H, br), 7.68 (1H, d, J = 9.06 Hz), 7.92 (1H, d, J = 8.79 Hz), 8.05 (2H, d, J = 8.79 Hz), 8.56 (1H, br), 9.12 (1H, br). m/z 380.9 (MH⁺).

Example 4**7d**

[0201] *2-(4'-Chlorophenyl)-8-(4-methylpiperazin-1-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (7d)*: The title compound was prepared following the procedure described for **7a** using **6b** and 1-methyl-piperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.25 (4H, br), 3.50 (7H, br), 3.75 (3H, s), 7.00 (1H, d, J = 9.06 Hz), 7.40 (1H, m), 7.48 (1H, br), 7.68 (1H, d, J = 9.06 Hz), 7.92 (1H, d, J = 8.79 Hz), 8.05 (2H, d, J = 8.79 Hz), 8.56 (1H, br), 9.12 (1H, br). m/z 394.9 (MH⁺).

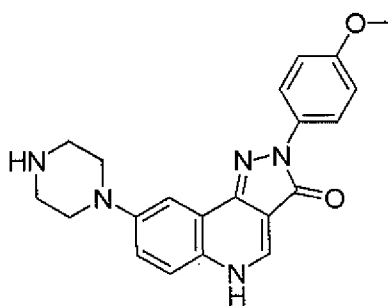


[0202] *2-(4'-Methoxyphenyl)-8-nitro-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (5c)*: The title compound was prepared following the procedure for 5a using 4-methoxy phenylhydrazine instead of phenylhydrazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.77 (3H, s), 6.89 (1H, dd, $J = 8.91, 2.37$ Hz), 6.95 (2H, m), 7.25 (1H, d, $J = 2.08$ Hz), 7.44 (1H, d, $J = 8.91$ Hz), 8.05 (2H, m), 8.39 (1H, d, $J = 6.53$ Hz). m/z 337.3 (MH^+).

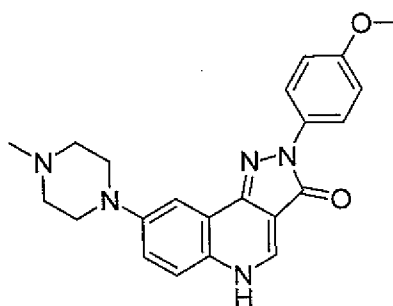


6c

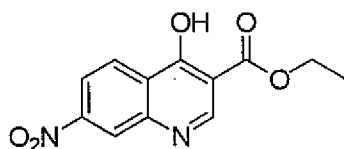
[0203] *8-Amino-2-(4'-methoxyphenyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (6c)*: The title compound was prepared following the procedure for 6a using 5c. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.77 (3H, s), 6.75 (1H, dd, $J = 8.91, 2.37$ Hz), 6.90 (2H, m), 7.10 (1H, d, $J = 2.08$ Hz), 7.44 (1H, d, $J = 8.91$ Hz), 8.05 (2H, m), 8.39 (1H, d, $J = 6.53$ Hz). m/z 307.3 (MH^+).

Example 5**7e**

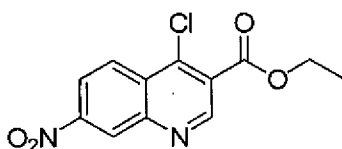
[0204] *2-(4'-Methoxyphenyl)-8-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (7e)*: The title compound was prepared following the procedure for **7a** using **6c**. ¹H-NMR (DMSO-d₆) δ (ppm): 3.25 (4H, br), 3.50 (4H, br), 3.75 (3H, s), 7.00 (1H, d, J = 9.06 Hz), 7.40 (1H, m), 7.48 (1H, br), 7.68 (1H, d, J = 9.06 Hz), 7.92 (1H, d, J = 8.79 Hz), 8.05 (2H, d, J = 8.79 Hz), 8.56 (1H, br), 9.12 (1H, br). m/z 376.4 (MH⁺).

Example 6**7f**

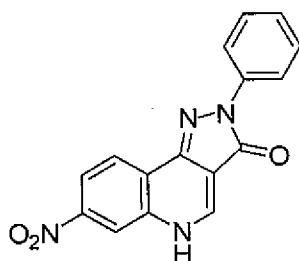
[0205] *2-(4'-Methoxyphenyl)-8-(4-methylpiperazin-1-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (7f)*: The title compound was prepared following the procedure for **7a** using **6c** and 1-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.25 (4H, br), 3.45 (3H, s), 3.50 (4H, br), 3.75 (3H, s), 7.00 (1H, d, J = 9.06 Hz), 7.40 (1H, m), 7.48 (1H, br), 7.68 (1H, d, J = 9.06 Hz), 7.92 (1H, d, J = 8.79 Hz), 8.05 (2H, d, J = 8.79 Hz), 8.56 (1H, br), 9.12 (1H, br). m/z 390.4 (MH⁺).

**10a**

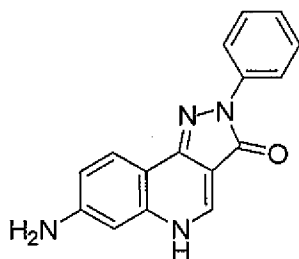
[0206] *Ethyl 4-hydroxy-7-nitroquinoline-3-carboxylate (10a)*: The title compound was prepared following the procedure described in Step 1 using 3-nitroaniline instead of 4-nitroaniline. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 1.24 (3H, t, $J = 7.14$ Hz), 4.18 (2H, q, $J = 7.14$ Hz), 8.10 (1H, dd, $J = 9.06, 2.19$ Hz), 8.32 (1H, d, $J = 8.79$ Hz), 8.48 (1H, d, $J = 2.19$ Hz), 8.71 (1H, d, $J = 5.76$ Hz). m/z 263.3 (MH^+).

**11a**

[0207] *Ethyl 4-chloro-7-nitroquinoline-3-carboxylate (11a)*: The title compound was prepared following the procedure described in Step 2 using **10a**. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.46 (3H, t, $J = 7.14$ Hz), 4.54 (2H, q, $J = 7.14$ Hz), 8.47 (1H, dd, $J = 9.34, 2.20$ Hz), 8.60 (1H, d, $J = 9.07$ Hz), 9.02 (1H, d, $J = 2.19$ Hz), 9.32 (1H, s). m/z 281.7 (MH^+).

**12a**

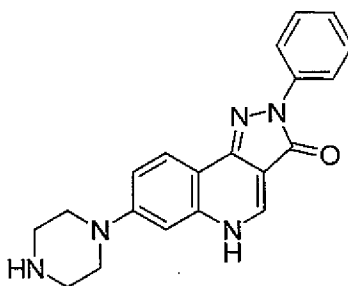
[0208] *7-Nitro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (12a)*: The title compound was prepared following the procedure described in Step 3 using **11a**. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 7.20 (1H, t, $J = 7.41$ Hz), 7.48 (3H, m), 8.19 (2H, m), 8.43 (1H, dd, $J = 8.79, 2.46$ Hz), 8.54 (1H, d, $J = 2.20$ Hz), 8.92 (1H, s). m/z 307.3 (MH^+).

**13a**

[0209] *7-Amino-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (13a):*

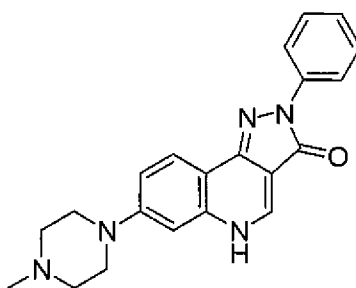
The title compound was prepared following the procedure described in Step 4 using **12a**. ¹H-NMR (DMSO-d₆) δ (ppm): 6.73 (1H, d, J = 1.93 Hz), 6.79 (1H, dd, J = 8.51, 2.20 Hz), 7.12 (1H, t, J = 7.14 Hz), 7.39 (2H, t, J = 7.96 Hz), 7.87 (1H, d, J = 8.79 Hz), 8.17 (2H, dd, J = 7.41, 1.10 Hz), 8.49 (1H, d, J = 6.32 Hz). m/z 277.3 (MH⁺).

Example 7

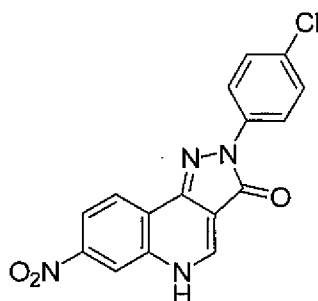
**14a**

[0210] *2-Phenyl-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one*

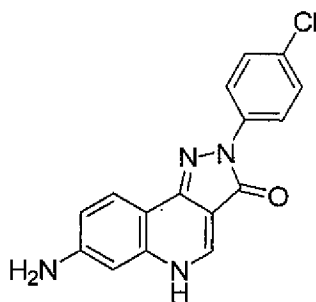
(14a): The title compound was prepared following the procedure in Step 5 using **13a**. ¹H-NMR (DMSO-d₆) δ (ppm): 2.84 (4H, brm), 3.17 (4H, brm), 6.99 (1H, d, J = 2.47 Hz), 7.10 (1H, t, J = 7.42 Hz), 7.21 (1H, dd, J = 8.79, 2.47 Hz), 7.41 (2H, m), 8.00 (1H, d, J = 8.79 Hz), 8.17 (2H, dd, J = 8.79, 1.10 Hz), 8.54 (1H, s). m/z 346.4 (MH⁺).

EXAMPLE 8**14b**

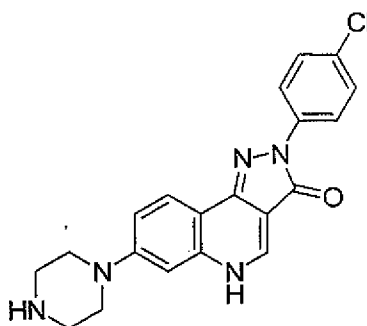
[0211] *7-(4-Methylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (14b)*: The title compound was prepared following the procedure in Step 5 using **13a** and 1-methylpiperazine. ¹H-NMR (CD₃OD) δ (ppm): 2.44 (3H, s), 2.74 (4H, brm), 3.44 (4H, brm), 7.03 (1H, d, J = 2.20 Hz), 7.27 (1H, ddd, J = 7.41, 1.64, 1.10 Hz), 7.35 (1H, dd, J = 9.07, 2.47 Hz), 7.65 (2H, m), 7.99 (2H, m), 8.17 (1H, d, J = 9.07 Hz), 8.53 (1H, s). m/z 360.4 (MH⁺).

**12b**

[0212] *2-(4'-Chlorophenyl)-7-nitro-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (12b)*: The title compound was prepared following the procedure described for **12a** using **11a** and 4-chlorophenylhydrazine. ¹H-NMR (DMSO-d₆) δ (ppm): 7.48 (2H, d, m), 8.20 (2H, m), 8.26 (1H, dd, J = 8.61, 2.08 Hz), 8.40 (1H, d, J = 8.61 Hz), 8.52 (1H, d, J = 2.08 Hz), 8.92 (1H, s). m/z 341.8 (MH⁺).

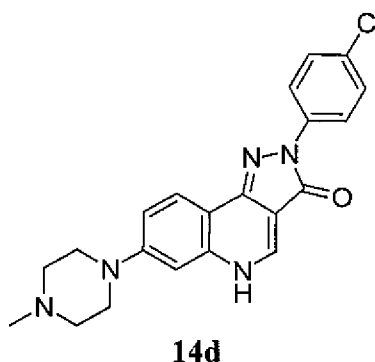
**13b**

[0213] *7-Amino-2-(4'-chlorophenyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (13b)*: The title compound was prepared following the procedure described in Step 4 using **12b**. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 6.74 (1H, d, $J = 2.20$ Hz) 6.79 (1H, dd, $J = 8.79, 2.19$ Hz), 7.42 (1H, d, $J = 8.79$ Hz), 7.43 (1H, q, $J = 5.22$ Hz), 7.86 (1H, d, $J = 8.51$ Hz), 8.20 (1H, d, $J = 9.06$ Hz), 8.21 (1H, q, $J = 5.21$ Hz), 8.47 (1H, d, $J = 6.32$ Hz). m/z 311.8 (MH^+).

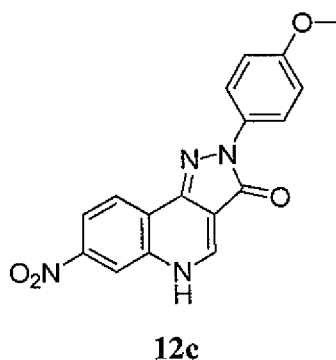
Example 9**14c**

[0214] *2-(4'-Chlorophenyl)-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c] quinolin-3-one (14c)*: The title compound was prepared following the procedure for **14a** using **13b**. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.07 (2H, br), 3.38 (4H, br), 3.48 (2H, br), 7.12 (1H, br), 7.48 (3H, m), 8.07 (1H, d, $J = 9.06$ Hz), 8.25 (2H, dd, $J = 9.07, 2.20$ Hz), 8.62 (1H, d, $J = 6.32$ Hz). m/z 380.9 (MH^+).

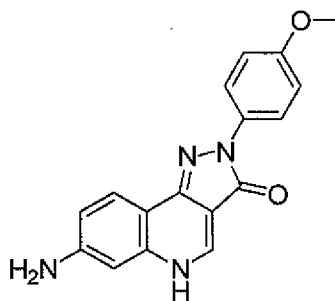
Example 10



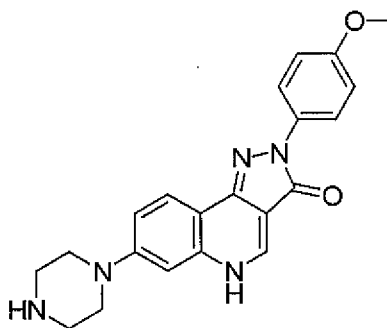
[0215] *2-(4-Chlorophenyl)-7-(4-methylpiperazin-1-yl)-2,5-dihydro-pyrazolo [4,3-c]quinolin-3-one (14d)*: The title compound was prepared following the procedure for **14a** using **13b** and 1-methylpiperazine. ¹H-NMR (CD₃OD) δ (ppm): 2.39 (3H, s), 2.67 (4H, brm), 3.40 (4H, brm), 7.01 (1H, d, J = 2.47 Hz), 7.34 (1H, dd, J = 9.07, 2.47 Hz), 7.46 (2H, dd, J = 6.87, 2.20 Hz), 8.09 (2H, dd, J = 7.14, 1.92 Hz), 8.19 (1H, d, J = 9.07 Hz), 8.51 (1H, s). m/z 394.9 (MH⁺).



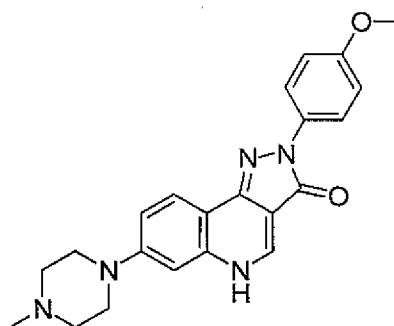
[0216] *2-(4'-Methoxyphenyl)-7-nitro-2,5-dihydro-pyrazolo-(4,3-c) quinolin-3-one (12c)*: The title compound was prepared following the procedure described **12a** using **11a** and 4-methoxyphenylhydrazine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.76(3H, s), 7.02 (2H, d, J = 9.34 Hz), 8.02 (2H, d, J = 9.06 Hz), 8.27 (1H, dd, J = 8.79, 2.19 Hz), 8.39 (1H, d, J = 8.79 Hz), 8.52 (1H, q, J = 2.20 Hz), 8.88 (1H, d, J = 6.04 Hz). m/z 337.3 (MH⁺).

**13c**

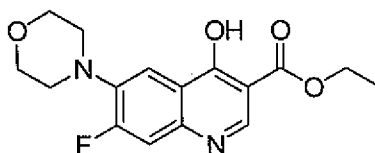
[0217] *7-amino-2-(4'-Methoxyphenyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (13c)*: The title compound was prepared following the procedure described for **13a** using **12c**. ¹H-NMR (DMSO-d₆) δ (ppm): 6.74 (1H, d, J = 2.20 Hz) 6.79 (1H, dd, J = 8.79, 2.19 Hz), 7.42 (1H, d, J = 8.79 Hz), 7.43 (1H, q, J = 5.22 Hz), 7.86 (1H, d, J = 8.51 Hz), 8.20 (1H, d, J = 9.06 Hz), 8.21 (1H, q, J = 5.21 Hz), 8.47 (1H, d, J = 6.32 Hz). m/z 307.3 (MH⁺).

Example 11**14e**

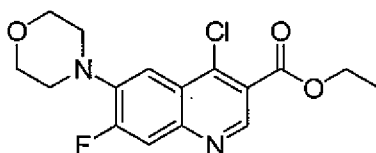
[0218] *2-(4-Methoxyphenyl)-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c] quinolin-3-one (14e)*: The title compound was prepared following the procedure for **14a** using **13c**. ¹H-NMR (DMSO-d₆) δ (ppm): 3.04 (4H, br), 3.75 (3H, s), 3.90 (4H, br), 6.8 (1H, m), 7.26 (2H, m), 7.42 (1H, m), 7.87 (1H, d, J = 8.79 Hz), 8.05 (2H, d, J = 9.06 Hz), 8.62 (1H, br). m/z 376.4 (MH⁺).

Example 12**14f**

[0219] *2-(4-Methoxyphenyl)-7-(4-methylpiperazin-1-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (14f)*: The title compound was prepared following the procedure for **14a** using **13c** and 1-methylpiperazine. ¹H-NMR (CD₃OD) δ (ppm): 2.32 (3H, s), 2.67 (4H, brn), 3.40 (4H, brn), 3.85 (3H, s), 6.88 (2H, m), 7.02 (1H, d, J = 2.47 Hz), 7.31 (1H, dd, J = 9.06, 2.20 Hz), 7.66 (2H, m), 8.16 (1H, d, J = 9.06 Hz), 8.52 (1H, s). m/z 390.4 (MH⁺).

**17a**

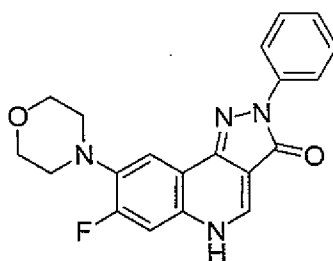
[0220] *Ethyl 7-fluoro-4-hydroxy-6-morpholino-quinoline-3-carboxylate (17a)*: The title compound was prepared following the procedure described in Step 1 using 3-fluoro-4-morpholinoaniline instead of 4-nitroaniline. ¹H-NMR (DMSO-d₆) δ (ppm): 1.22 (3H, t, J = 7.28 Hz), 3.00 (4H, m), 3.75 (4H, m), 4.1 (2H, q, J = 7.28 Hz), 7.40 (1H, s), 7.63 (1H, m), 8.50 (1H, m). m/z 321.3 (MH⁺).

**18a**

[0221] *Ethyl 4-chloro-7-fluoro-6-morpholino-quinoline-3-carboxylate (18a):*

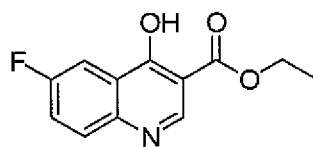
The title compound was prepared following the procedure described in Step 2 using **17a** instead of **3a**. ¹H-NMR (CDCl₃) δ (ppm): 1.42 (3H, t, J = 7.33 Hz), 3.23 (4H, m), 3.95 (4H, m), 4.1 (2H, q, J = 7.33 Hz), 7.78 (2H, m), 7.63 (1H, m), 9.07 (1H, s). m/z 339.8 (MH⁺).

Example 13

**19a**

[0222] *7-Fluoro-8-morpholin-4-yl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]*

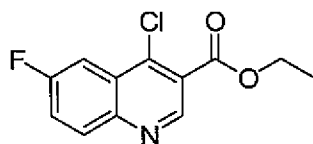
quinolin-3-one (19a): The title compound was prepared following the procedure described in Step 3 using **18a** instead of **5a**. ¹H-NMR (DMSO-d₆) δ (ppm): 3.15 (4H, m), 3.80 (4H, m), 7.16 (1H, tt, J = 7.32, 1.22 Hz), 7.40 (3H, m), 7.64 (1H, d, J = 9.03 Hz), 8.20 (2H, dd, J = 8.79, 1.22 Hz), 8.75 (1H, br), 12.65 (1H, br). m/z 364.4 (MH⁺).

**21a**

[0223] *Ethyl 4-hydroxy-6-fluoro-quinoline-3-carboxylate (21a):* The title

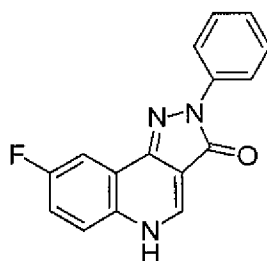
compound was prepared following the procedure described in Step 1 using 4-fluoroaniline instead of 4-nitroaniline. ¹H-NMR (DMSO-d₆) δ (ppm): 1.15 (3H, t, J = 7.080 Hz), 4.1

(2H, q, $J = 7.08$ Hz), 7.61 (1H, dd, $J = 8.30, 2.93$ Hz), 7.68 (1H, dd, $J = 9.03, 4.63$ Hz), 7.80 (1H, dd, $J = 9.27, 2.93$ Hz), 8.56 (1H, s). m/z 237.3 (MH^+).



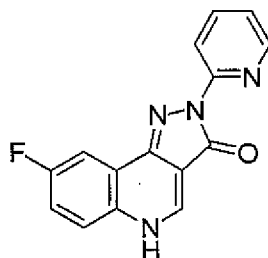
22a

[0224] *Ethyl 4-chloro-6-fluoroquinoline-3-carboxylate (22a)*: The title compound was prepared following the procedure described in Step 2 using **21a** instead of **3**. 1H -NMR ($CDCl_3$) δ (ppm): 1.47 (3H, t, $J = 7.08$ Hz), 4.51 (2H, q, $J = 7.08$ Hz), 7.63 (1H, m), 8.02 (1H, dd, $J = 9.52, 2.68$ Hz), 8.15 (1H, dd, $J = 9.27, 5.37$ Hz), 9.15 (1H, s). m/z 255.7 (MH^+).



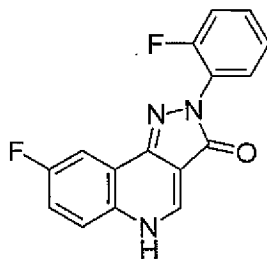
23a

[0225] *8-Fluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (23a)*: The title compound was prepared following the procedure described in Step 3 using **22a** instead of **4a**. 1H -NMR ($DMSO-d_6$) δ (ppm): 7.16 (1H, t, $J = 13.67$ Hz), 7.41 (2H, t, $J = 7.56$ Hz), 7.55 (1H, dt, $J = 8.54, 2.93$ Hz), 7.77 (1H, dd, $J = 9.27, 4.88$ Hz), 7.90 (1H, dd, $J = 9.27, 2.93$ Hz), 8.18 (2H, dd, $J = 7.58, 1.95$ Hz), 8.73 (1H, s). m/z 280.2 (MH^+).

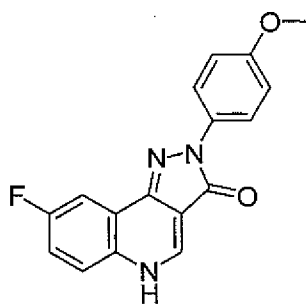


23b

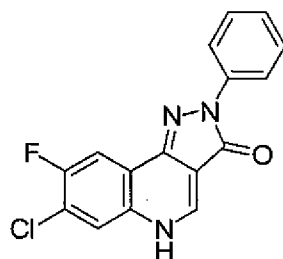
[0226] *8-Fluoro-2-(2'-pyridyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one* (**23b**): The title compound was prepared following procedure for **23a** using pyridyl-2-hydrazine instead of phenyl hydrazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 7.24 (1H, ddd, $J = 7.42, 4.95, 1.10$ Hz), 7.57 (1H, dt, $J = 9.06, 3.02$ Hz), 7.76 (1H, dd, $J = 9.34, 4.95$ Hz), 7.88 (2H, m), 8.18 (1H, brd, $J = 8.24$ Hz), 8.49 (1H, ddd, $J = 4.95, 2.75, 1.10$ Hz), 8.76 (1H, s). m/z 281.3 (MH^+).

**23c**

[0227] *8-Fluoro-2-(2'-fluorophenyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one* (**23c**): The title compound was prepared following procedure for **23a** using 2-fluorophenyl hydrazine instead of phenyl hydrazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 7.37 (3H, m), 7.52 (2H, m), 7.81 (2H, m), 8.74 (1H, s). m/z 298.3 (MH^+).

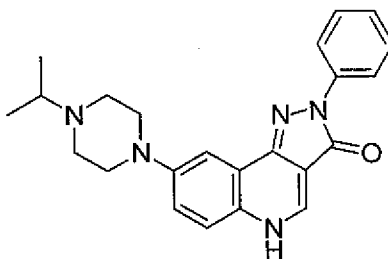
**23d**

[0228] *8-Fluoro-2-(4'-methoxyphenyl)-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one* (**23d**): The title compound was prepared following procedure for **23a** using 4-methoxy phenylhydrazine instead of phenyl hydrazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 7.05 (3H, m), 7.52 (1H, dt, $J = 8.52, 3.02$ Hz), 7.80 (1H, dd, $J = 9.07, 4.94$ Hz), 7.88 (1H, dd, $J = 9.06, 2.75$ Hz), 8.05 (2H, m), 8.74 (1H, d, $J = 5.49$ Hz). m/z 310.3 (MH^+).

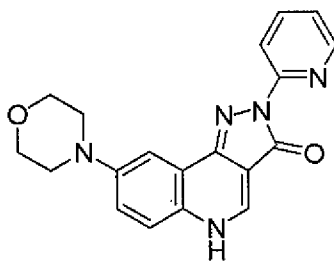
**23e**

[0229] *7-Chloro-8-fluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c] quinolin-3-one (23e)*: The title compound was prepared following procedure for **23a** using ethyl-4, 7-dichloro-6-fluoro-quinoline-3-carboxylate. ¹H-NMR (DMSO-d₆) δ (ppm): 7.20 (1H, t, J = 7.41 Hz), 7.48 (3H, m), 8.19 (2H, m), 8.43 (1H, dd, J = 8.79, 2.46 Hz), 8.54 (1H, d, J = 2.20 Hz), 8.92 (1H, s). m/z 314.7 (MH⁺).

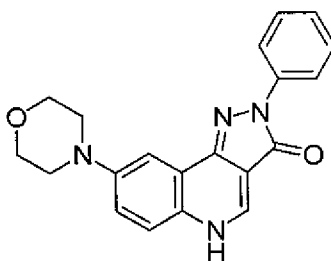
Example 14

**19b**

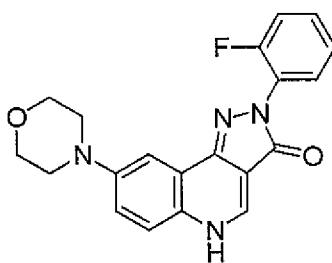
[0230] *8-(4-Isopropylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c] quinolin-3-one (19b)*: **23a** was stirred with excess of N-isopropylpiperazine at 175 °C for 72 hours. The precipitates were collected by filtration and washed with ethyl acetate and purified using column chromatography to obtain title compound in 84% yield. ¹H-NMR (DMSO-d₆) δ (ppm): 1.01 (6H, d, J = 6.03 Hz), 2.63 (4H, br), 2.70 (1H, m), 3.22 (4H, br), 7.13 (2H, brt, J = 7.32 Hz), 7.42 (3H, m), 7.58 (1H, d, J = 9.32 Hz), 8.23 (2H, d, J = 8.54 Hz), 8.54 (1H, s). m/z 388.5 (MH⁺).

Example 15**19c**

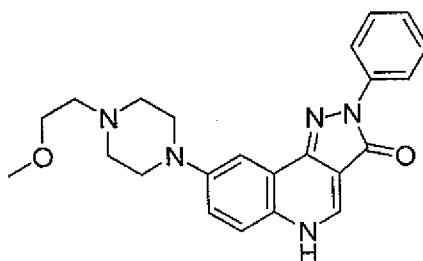
[0231] *8-Morpholin-4-yl-2-pyridin-2-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19c)*: The title compound was obtained following procedure described in the synthesis of **19b** using **23b** and morpholine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.22 (4H, br), 3.80 (4H, br), 7.20 (1H, ddd, $J = 7.32, 4.88, 0.98$ Hz), 7.44 (2H, m), 7.58 (1H, d, $J = 7.57$ Hz), 7.86 (1H, ddd, $J = 7.57, 1.19, 0.97$ Hz), 8.24 (1H, d, $J = 8.30$ Hz), 8.48 (1H, ddd, $J = 3.66, 1.95, 1.22$ Hz), 8.60 (1H, s). m/z 348.6 (MH^+).

Example 16**19d**

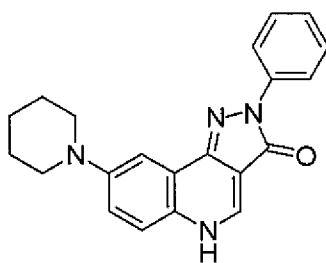
[0232] *8-Morpholin-4-yl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19d)*: The title compound was obtained following procedure described in the synthesis of **19b** using **23a** and morpholine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.24 (4H, br), 3.77 (4H, br), 7.13 (1H, t, $J = 7.42$ Hz), 7.38 (4H, m), 7.60 (1H, d, $J = 9.06$ Hz), 8.23 (2H, dd, $J = 8.24, 1.65$ Hz), 8.57 (1H, s). m/z 347.4 (MH^+).

Example 17**19e**

[0233] *2-(2-Fluorophenyl)-8-morpholin-4-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19e)*: The title compound was obtained following procedure described in the synthesis of **19b** using **23c** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.21 (4H, br), 3.76 (4H, br), 7.2 (5H, m), 7.54 (1H, dt, J = 7.97, 1.37 Hz), 7.62 (1H, d, J = 8.79 Hz), 8.58 (1H, d, J = 6.32 Hz). m/z 365.4 (MH⁺).

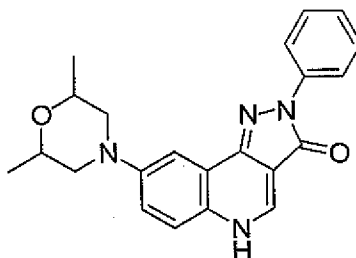
Example 18**19f**

[0234] *8-[4-(2-Methoxyethyl)-piperazin-1-yl]-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19f)*: The title compound was obtained following procedure described in the synthesis of **19b** using 1-methoxyethylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.18 (3H, d, J = 11.86 Hz), 1.21 (3H, d, J = 11.72 Hz), 2.67 (2H, dd, J = 11.72, 11.47 Hz), 3.72 (4H, br), 7.11 (2H, t, J = 7.32 Hz), 7.39 (4H, m), 7.57 (1H, d, J = 9.03 Hz), 8.21 (2H, m), 8.57 (1H, s). m/z 404.5 (MH⁺).

Example 19**19g**

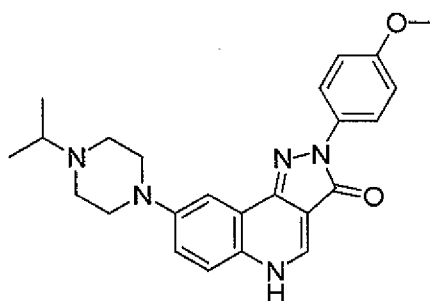
[0235] *2-Phenyl-8-piperidin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one*

(19g): The title compound was obtained following procedure described in the synthesis of **19b** using **23a** and piperidine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 1.1-1.4 (6H, m), 2.84 (2H, br), 3.15 (2H, br), 7.14 (1H, t, $J = 7.33$ Hz), 7.41 (3H, m), 7.86 (1H, d, $J = 12.94$ Hz), 8.20 (2H, dd, $J = 8.79, 1.22$ Hz), 8.66 (1H, s), 8.80 (1H, br). m/z 345.4 (MH^+).

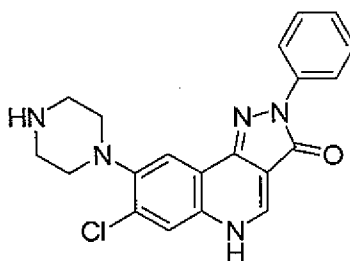
Example 20**19h**

[0236] *8-(2,6-Dimethylmorpholin-4-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]*

quinolin-3-one (19h): The title compound was obtained following procedures described in the synthesis of **19b** using 2,6-dimethylmorpholine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 2.54 (2H, t, $J = 5.62$ Hz), 2.60 (4H, br), 3.24 (3H, s), 3.26 (4H, br), 3.47 (2H, t, $J = 5.62$ Hz), 7.11 (2H, tt, $J = 7.32, 1.22$ Hz), 7.41 (4H, m), 7.59 (1H, d, $J = 9.03$ Hz), 8.20 (2H, dd, $J = 8.54, 1.22$ Hz), 8.56 (1H, s). m/z 375.5 (MH^+).

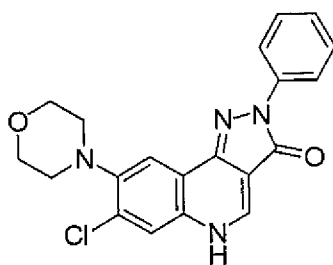
Example 21**19i**

[0237] *8-(4-Isopropylpiperazin-1-yl)-2-(4-methoxyphenyl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19i)*: The title compound was obtained following procedure described in the synthesis of **19b** using **23d**. ¹H-NMR (DMSO-d₆) δ (ppm): 1.12 (6H, d, J = 6.08 Hz), 3.20 (4H, br), 3.78 (4H, br), 3.76 (3H, s), 6.80 (2H, d, J = 8.97 Hz), 7.44 (2H, m), 7.60 (1H, d, J = 8.79 Hz), 7.91 (1H, d, J = 9.07 Hz), 8.56(1H, br), 9.33 (1H, s). m/z 418.4 (MH⁺).

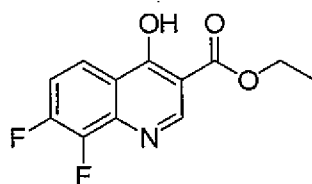
Example 22**19j**

[0238] *7-Chloro-2-phenyl-8-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19j)*: The title compound was obtained following procedure described in the synthesis of **19b** using **23e** and piperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.11 (4H, br), 3.33 (4H, br), 7.15 (1H, t, J = 7.32 Hz), 7.41 (2H, dd, J = 8.54, 7.32 Hz), 7.74 (2H, d, J = 2.93 Hz), 8.20 (2H, dd, J = 8.54, 1.22 Hz), 8.65 (1H, s). m/z 380.9 (MH⁺).

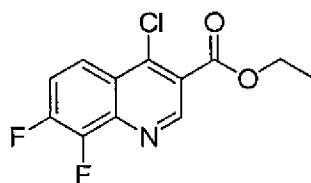
Example 23

**19k**

[0239] *7-Chloro-8-morpholin-4-yl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (19k)*: The title compound was obtained following procedure described in the synthesis **19b** using **23e** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.08 (4H, br), 3.78 (4H, br), 7.18 (1H, tt, J = 7.32, 1.32 Hz), 7.43 (2H, t, J = 7.56 Hz), 7.78 (2H, d, J = 2.44 Hz), 8.21 (2H, dd, J = 8.54, 1.22 Hz), 8.71 (1H, s). m/z 381.8 (MH⁺).

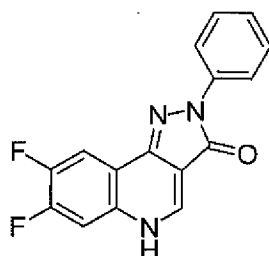
**25a**

[0240] *Ethyl 7,8-difluoro-4-hydroxyquinoline-3-carboxylate (25a)*: The title compound was prepared following the procedure described in Step 1 using 3,4-difluoroaniline instead of 4-nitroaniline. ¹H-NMR (DMSO-d₆) δ (ppm): 1.15 (3H, t, J = 7.08 Hz), 4.1 (2H, q, J = 7.08 Hz), 7.61 (1H, dd, J = 8.30, 2.93 Hz), 7.68 (1H, dd, J = 4.63, 9.03 Hz), 7.80 (1H, dd, J = 9.27, 2.93 Hz), 8.56 (1H, s). m/z 254.2 (MH⁺).

**26a**

[0241] *Ethyl 4-chloro-7,8-difluoroquinoline-3-carboxylate (26a)*: The title compound was prepared following the procedure described in Step 2 using **25a** instead of

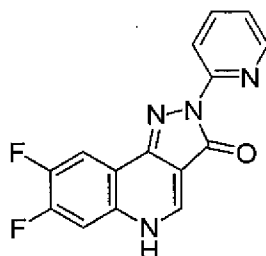
3. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.47 (3H, t, $J = 7.08$ Hz), 4.56 (2H, q, $J = 7.08$ Hz), 7.72 (1H, d, $J = 8.79$ Hz), 8.39 (1H, d, $J = 8.78$ Hz), 9.23 (1H, s). m/z 272.7 (MH^+).



27a

[0242] *7,8-Difluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one*

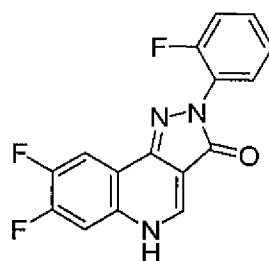
(27a): The title compound was prepared following the procedure described for 4a using 26a. $^1\text{H-NMR}$ (DMSO-d_6) δ (ppm): 7.18 (1H, t, $J = 7.82$ Hz), 7.43 (2H, dd, $J = 8.30, 7.33$ Hz), 7.75 (1H, dd, $J = 11.22, 7.32$ Hz), 8.18, 3H, m), 8.90 (1H, s). m/z 298.3 (MH^+).



27b

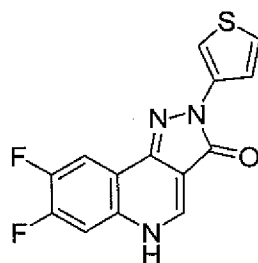
[0243] *7,8-Difluoro-2-(2'-pyridyl)-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one*

(27b): The title compound was prepared following the procedure described for 23b using 26. $^1\text{H-NMR}$ (DMSO-d_6) δ (ppm): 7.31 (1H, t, $J = 7.86$ Hz), 7.73 (1H, dd, $J = 11.26, 7.14$ Hz), 8.01 (1H, dt, $J = 8.79, 1.65$ Hz), 8.16 (1H, t, $J = 8.24$ Hz), 8.24 (1H, d, $J = 8.24$ Hz), 8.50 (1H, d, $J = 3.85$ Hz), 8.82 (1H, s). m/z 299.3 (MH^+).



27c

[0244] 7,8-Difluoro-2-(2'-fluorophenyl)-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (27c): The title compound was prepared following the procedure described for 23b using 26 and 2-fluorophenylhydrazine·HCl. ¹H-NMR (DMSO-d₆) δ (ppm): 7.31 (3H, m), 7.54 (1H, dd, J = 7.3, 6.0 Hz), 7.69 (1H, dd, J = 11.1, 7.1 Hz), 8.06 (1H, dd, J = 10.5, 8.4 Hz), 8.76 (1H, d, J = 6.2 Hz). m/z 316.2 (MH⁺).

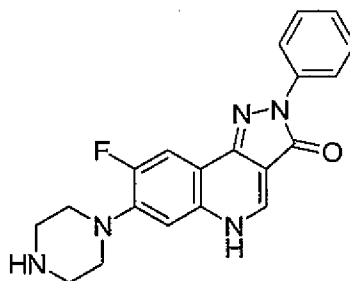


27d

[0245] 7,8-Difluoro-2-(thiophen-3-yl)-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (27d): 1.05 equiv. of methyl 3-hydrazinthiophene-2-carboxylate was added to a solution of 3c in ethanol. After 1.5 hr of stirring at room temperature, the solution was concentrated *in vacuo* and residue was dissolved in chloroform and washed with aq. sodium bicarbonate solution, dried and concentrated *in vacuo*. The resulting solid was suspended in ethanol and stirred with 1N sodium hydroxide solution for 30 minutes, acidified with acetic acid and concentrated *in vacuo*. The solid was filtered, washed with water, dried and suspended in ethanol. 1N sodium hydroxide was added and the reaction mixture was refluxed for 1 hr, acidified with acetic acid and the crystals were collected by filtration. The yellow solid was combined with copper powder and quinoline and stirred at 190 °C for 1 hour. The copper was removed by filtration and the filtrate was mixed with 1N sodium hydroxide solution, followed by extraction with ether. The separated aqueous layer was treated with active charcoal, acidified with acetic acid to yield 41 as yellow solid.

$^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 7.58 (1H, dd, $J = 5.22, 3.30$ Hz), 7.69 (1H, dd, $J = 11.26, 7.14$ Hz), 7.74 (1H, dd, $J = 5.22, 1.38$ Hz), 7.80 (1H, m), 8.15 (1H, dd, $J = 10.7, 8.2$ Hz), 8.77 (1H, d, $J = 6.2$ Hz). m/z 304.2 (MH^+).

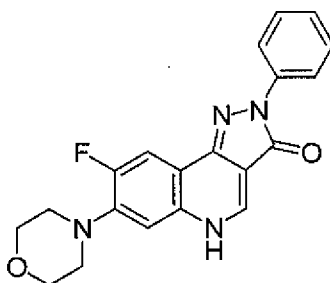
Example 24



28a

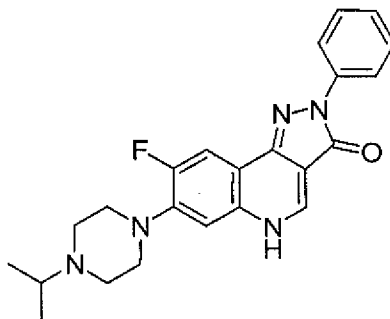
[0246] *8-Fluoro-2-phenyl-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28a)*: The title compound was obtained following procedure described in the synthesis of **19b** using **27a** and piperazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 2.92 (4H, brm), 3.04 (4H, brm), 7.11 (1H, t, $J = 7.41$ Hz), 7.23 (1H, d, $J = 7.97$ Hz), 7.39 (2H, m), 7.79 (1H, d, $J = 13.18$ Hz), 8.21 (2H, dd, $J = 8.52, 1.10$ Hz), 8.62 (1H, s). m/z 364.4 (MH^+).

Example 25

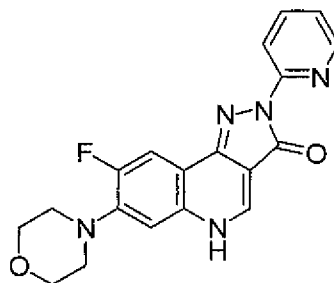


28b

[0247] *8-Fluoro-7-morpholin-4-yl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28b)*: The title compound was obtained following procedure described in the synthesis of **28a** using **27a** and morpholine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.11 (4H, br), 3.80 (4H, m), 7.11 (1H, t, $J = 7.08$ Hz), 7.24 (1H, d, $J = 7.81$ Hz), 7.38 (2H, t, $J = 7.38$ Hz), 7.80 (1H, d, $J = 12.93$ Hz), 8.17 (2H, d, $J = 8.30$ Hz), 8.67 (1H, s). m/z 365.4 (MH^+).

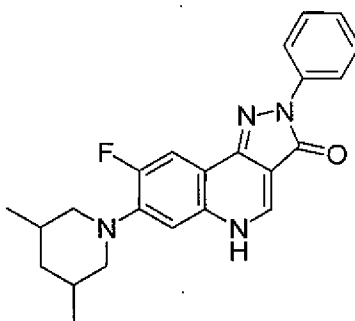
Example 26**28c**

[0248] *8-Fluoro-7-(4-isopropylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28c)*: The title compound was obtained following procedure described in the synthesis of **28a** using **27a** and 1-isopropylpiperazine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 1.03 (6H, d, $J = 6.04$ Hz), 2.70 (4H, br), 3.02 (1H, m), 3.13 (4H, m), 7.13 (1H, t, $J = 7.41$ Hz), 7.22 (1H, d, $J = 7.69$ Hz), 7.40 (2H, t, $J = 7.97$ Hz), 7.77 (1H, d, $J = 13.19$ Hz), 8.19 (2H, d, $J = 7.42$ Hz), 8.66 (1H, s). m/z 406.5 (MH^+).

Example 27**28d**

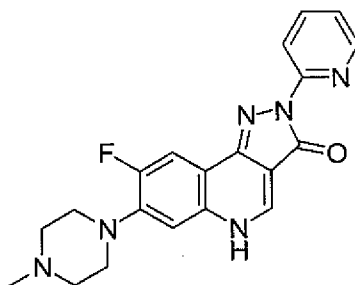
[0249] *8-Fluoro-7-(morpholin-4-yl)-2-pyridin-2-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28d)*: The title compound was obtained following procedure described in the synthesis of **28a** using **27b** and morpholine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.10 (4H, br), 3.77 (4H, m), 7.18 (1H, t, $J = 7.08$ Hz), 7.25 (1H, d, $J = 7.92$ Hz), 7.79 (1H, d, $J = 13.18$ Hz), 7.86 (1H, m), 8.20 (1H, d, $J = 8.24$ Hz), 8.46 (1H, m), 8.66 (1H, d, $J = 1.65$ Hz). m/z 366.4 (MH^+).

Example 28

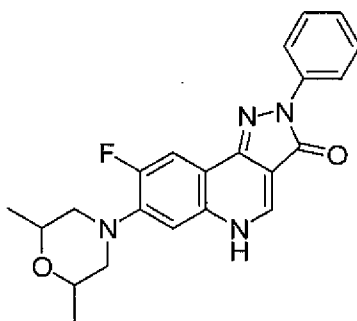
**28e**

[0250] *7-(3,5-Dimethylpiperidin-1-yl)-8-fluoro-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28e)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and 3,5-dimethylpiperidine. ¹H-NMR (DMSO-d₆) δ (ppm): 0.99 (6H, d, J = 6.33 Hz), 1.80 (4H, br), 2.47 (2H, t, J = 8.62 Hz), 3.46 (2H, brd, J = 11.81 Hz), 7.13 (1H, m), 7.26 (1H, d, J = 7.97 Hz), 7.40 (2H, t, J = 7.69 Hz), 7.79 (1H, d, J = 13.18 Hz), 8.19 (2H, d, J = 7.69 Hz), 8.65 (1H, s). m/z 391.5 (MH⁺).

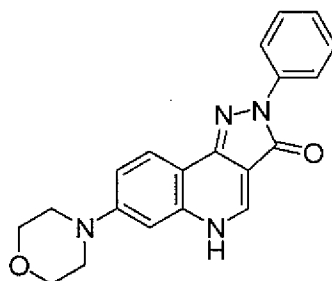
Example 29

**28f**

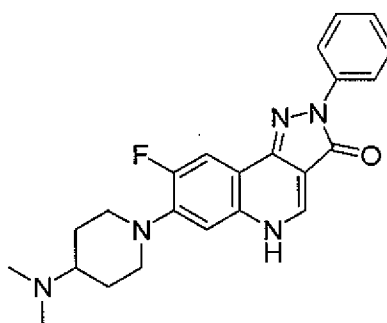
[0251] *8-Fluoro-7-(4-methylpiperazin-1-yl)-2-pyridin-2-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28f)*: The title compound was obtained following procedure described in the synthesis of **28a** using **27b** and 1-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.46 (3H, s), 3.09 (4H, br), 3.29 (4H, brm), 7.16 (1H, m), 7.22 (1H, d, J = 8.24 Hz), 7.84 (2H, m), 8.26 (1H, dd, J = 8.24, 0.83 Hz), 8.45 (1H, m), 8.56 (1H, s). m/z 379.4 (MH⁺).

Example 30**28g**

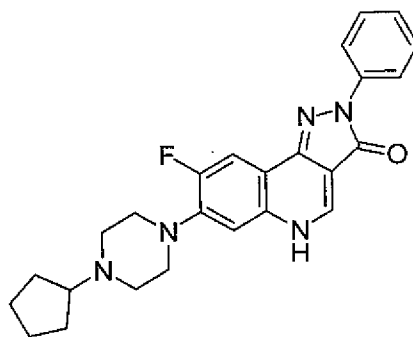
[0252] *7-(2,6-Dimethylmorpholin-4-yl)-8-fluoro-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28g)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and 2,6-dimethylmorpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.15 (6H, d, J = 6.73 Hz), 2.40 (2H, brm), 3.41 (2H, d, J = 10.99 Hz), 3.76 (2H, brm), 7.13 (1H, m), 7.26 (1H, d, J = 7.69 Hz), 7.41 (2H, t, J = 7.42 Hz), 7.83 (2H, d, J = 12.91 Hz), 8.19 (2H, m), 8.66 (1H, s). m/z 393.4 (MH⁺).

Example 31**28h**

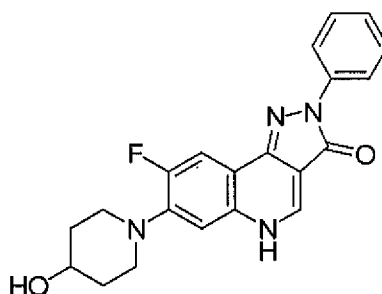
[0253] *7-Morpholin-4-yl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28h)*: The title compound was prepared following the procedure described in Step 3 using ethyl-4-chloro-7-morpholinoquinoline-3-carboxylate instead of **4a**. ¹H-NMR (DMSO-d₆) δ (ppm): 3.25 (4H, br), 3.77 (4H, m), 7.01 (1H, d, J = 2.95 Hz), 7.12 (1H, t, J = 7.32 Hz), 7.29 (1H, dd, J = 9.52, 2.19 Hz), 7.40 (2H, t, J = 7.32 Hz), 8.00 (1H, d, J = 9.03 Hz), 8.17 (2H, d, J = 9.03 Hz), 8.59 (1H, s). m/z 347.4 (MH⁺).

Example 32**28i**

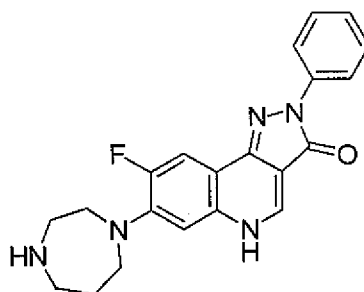
[0254] 7-(4-Dimethylaminopiperidin-1-yl)-8-fluoro-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (**28i**): The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and 4-dimethylaminopiperidine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.56 (2H, brm), 1.89 (2H, brm), 2.22 (6H, s), 2.74 (2H, brm), 3.13 (1H, brm), 3.52 (2H, brm), 7.10 (1H, m), 7.22 (1H, d, J = 7.96 Hz), 7.40 (2H, t, J = 7.42 Hz), 7.76 (2H, d, J = 2.91 Hz), 8.20 (2H, m), 8.64 (1H, s). m/z 406.4 (MH⁺).

Example 33**28j**

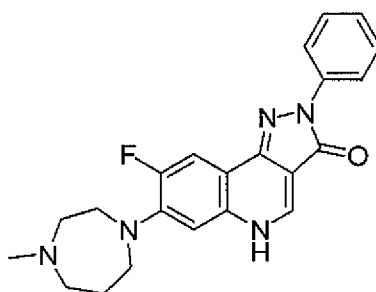
[0255] 7-(4-Cyclopentylpiperazin-1-yl)-8-fluoro-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (**28j**): The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and 1-cyclopentylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.20-1.85 (9H, brm), 2.58 (4H, brm), 3.11 (4H, brm), 7.10 (1H, m), 7.22 (1H, d, J = 7.94 Hz), 7.40 (2H, m), 7.76 (1H, d, J = 2.91 Hz), 8.19 (2H, m), 8.64 (1H, s). m/z 431.2 (MH⁺).

Example 34**28k**

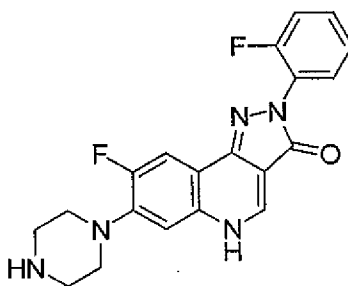
[0256] *8-Fluoro-7-(4-hydroxypiperidin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28k)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and 4-hydroxypiperidine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.54 (2H, brm), 1.87 (2H, brm), 2.85 (2H, brm), 3.20 (1H, m), 3.64 (1H, brm), 4.74 (1H, brd, J = 3.84 Hz), 7.10 (1H, m), 7.22 (1H, d, J = 7.97 Hz), 7.40 (2H, m), 7.76 (1H, d, J = 2.90 Hz), 8.20 (2H, m), 8.64 (1H, s). m/z 379.2 (MH⁺).

Example 35**28l**

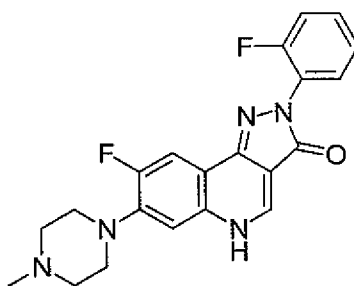
[0257] *8-Fluoro-7-(perhydro[1,4]-diazepin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28l)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and homopiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.98 (2H, brm), 2.48 (2H, brm), 2.67 (2H, brm), 3.45 (4H, brm), 7.15 (2H, m), 7.40 (2H, m), 7.76 (1H, d, J = 2.91 Hz), 8.20 (2H, m), 8.64 (1H, s). m/z 378.2 (MH⁺).

Example 36**28m**

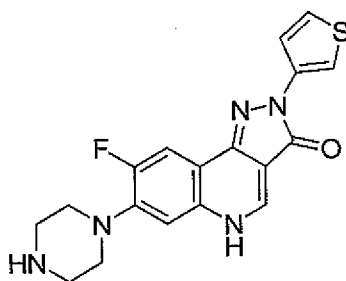
[0258] *8-Fluoro-7-(4-methylperhydro[1,4]-diazepin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28m)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27a** and 1-methylperhydro[1,4]-diazepine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.98 (2H, brm), 2.27 (3H, s), 2.68 (4H, brm), 3.24 (4H, brm), 7.15 (2H, m), 7.40 (2H, m), 7.76 (1H, d, J = 2.91 Hz), 8.20 (2H, m), 8.64 (1H, s). m/z 392.2 (MH⁺).

Example 37**28n**

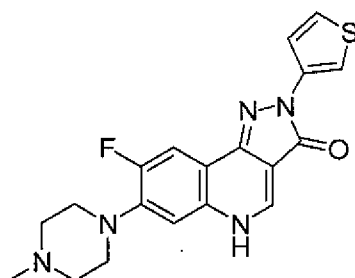
[0259] *8-Fluoro-2-(2-fluorophenyl)-7-(piperazin-1-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28n)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27c** and piperazine. ¹H-NMR (CD₃OD) δ (ppm): 3.01 (4H, brm), 3.34 (4H, brm), 7.05 (1H, d, J = 7.7 Hz), 7.16 (2H, m), 7.31 (1H, m), 7.40 (1H, m), 7.66 (1H, d, J = 13.1 Hz), 8.44 (1H, s). m/z 382.2

Example 38**28o**

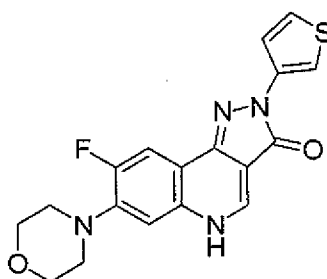
[0260] *8-fluoro-2-(2-fluorophenyl)-7-(4-methylpiperazin-1-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28o)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27c** and 1-methylpiperazine. ¹H-NMR (CD₃OD) δ (ppm): 2.23 (3H, s), 2.48 (4H, brm), 2.68 (4H, brm), 7.05 (1H, d, J = 7.7 Hz), 7.16 (2H, m), 7.31 (1H, m), 7.40 (1H, m), 7.66 (1H, d, J = 13.1 Hz), 8.44 (1H, s). m/z 396.2

Example 39**28p**

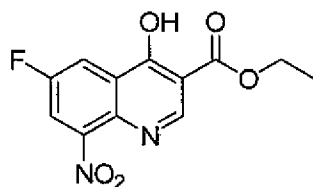
[0261] *8-fluoro-7-(piperazin-1-yl)-2-(thiophen-3-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28p)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27d** and piperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.92 (4H, brm), 3.05 (4H, brm), 7.21 (1H, m), 7.58 (1H, m), 7.79 (3H, m), 8.67 (1H, m). m/z 370.2

Example 40**28q**

[0262] *8-fluoro-7-(4-methylpiperazin-1-yl)-2-(thiophen-3-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28q)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27d** and 1-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.28 (3H, s), 2.64 (4H, brm), 3.22 (4H, brm), 7.21 (1H, m), 7.58 (1H, m), 7.79 (3H, m), 8.67 (1H, m). m/z 384.2

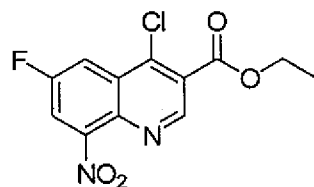
Example 41**28r**

[0263] *8-fluoro-7-(morpholin-4-yl)-2-(thiophen-3-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (28r)*: The title compound was prepared following the procedure described in the synthesis of **28a** using **27d** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.11 (4H, brm), 3.79 (4H, brm), 7.21 (1H, m), 7.58 (1H, m), 7.79 (3H, m), 8.67 (1H, m). m/z 371.2



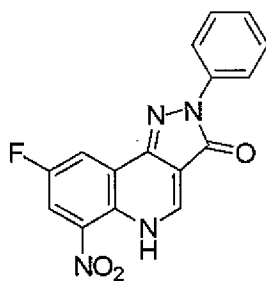
35

[0264] *Ethyl 6-fluoro-4-hydroxy-8-nitroquinoline-3-carboxylate (35)*: The title compound was prepared following the procedure described in Step 1 using 4-fluoro-2-nitroaniline instead of 4-nitroaniline. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 1.26 (3H, t, $J = 7.14$ Hz), 4.20 (2H, q, $J = 7.15$ Hz), 8.31 (1H, dd, $J = 8.24, 3.02$ Hz), 8.57 (1H, brs), 8.64 (1H, dd, $J = 8.24, 3.02$ Hz). m/z 281.3 (MH^+).



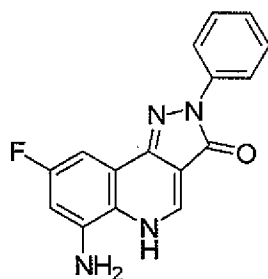
36

[0265] *Ethyl 4-chloro-6-fluoro-8-nitroquinoline-3-carboxylate (36)*: The title compound was prepared following the procedure described in Step 2 using **35**. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.46 (3H, t, $J = 7.14$ Hz), 4.55 (2H, q, $J = 7.14$ Hz), 7.94 (1H, dd, $J = 7.14, 2.75$ Hz), 8.29 (1H, dd, $J = 8.79, 2.74$ Hz), 9.27 (1H, s). m/z 299.7 (MH^+).



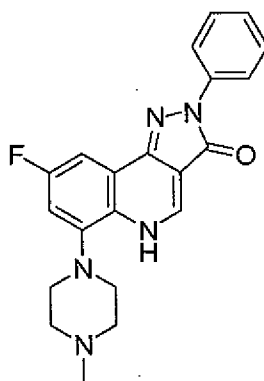
37

[0266] *8-Fluoro-6-nitro-2-phenyl-2,5-dihydropyrazolo-[4,3-c]quinolin-3-one (37)*: The title compound was prepared following the procedure described in Step 3 using **36**. m/z 325.3 (MH^+).

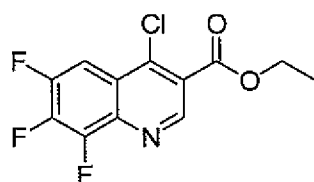
**38**

[0267] *6-Amino-8-fluoro-2-phenyl-2,5-dihydropyrazolo-[4,3-c]quinolin-3-one* (**38**): The title compound was prepared following the procedure described in Step 4 using **37**. m/z 295.3 (MH^+).

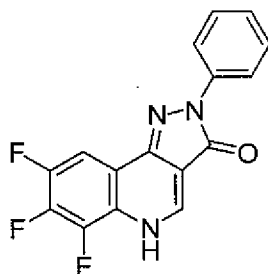
Example 42

**39**

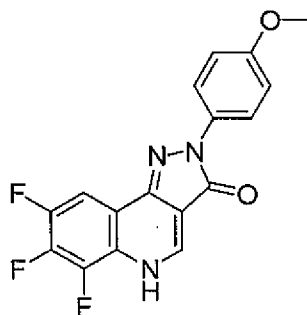
[0268] *8-Fluoro-6-(4-methylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo [4,3-c]quinolin-3-one* (**39**): The title compound was prepared following the procedure in Step 5 using **38**. 1H -NMR (DMSO- d_6) δ (ppm): 2.40 (3H, s), 3.18 (4H, brm), 3.67 (4H, brm), 7.16 (1H, m), 7.39 (2H, m), 7.48 (1H, dd, $J = 9.17, 2.74$ Hz), 7.69 (2H, dd, $J = 8.51, 2.75$ Hz), 8.19 (2H, d, $J = 7.70$ Hz), 8.46 (1H, d, $J = 6.59$ Hz). m/z 378.4 (MH^+).

Example 43**42**

[0269] *Ethyl 4-chloro-6,7,8-trifluoro-quinoline-3-carboxylate (42)*: The title compound was prepared following the procedure described in Step 2 using ethyl 4-hydroxy-6,7,8-trifluoro-quinoline-3-carboxylate instead of **3**. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.44 (3H, t, $J = 7.14$ Hz), 4.55 (2H, q, $J = 7.14$ Hz), 8.04 (1H, m), 9.22 (1H, s). m/z 290.7 (MH^+).

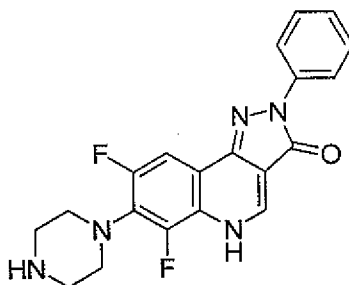
**43a**

[0270] *6,7,8-Trifluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (43a)*: The title compound was prepared following the procedure described for **4a** using **42**. $^1\text{H-NMR}$ (DMSO-d_6) δ (ppm): 7.22 (1H, m), 7.44 (2H, m), 8.05 (1H, m), 8.18, 3H, m), 8.16 (2H, m), 8.60 (1H, s). m/z 316.2 (MH^+).

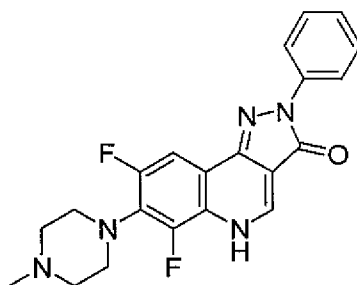
**43b**

[0271] *6,7,8-Trifluoro-2-(4-methoxyphenyl)-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (43b)*: The title compound was prepared following the procedure described for **4a** using **42** and 4-methoxyphenylhydrazine. m/z 346.2 (MH^+).

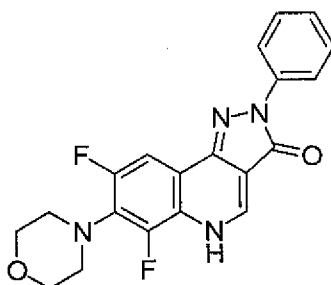
Example 44

**44a**

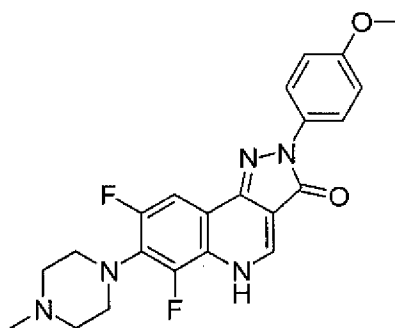
[0272] *6,8-Difluoro-2-phenyl-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (44a)*: The title compound was obtained following procedure described in the synthesis of **19b** using **43a** and piperazine. 1H -NMR (DMSO- d_6) δ (ppm): 3.05 (4H, brm), 3.32 (4H, brm), 7.02 (1H, m), 7.36 (3H, m), 7.54 (1H, d, $J = 12.0$ Hz), 8.28 (2H, d, $J = 7.8$ Hz), 8.40 (1H, s). m/z 382.4 (MH^+).

Example 45**44b**

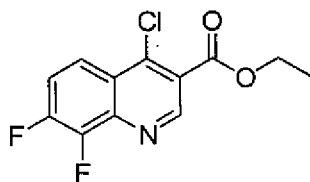
[0273] *6,8-Difluoro-7-(4-methyl-piperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo [4,3-c]quinolin-3-one (44b)*: The title compound was obtained following procedure described in the synthesis of **19b** using **43a** and 1-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.33 (3H, s), 2.64 (4H, brm), 3.24 (4H, brm), 7.15 (1H, m), 7.38 (3H, m), 8.18 (2H, m), 8.47 (1H, s). m/z 396.4 (MH⁺).

Example 46**44c**

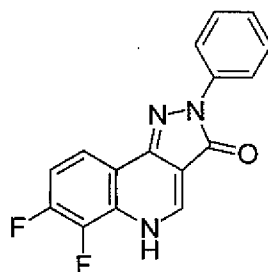
[0274] *6,8-Difluoro-7-(morpholin-4-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c] quinolin-3-one (44c)*: The title compound was obtained following procedure described in the synthesis of **19b** using **43a** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.17 (4H, brm), 3.78 (4H, brm), 7.15 (1H, m), 7.42 (3H, m), 8.17 (2H, m), 8.49 (1H, s). m/z 383.4 (MH⁺).

Example 47**44d**

[0275] *6,8-Difluoro-2-(4-methoxyphenyl)-7-(4-methylpiperazin-1-yl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (44d)*: The title compound was obtained following procedure described in the synthesis of **19b** using **43b** and 1-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.28 (3H, s), 2.75 (2H, brm), 2.82 (2H, brm), 3.09 (4H, brm), 3.75 (3H, s), 6.99 (2H, d, J = 9.0 Hz), 7.45 (1H, m), 8.06 (2H, d, J = 9.0 Hz), 8.33 (1H, s). m/z 426.2 (MH⁺).

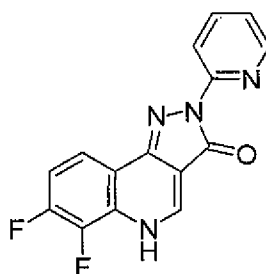
**46**

[0276] *Ethyl 4-chloro-7,8-difluoroquinoline-3-carboxylate (46)*: The title compound was prepared following the procedure described in Step 2 using Ethyl-7,8-difluoro-4-hydroxy-quinoline-3-carboxylate instead of **3**. ¹H-NMR (CDCl₃) δ (ppm): 1.46 (3H, t, J = 7.14 Hz), 4.52 (2H, q, J = 7.14 Hz), 7.60 (1H, m), 8.24 (1H, m), 9.25 (1H, s). m/z 272.7 (MH⁺).

**47a**

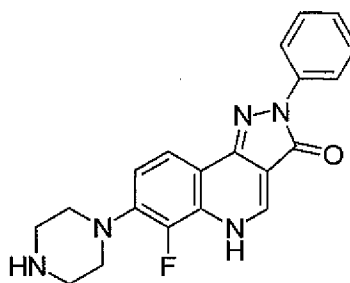
[0277] *6,7-Difluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one*

(47a): The title compound was prepared following the procedure described for **4a** using **46**. ¹H-NMR (DMSO-d₆) δ (ppm):7.17 (1H, m), 7.44 (2H, m), 8.04 (1H, ddd, J = 9.07, 5.22, 2.20 Hz), 8.17, 2H, m), 8.56 (1H, s). m/z 298.3 (MH⁺).

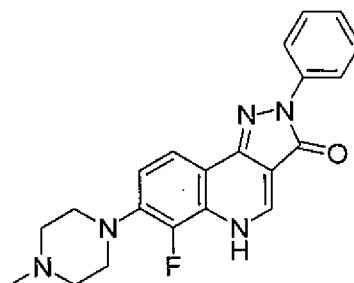
**47b**

[0278] *6,7-Difluoro-2-(2-pyridyl)-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one*

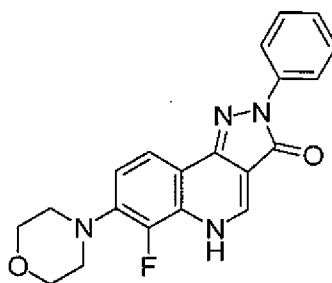
(47b): The title compound was prepared following the procedure described for **4a** using **46** and pyridyl-2-hydrazine. ¹H-NMR (DMSO-d₆) δ (ppm):7.24 (1H, ddd, J = 7.42, 4.94, 1.10 Hz), 7.60 (1H, m), 7.90 (1H, m), 8.02 (1H, m), 8.18 (1H, d, J = 8.24 Hz), 8.49 (1H, ddd, J = 4.95, 1.92, 0.83 Hz), 8.57 (1H, s). m/z 299.3 (MH⁺).

Example 48**48a**

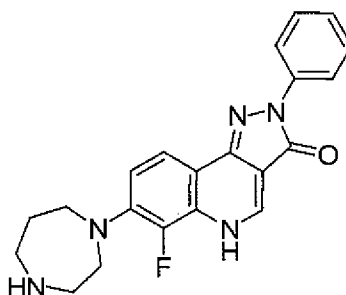
[0279] *6-Fluoro-2-phenyl-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (48a)*: The title compound was obtained following procedure described in the synthesis of **19b** using **47a** and piperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.03 (4H, brm), 3.14 (4H, brm), 7.08 (1H, m), 7.17 (1H, t, J = 8.52 Hz), 7.36 (2H, m), 7.87 (1H, dd, J = 8.79, 1.37 Hz), 8.23 (2H, ddd, J = 7.42, 1.65, 1.37 Hz), 8.41 (1H, s). m/z 364.3 (MH⁺).

Example 49**48b**

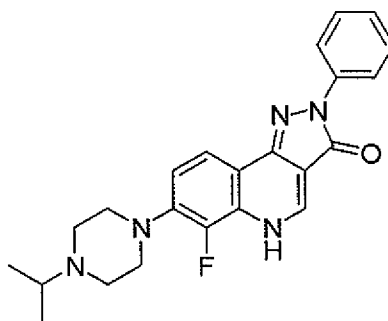
[0280] *6-Fluoro-7-(4-methyl-piperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (48b)*: The title compound was obtained following procedure described in the synthesis of **19b** using **47a** and 1-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.24 (3H, s), 2.53 (4H, brm), 3.18 (4H, brm), 7.13 (1H, m), 7.26 (1H, t, J = 8.79 Hz), 7.42 (2H, m), 7.90 (1H, dd, J = 8.79, 1.37 Hz), 8.23 (2H, ddd, J = 7.42, 1.65, 1.37 Hz), 8.41 (1H, s). m/z 378.4 (MH⁺).

Example 50**48c**

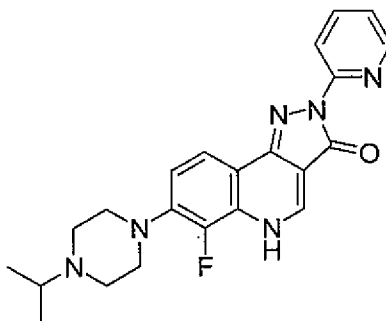
[0281] *6-Fluoro-7-(morpholin-4-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (48c)*: The title compound was obtained following procedure described in the synthesis of **19b** using **47a** and morpholine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 3.16 (4H, brm), 3.76 (4H, brm), 7.11 (1H, m), 7.26 (1H, t, $J = 8.79$ Hz), 7.41 (2H, m), 7.93 (1H, dd, $J = 8.79, 1.33$ Hz), 8.17 (2H, m), 8.42 (1H, s). m/z 365.3 (MH^+).

Example 51**48d**

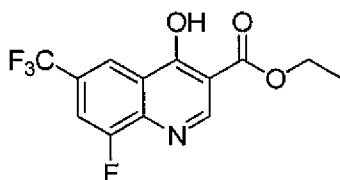
[0282] *6-Fluoro-7-(perhydro[1,4]-diazepine-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (48d)*: The title compound was obtained following procedure described in the synthesis of **19b** using **47a** and perhydro[1,4]-diazepine. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 1.96 (2H, brm), 2.98 (2H, brm), 3.10 (2H, brm), 3.53 (4H, brm), 7.10 (2H, m), 7.39 (2H, m), 7.78 (1H, d, $J = 8.79$ Hz), 8.23 (2H, m), 8.36 (1H, s). m/z 378.3 (MH^+).

Example 52**48e**

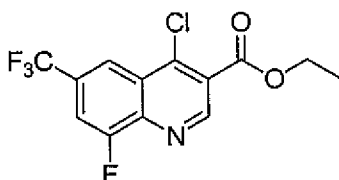
[0283] *6-Fluoro-7-(4-iso-propylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo [4,3-c]quinolin-3-one (48e)*: The title compound was obtained following procedure described in the synthesis of **19b** using **47a** and 1-*iso*-propylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.02 (6H, d, J = 6.59 Hz), 2.75 (4H, brm), 2.82 (1H, m), 3.24 (4H, brm), 7.12 (1H, m), 7.41 (3H, m), 8.08 (1H, m), 8.18 (2H, m), 8.42 (1H, s). m/z 406.3 (MH⁺).

Example 53**48f**

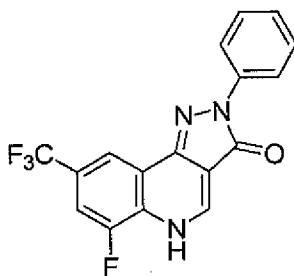
[0284] *6-Fluoro-7-(4-iso-propylpiperazin-1-yl)-2-(2'-pyridyl)-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (48f)*: The title compound was obtained following procedure described in the synthesis of **19b** using **47b** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.18 (4H, brm), 3.80 (4H, brm), 7.19 (1H, dd, J = 7.2, 4.9 Hz), 7.25 (1H, t, J = 8.5 Hz), 7.84 (1H, dd, J = 8.5, 2.0 Hz), 7.88 (1H, dd, J = 8.6, 2.07 Hz), 8.18 (1H, d, J = 8.4 Hz), 8.43 (1H, s), 8.47 (1H, m). m/z 365.3 (MH⁺).

**49**

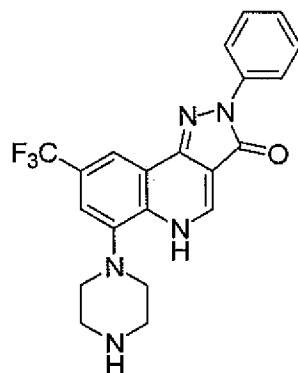
[0285] *Ethyl 8-fluoro-4-hydroxy-6-trifluoromethyl-quinoline-3-carboxylate (49)*: The title compound was prepared following the procedure described in Step 1 using 2-fluoro-4-trifluoromethyl-aniline instead of 4-nitroaniline. ¹H-NMR (DMSO-d₆) δ (ppm): 1.25 (3H, t, J = 7.14 Hz), 4.11 (2H, q, J = 7.14 Hz), 8.00 (2H, m), 8.70 (1H, s). m/z 304.2 (MH⁺).

**50**

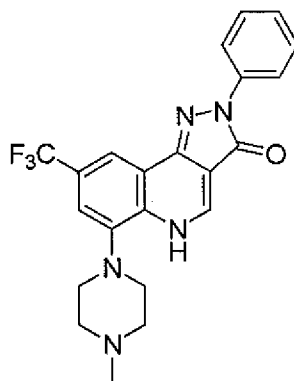
[0286] *Ethyl 4-chloro-8-fluoro-6-trifluoromethyl-quinoline-3-carboxylate (50)*: The title compound was prepared following the procedure described in Step 2 using **49** instead of **3**. ¹H-NMR (CDCl₃) δ (ppm): 1.47 (3H, t, J = 7.14 Hz), 4.56 (2H, q, J = 7.14 Hz), 8.16 (1H, d, J = 10.89 Hz), 8.48 (1H, d, J = 6.59 Hz), 9.24 (1H, s). m/z 322.7 (MH⁺).

**51**

[0287] *6-Fluoro-2-phenyl-8-trifluoromethyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (51)*: The title compound was prepared following the procedure described for **4a** using **50**. ¹H-NMR (DMSO-d₆) δ (ppm): 7.18 (1H, m), 7.21 (2H, m), 8.17 (4H, m), 8.88 (1H, s). m/z 348.3 (MH⁺).

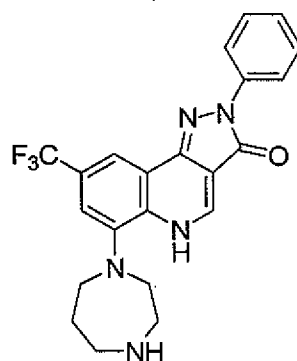
Example 54**52a**

[0288] *2-Phenyl-6-piperazin-1-yl-8-trifluoromethyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (52a)*: The title compound was obtained following procedure described in the synthesis of **19b** using **51** and piperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 3.04 (4H, brm), 3.31 (4H, brm), 7.07 (1H, m), 7.40 (2H, m), 7.93 (1H, s), 8.09 (1H, s), 8.28 (2H, m), 8.61 (1H, s). m/z 414.3 (MH⁺).

Example 55**52b**

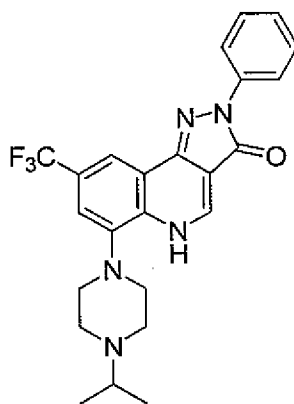
[0289] *2-Phenyl-6-(4-methylpiperazin-1-yl)-8-trifluoromethyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (52b)*: The title compound was obtained following procedure described in the synthesis of **19b** using **51** and 4-methylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.25 (3H, s), 2.55 (4H, brm), 3.01 (4H, brm), 7.16 (1H, m), 7.45 (2H, t, J = 7.96 Hz), 8.01 (1H, s), 8.19 (1H, s), 8.22 (2H, m), 8.80 (1H, s). m/z 428.3 (MH⁺).

Example 56

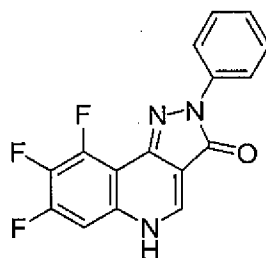
**52c**

[0290] *2-Phenyl-6-(perhydro[1,4]-diazepine-1-yl)-8-trifluoromethyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (52c)*: The title compound was obtained following procedure described in the synthesis of **19b** using **51** and perhydro[1,4]-diazepine. ¹H-NMR (DMSO-d₆) δ (ppm): 1.94 (2H, brm), 2.20 (2H, brm), 3.17 (4H, brm), 3.38 (2H, brm), 7.17 (1H, m), 7.43 (2H, t, J = 7.96 Hz), 8.04 (1H, s), 8.20 (1H, m), 8.26 (2H, s), 8.80 (1H, s). m/z 428.3 (MH⁺).

Example 57

**52d**

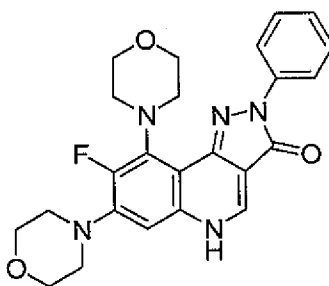
[0291] *2-Phenyl-6-(4-iso-propylpiperazin-1-yl)-8-trifluoromethyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (52d)*: The title compound was obtained following procedure described in the synthesis of **19b** using **51** and 1-iso-propylpiperazine. ¹H-NMR (CD₃OD) δ (ppm): 2.05 (4H, brm), 2.50 (6H, brd), 2.94 (4H, brm), 3.24 (1H, m), 7.30 (1H, m), 7.48 (2H, m), 7.95 (2H, m), 8.04 (1H, s), 8.36 (1H, s), 8.75 (1H, s). m/z 456.3 (MH⁺).



54

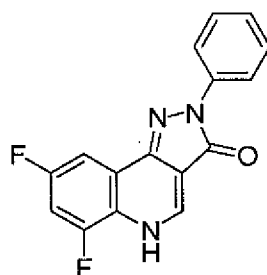
[0292] *7,8,9-Trifluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one* (54): The title compound was prepared following the procedure described for 4a in four steps starting from 3,4,5-trifluoroaniline. $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm): 7.15 (1H, t, $J = 7.82$ Hz), 7.42 (2H, m), 7.51 (1H, m), 8.15 (2H, m), 8.77 (1H, s). m/z 316.3 (MH^+).

Example 58



55

[0293] *7,9-Bis(morpholin-4-yl)-8-fluoro-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one* (55): The title compound was obtained following procedure described in the synthesis of 19b using 53 and morpholine. $^1\text{H-NMR}$ (DMSO) δ (ppm): 3.06 (4H, brm), 3.22 (4H, brm), 3.76 (4H, brm), 3.86 (4H, brm), 6.81 (1H, d, $J = 6.7$ Hz), 7.15 (1H, m), 7.46 (2H, m), 8.18 (2H, m), 8.57 (1H, s). m/z 450.3 (MH^+).

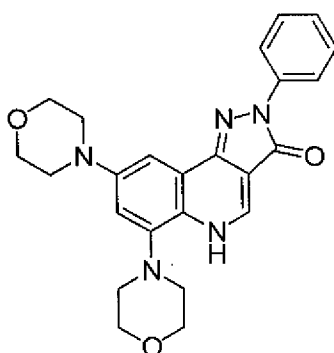


57

[0294] *6,8-Difluoro-2-phenyl-2,5-dihydro-pyrazolo-[4,3-c]quinolin-3-one (57):*

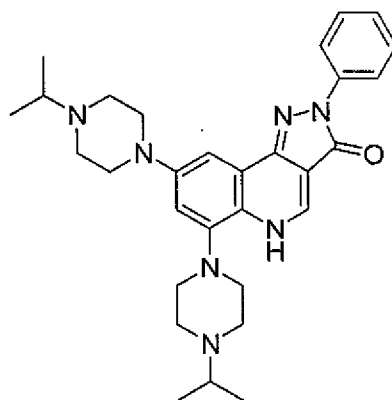
The title compound was prepared following the procedure described for **4a** in four steps starting from 2, 4-difluoroaniline. ¹H-NMR (DMSO-d₆) δ (ppm): 7.17 (1H, dt, J = 0.8, 7.7 Hz), 7.42 (2H, t, J = 7.7 Hz), 7.74 (2H, m), 8.18 (2H, dd, J = 7.8, 0.7 Hz), 8.52 (1H, s). m/z 298.2 (MH⁺).

Example 59

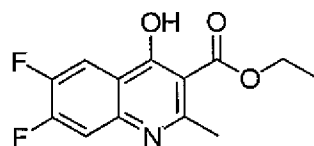


58a

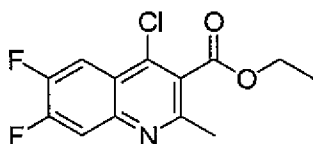
[0295] *6,8-Bis(morpholin-4-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (58a):* The title compound was obtained following procedure described in the synthesis of **19b** using **53** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.83 (4H, brm), 3.22 (4H, brm), 3.56 (4H, brm), 3.77 (4H, brm), 7.11 (1H, m), 7.26 (2H, dd, J = 6.2, 1.9 Hz), 7.41 (2H, dd, J = 7.8, 7.6 Hz), 8.20 (2H, d, J = 8.6 Hz), 8.26 (1H, s). m/z 432.4 (MH⁺).

Example 60**58b**

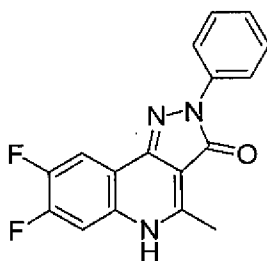
[0296] *6,8-Bis(4-isopropylpiperazin-1-yl)-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (58b)*: The title compound was obtained following procedure described in the synthesis of **19b** using **53** and 1-*iso*-propylpiperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 0.99 (6H, d, J = 6.8 Hz), 1.01 (6H, d, J = 7.4 Hz), 2.72 (4H, brm), 2.83 (6H, br,m), 2.92 (4H, brm), 3.22 (4H, brm), 7.19 (3H, m), 7.41 (2H, m), 8.24 (3H, m). m/z 514.4 (MH⁺).

**60**

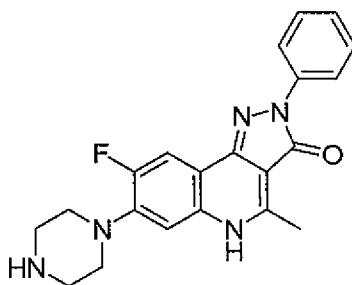
[0297] *Ethyl 6,7-difluoro-4-hydroxy-2-methyl-quinoline-3-carboxylate (60)*: A solution of difluoro-isatoic anhydride in N,N-dimethylacetamide was added to a solution of sodium hydride (1.1 equiv.) and ethyl acetoacetate (1.1 equiv.) in N,N-dimethylacetamide with stirring at room temperature. The mixture was heated at 120 °C for 10 minutes. The solvent was removed *in vacuo* and 6, 7,4-hydroxy-2-methyl-quinoline-3-carboxylic acid ethyl ester (**2g**) was precipitated with water followed by filtration. ¹H NMR (DMSO-d₆) δ (ppm): 1.21 (3H, t, J = 7.14 hz), 2.30 (3H, s), 4.10 (2H, q, J = 7.14 Hz), 7.43 (1H, dd, J = 10.71, 7.69 Hz), 7.82 (1H, dd, J = 10.69, 8.24 Hz. m/z 268.7 (MH⁺).

**61**

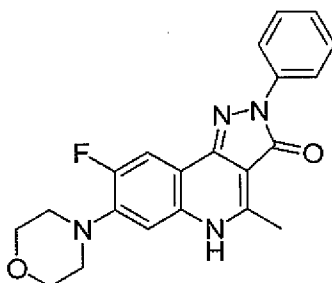
[0298] *Ethyl 4-chloro-6,7-difluoro-2-methyl-quinoline-3-carboxylate (61)*: A suspension of 4-hydroxy quinoline **60** was refluxed with phosphorus oxychloride for 30 minutes. To the cooled reaction mixture was added aqueous ammonia and the product was obtained by extracting with methylene chloride, dried over sodium sulfate and concentrated *in vacuo*. $^1\text{H NMR}$ (CDCl_3) δ (ppm): 1.44 (3H, t, $J = 7.14$ Hz), 2.70 (3H, s), 4.50 (2H, q, $J = 7.14$ Hz), 7.62 (1H, t, $J = 7.69$ Hz), 7.78 (1H, dd, $J = 10.71, 7.69$ Hz), 7.95 (2H, d, $J = 10.72, 8.24$ Hz). m/z 286.7 (MH^+).

**62**

[0299] *7,8-Difluoro-4-methyl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (62)*: The title compound was synthesized following the procedure described in synthesis of 4a using **61** and phenyl hydrazine. $^1\text{H NMR}$ (DMSO-d_6) δ (ppm): 2.80 (3H, s), 6.87 (1H, m), 7.19 (1H, m), 7.34 (1H, m), 7.42 (1H, m), 7.61 (1H, m), 8.17 (1H, m). m/z 312.2 (MH^+).

Example 61**63a**

[0300] *8-Fluoro-4-methyl-2-phenyl-7-piperazin-1-yl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (63a)*: The title compound was obtained following procedure described in the synthesis of **19b** using **62** and piperazine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.76 (3H, s), 2.87 (4H, brm), 3.01 (4H, brm), 7.10 (2H, m), 7.40 (2H, dd, J = 8.24, 7.69 Hz), 7.72 (1H, d, J = 13.19 Hz), 8.19 (2H, dd, J = 8.79, 1.10 Hz), m/z 378.4 (MH⁺).

Example 62**63b**

[0301] *8-Fluoro-4-methyl-7-morpholin-4-yl-2-phenyl-2,5-dihydro-pyrazolo[4,3-c]quinolin-3-one (63b)*: The title compound was obtained following procedure described in the synthesis of **19b** using **62** and morpholine. ¹H-NMR (DMSO-d₆) δ (ppm): 2.74 (3H, s), 3.11 (4H, brm), 3.77 (4H, brm), 7.15 (2H, m), 7.41 (2H, dd, m), 7.76 (1H, d, J = 12.91 Hz), 8.18 (2H, d, J = 8.51 Hz), m/z 379.4 (MH⁺).

BIOLOGICAL EXAMPLES

[0302] The ability of a compound disclosed herein to act as ligand to the benzodiazepine site of GABA_A can be determined using pharmacological models which are

well known in the art using the following assay. The IC₅₀ values for the exemplified compounds range from sub nM to 10 μM in a 3-concentration dose response curve.

Benzodiazepine binding assay

[0303] Whole brain (except cerebellum) of male Wistar derived rats weighing 175 ± 25 g were used to prepare GABA_A central benzodiazepine receptor in Na-K phosphate buffer pH 7.4. A 5 mg aliquot was incubated with 1 nM (³H)-flunitrazepam for 60 minutes at 25°C. Experiments were performed in the presence or absence of 30 μM of GABA. Non-specific binding was estimated in the presence of 10 μM of diazepam. Membranes were filtered and washed, the filters were then counted to determine (³H)-flunitrazepam specifically bound. Test compounds were tested in duplicate according to the required concentrations (Damm, H.W., *et al.* (1978) *Res. Comm. Chem. Pathol. Pharmacol.* 22: 597-560 incorporated herein in its entirety; Speth, R.C., *et al.* (1979) *Life Sci.* 24: 351-357 incorporated herein in its entirety).

Examples of activity:

[0304] wherein:

A indicates an IC₅₀ of >1mM

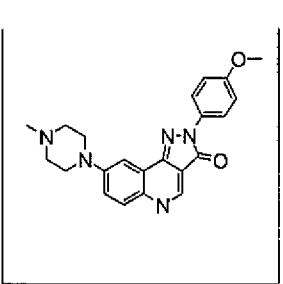
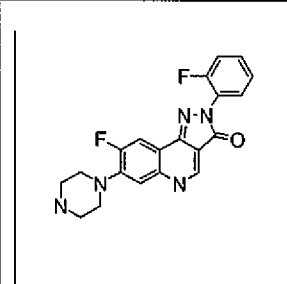
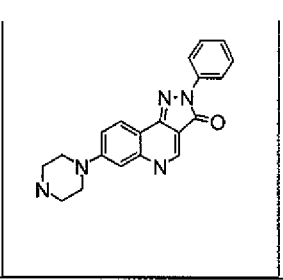
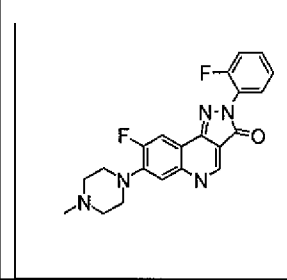
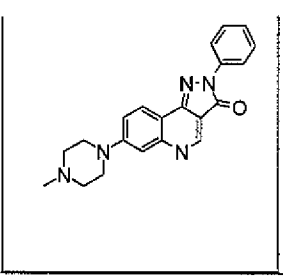
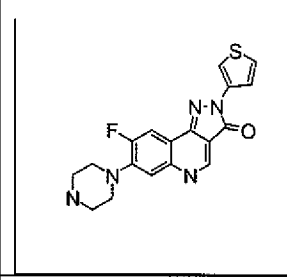
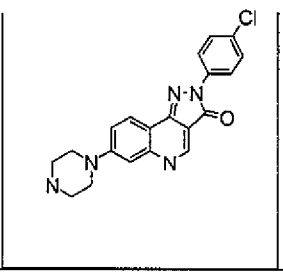
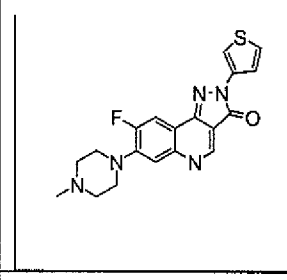
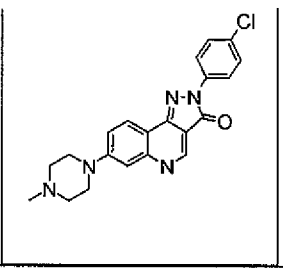
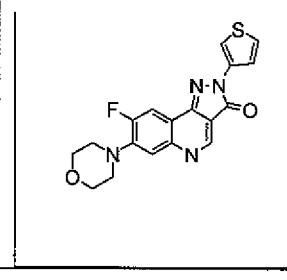
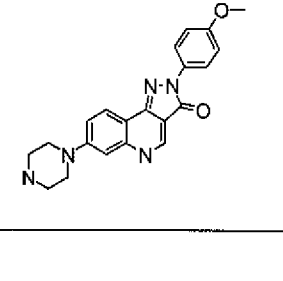
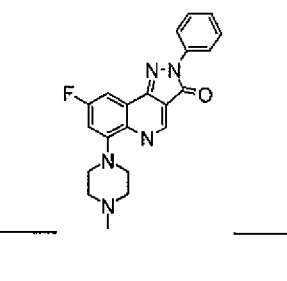
B indicates an IC₅₀ of <1mM

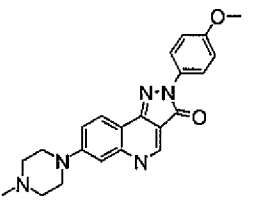
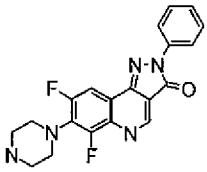
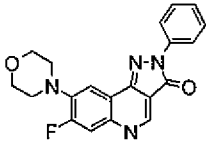
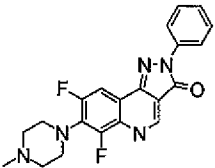
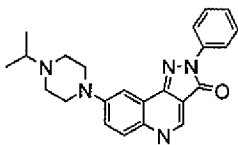
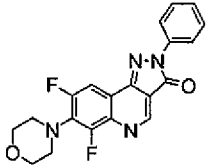
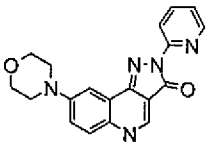
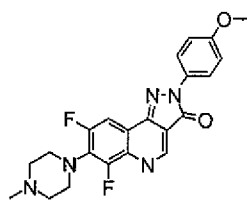
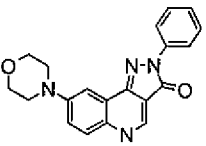
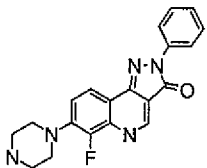
C indicates an IC₅₀ of <1nM

[0305] All compounds disclosed in Table 1 are assumed to be drawn as neutral. If not indicated, a hydrogen atom is assumed to be present on nitrogen atoms to provide a neutral compound. The compounds of Table 1 can exist in additional isomeric forms, for example, the compounds can exist as tautomers of the drawn structures. The compounds disclosed in Table 1 encompass all possible tautomers of the drawn structures. One of skill in the art will understand that a compound can exist in different tautomeric forms or mixtures thereof depending on the environment encompassing the compound, that is an equilibrium can exist between the different tautomeric forms of the compounds and the equilibrium between said forms can be influenced by outside factors. Note that salts, including acid addition salts are also contemplated.

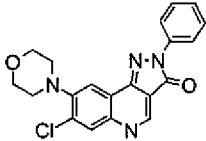
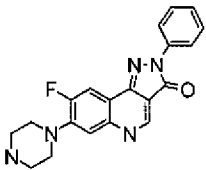
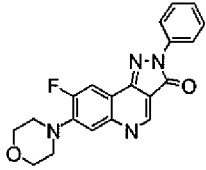
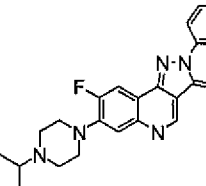
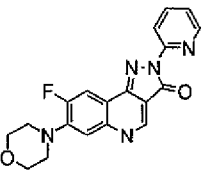
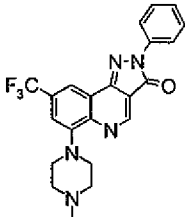
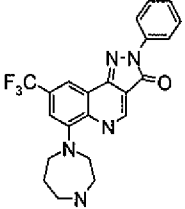
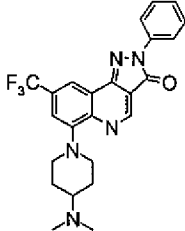
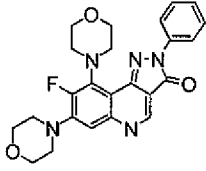
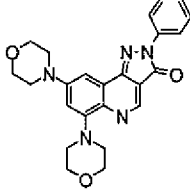
Table 1

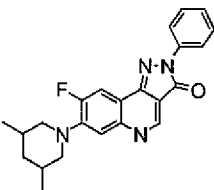
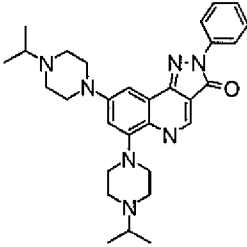
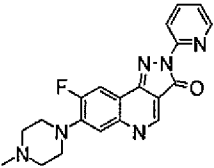
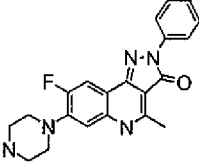
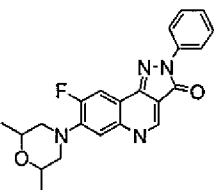
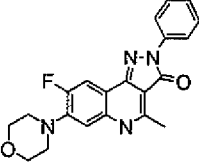
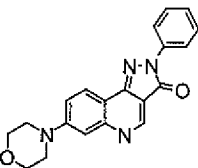
No.	Structure	BZ binding assay (IC ₅₀)	EP Result	No.	Structure	BZ binding assay (IC ₅₀)	EP Result
7a		B	Pos	28i		B	
7b		B	Pos	28j		B	
7c		B	Pos	28k		B	
7d		B	Pos	28l		B	
7e		B	Pos	28m		B	

7f		B	Pos	28n		A	
14a		A	Neg	28o		B	
14b		B	Neg	28p		B	Neg
14c		B	Neg	28q		A	
14d		B	Neg	28r		B	
14e		B	Neg	39		A	

14f		A	Neg	44a		B	Neg
19a		C	Pos	44b		B	Pos
19b		B	Pos	44c		B	Pos
19c		B	Neg	44d		B	Pos
19d		B	Neg	48a		A	

19e		B	Neg	48b		A	
19f		B	Pos	48c		B	
19g		B	Pos	48d		B	
19h		B		48e		B	
19i		B	Pos	48f		B	
19j		B	Neg	52a		B	

19k		B	Pos		
28a		B	Pos		
28b		B	Pos		
28c		B	Pos		
28d		B	Neg		
52b		B			
52c		B			
52d		B			
55		B			
58a		B	Neg		

28e		B	Pos	58b		B	Neg
28f		B	Pos	63a		A	
28g		B	Pos	63b		A	
28h		B	Pos				

[0306] The modulation of GABA_A function is determined by changes in current as determined in an electrophysiology assay, as is detailed below.

Electrophysiology Assay

Preparation of RNA

[0307] mRNA was prepared from lyophilized plasmid pellets containing cDNA inserts encoding the specific GABA_A receptor subunit. cDNAs encoding the α 2, α 3, and γ 3 subunits were subcloned into pBluescript, SK⁻. cDNAs encoding the α 1 and α 5 subunits were subcloned into pRC while cDNA encoding the β 2 subunit was subcloned into

pcDNA1. The cDNA construct encoding the $\alpha 2$ subunit is in the pGH19 expression construct. Overnight cultures of transformed DH5a bacterial cells were performed to grow sufficient quantities for maxiprep isolation of the plasmid cDNA. The resulting plasmid cDNA was linearized by digestion with an appropriate restriction enzyme that cleaves distal to the cDNA insert [XbaI ($\alpha 1$, $\beta 2$), NotI ($\alpha 3$, $\gamma 2$ s), SacII ($\alpha 2$), or ApaI ($\alpha 5$)]. Following digestion, plasmid cDNA was treated with proteinase K and extracted with phenol/chloroform/isoamyl alcohol, followed by ethanol precipitation. cDNA quality was assessed by agarose-gel electrophoresis (1.5% agarose gel). Samples were stored at -20°C until use. *In vitro* transcription was performed with T7 RNA polymerase. mRNA was then stored at -80°C until use. Plasmids were linearized with appropriate restriction enzymes before *in vitro* transcription using the Message Machine kit (Ambion, Austin, TX).

GABA_A receptor expression in Xenopus oocytes

[0308] GABA_A receptor expression in Xenopus oocytes: Following 45 min of 0.15% Tricaine anesthesia, an ovarian section containing the follicular oocytes was removed from the frog through a lateral abdominal incision. Oocytes were immediately placed in a calcium-free solution (NaCl 96 mM, MgCl₂ 1 mM, KCl 2mM, Hepes 50 mM, pyruvate 2.5 mM, gentamycin 100 $\mu\text{g}/\text{mL}$, penicillin-streptomycin 50 U/mL, pH 7.4). Following 1.5-2 hour incubation in 0.2% collagenase (type II, Sigma Chemical Co., St. Louis, MO) at room temperature, individual Dumont stage V and VI oocytes were transferred to an incubator and maintained overnight in Barth's solution (NaCl 84 mM, NaHCO₃ 2.4 mM, MgSO₄ 0.82 mM, KCl 1 mM, Ca(NO₃)₂ 0.33 mM, CaCl₂ 0.41 mM, Tris/HCl 7.5 mM, pyruvate 2.5 mM, gentamycin 50 $\mu\text{g}/\text{mL}$, penicillin-streptomycin, 100 units/mL, pH 7.4) at 18-20°C and used for experiments 1-5 days post-injection. Oocytes were injected solution using an electronic microinjector (Drummond, Broomall, PA) with 50 nL of RNA containing 0.3-0.5 ng of each subunit RNA in a 1:1: 2 ratio. The injected oocytes were used for experiments after 1-5 days of incubation in Barth's solution at 18-20°C.

Electrophysiology

[0309] Measurements of ion currents from oocytes expressing GABA_A receptors were performed using a Warner two-electrode voltage-clamp amplifier (Warner Instruments, Inc., Foster City, CA) (Park-Chung, M.A., *et al.* (1999) *Brain Res.* 830: 72-87 incorporated herein in its entirety). Microelectrodes were fabricated from borosilicate glass capillaries with a programmed pipette puller (Sutter Instrument Co., CA). Microelectrode resistance was 1-3 MΩ when filled with 3 M KCl. The oocyte recording chamber was continuously perfused with ND-96 solution. Oocytes were clamped at a holding potential of -70mV during data acquisition. The membrane current was filtered at 10 Hz and sampled at 100 Hz. Compounds were applied by a gravity-driven external perfusion system. The working volume of the recording chamber was 30 mL and the rate of the perfusion was approximately 50 mL/sec. Compound application was 20-25 sec followed by a minimum of 150 sec wash. Data acquisition and external perfusion was computer controlled by custom-developed software. All experiments were performed at room temperature (22-24°C). Dose-response data from each oocyte were fitted to the Hill equation by non-linear regression using the equation:

$$I_{\text{GABA}} = E_{\text{max}} / (1 + (EC_{50}/c)^{n_H})$$

[0310] E_{max} is the maximum response, EC_{50} is the concentration producing 50% of the maximal response, n_H is the Hill coefficient and c is the concentration of agonist. Based on the GABA concentration-response curve fit, an EC_{20} for GABA was determined for each subunit combination, and this concentration was used for subsequent modulator concentration-response studies. Peak current measurements were normalized and expressed as a fraction of the peak control current measurements. Control current responses to an EC_{20} concentration of GABA were re-determined after every 2-4 modulator applications. Percent modulation was determined by the equation:

$$\% \text{ change} = (I'/I - 1) \times 100$$

where I is the control response at the GABA EC_{20} and I' the response in the presence of modulator (Lippa A, *et al.* (2005) *Proc. Natl. Acad. Sci. USA* 102(20): 7380-7385 incorporated herein in its entirety).

[0311] Some compounds showed positive modulation and some showed negative modulation at a screening concentration of 10 μM.

Object Recognition Assay

[0312] Effect on animal behavior, specifically improvement of cognitive function (including but not limited to both short-term/working memory and long-term memory), can be determined using a number of established protocols. One method, novel object recognition, is described below.

Object Recognition Assay

[0313] Object recognition is an ethologically relevant task for rodents, which does not result from negative reinforcement (foot shock). This task relies on the natural curiosity of rodents to explore novel objects in their environments more than familiar ones. Obviously, for an object to be “familiar,” the animal must have attended to it before and remembered that experience. Hence, animals with better memory will attend and explore a new object more than an object familiar to them. During testing, the animal is presented with the training object and a second, novel one. Memory of the training object renders it familiar to the animal, and it then spends more time exploring the new novel object rather than the familiar one (Bourtchouladze, R., *et al.* (2003) *Proc. Natl. Acad. Sci. USA* 100: 10518-10522 incorporated herein in its entirety). Recent neuroimaging studies in humans demonstrated that memory in object recognition depends on prefrontal cortex (PFC) (Deibert, E., *et al.* (1999) *Neurology* 52: 1413-1417 incorporated herein in its entirety). Consistent with these findings, rats with the PFC lesions show poor working memory when they are required to discriminate between familiar and novel objects (Mitchell, J.B. and Laiacona, J. (1998) *Behav. Brain Res.* 97: 107-113 incorporated herein in its entirety). Other studies on monkeys and rodents suggest that the hippocampus is important for novel object recognition (Teng, E. *et al.* (2000) *J. Neuroscience* 20: 3853-3863 incorporated herein in its entirety; Mumby, D.G. (2001) *Behavioural Brain Research* 127: 159-181 incorporated herein in its entirety). Hence, object recognition provides an excellent behavioral model to evaluate drug-compound effects on cognitive task associated with function of hippocampus and cortex.

[0314] The strength of memory retention in most cases is dependent on the amount of training (repetition of explicit or implicit trials). This “memory acquisition

curve” can be influenced by many experimental and physical variables, which include, but are not limited to, temperature, humidity, ambient noise, lighting levels, the size of the training arena, the size and dimensions of the objects, the physical textures and colors of the training arena and the animal’s stress levels, motivational states or experiences prior to training. To evaluate memory enhancing compounds for NOR, the experimenter must parameterize training duration to define (i) the duration (amount of training) required to reach an asymptotic (high) level of memory retention and (ii) a lesser duration at which memory retention is sub-maximal. Memory enhancing compounds will produce higher memory retention with submaximal training (but may have no measurable effect with asymptotic (“maximal”) training. Typically, the difference between sub-maximal and asymptotic memory must be sufficiently larger to yield appropriate statistical power. An example which follows:

[0315] Prior to initiation of training, animals were handled and habituated to the training arena. Appropriately sized arenas were used for different species (e.g. for mice: a Plexiglas box of L=48 cm; W=38 cm and H=20 cm; for rats: a Plexiglas box of L=70 cm; W=60 cm and H=35 cm). The day before training, an individual animal was placed into a training apparatus located in a dimly lit room and allowed to habituate to the environment for 15 minutes (also see (Pittenger, C., *et al.* (2002) *Neuron* 34: 447-462 incorporated herein in its entirety; Bourtchouladze, R., *et al.* (2003) *Proc. Natl. Acad. Sci. USA* 100: 10518-10522 incorporated herein in its entirety). Training was initiated 24h hours after habituation. An animal was placed back into the training box, which contained two identical objects (e.g. a small conus-shape object), and was allowed to explore these objects. The objects were placed into the central area of the box and the spatial position of objects (left-right sides) was counterbalanced between subjects. Animals were trained for 15 minutes. To test for memory retention, animals were observed for 10 minutes 24 hours after training. A rodent was presented with two objects, one of which was used during training, and thus was ‘familiar’ and the other of which was novel (e.g. a small pyramid-shape object). To ensure that the discrimination targets do not differ in smell, after each experimental subject, the apparatus and the objects were thoroughly cleaned with 90% ethanol, dried and ventilated for a few minutes.

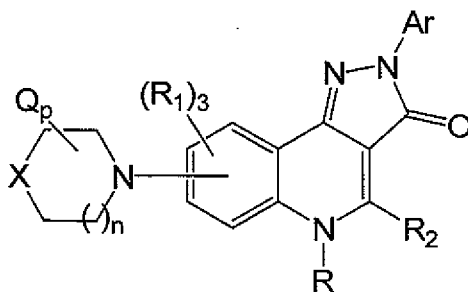
[0316] The experiments were videotaped via an overhead video camera system. Types were then reviewed by a blinded observer and the following behavioral parameters were determined: time of exploration of an each object; the total time of exploration of the objects; number of approaches to the objects; and time (latency) to first approach to an object. The discrimination index – memory score - was determined as described previously (Ennaceur, A. and Aggleton, J.P. (1997) *Behav. Brain Res.* 88: 181-193 incorporated herein in its entirety; Bourtchouladze, R., *et. al.* (2003) *Proc. Natl. Acad. Sci. USA* 100: 10518-10522 incorporated herein in its entirety). This Data was analyzed by Student's unpaired *t* test using a software package (Statview 5.0.1; SAS Institute, Inc). All values in the text and figures are expressed as mean \pm SEM.

[0317] For NOR, 1-hr memory retention represents a measure of decremental, short-term memory (usually transcription independent), which contributes to cognitive functions, such as working memory (radial arm maze, delayed match to sample, etc), executive function (task-switching, etc.) and attentional processes (priming, etc). Twenty-four hour memory retention represents a measure of long-term memory, to which STM is converted through the molecular and cellular processes of memory consolidation. LTM contributes to lasting cognitive functions such as reference memory.

[0318] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

WHAT IS CLAIMED:

1. A compound of formula (I):



(I)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein

R is hydrogen, or oxide;

each **R₁** is selected from the group consisting of hydrogen, hydroxy, halo, cyano, $-\text{CONR}_a\text{R}_b$, $-\text{NR}_a\text{R}_b$, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, amino(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

R₂ is selected from the group consisting of hydrogen, hydroxy, halo, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

each **R_a** and **R_b** is independently hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, (C₁-C₆)alkylaryl, $-\text{S}(\text{O})_z(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{O})_z\text{aryl}$, $-\text{C}(\text{O})(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{NR}_g(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{NR}_g\text{aryl}$, $-\text{C}(\text{O})\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, arylOC(O)- or arylC(O)-, or **R_a** together with **R_b** form a heterocycle group optionally substituted with one or more **R_d**; wherein the heterocycle group optionally include one or more groups selected from O (oxygen), S (sulfur), and **NR_c**;

each **R_c** is independently hydrogen, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, $-\text{C}(\text{O})\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{Oaryl}$, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, arylO(C₁-C₆)alkyl, $-\text{C}(\text{O})\text{NR}_g(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{NR}_g\text{aryl}$, $-\text{S}(\text{O})_z(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{O})_z\text{aryl}$, $-\text{C}(\text{O})(\text{C}_1\text{-C}_6)\text{alkyl}$, arylC(O)-,

(C₁-C₆)alkyl optionally substituted with up to 5 fluoro, or (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

each **R_d** is independently selected from the group consisting of hydrogen, halo, oxo, hydroxy, -C(O)NR_aR_b, -NR_aR_b, hydroxy(C₁-C₆)alkyl, aryl, aryl(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, and (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

each **R_e** and **R_f** is independently selected from hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, (C₁-C₆)alkylaryl, aryl(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl, -S(O)_z(C₁-C₆)alkyl, -S(O)_zNR_g(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)NR_g(C₁-C₆)alkyl, -C(O)(C₁-C₆)alkyl, arylC(O)-, arylOC(O)-, or -C(O)O(C₁-C₆)alkyl;

R_g is hydrogen, aryl, heteroaryl, heterocycle or (C₁-C₆)alkyl optionally substituted with up to 5 fluoro;

Ar is aryl optionally substituted with one or more **M** or heteroaryl optionally substituted with one or more **M**;

each **Q** is independently hydrogen, halo, oxo, hydroxy, -C(O)NR_aR_b, -NR_aR_b, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro, (C₁-C₆)alkyl optionally substituted with one or more **R_d**, hydroxy(C₁-C₆)alkyl optionally substituted with one or more **R_d**, aryl optionally substituted with one or more **R_d**, or aryl(C₁-C₆)alkyl optionally substituted with one or more **R_d**;

each **M** is independently hydrogen, halo, CF₃, CF₂H, hydroxy, cyano, nitro, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy, -NR_aR_b, aryl, heteroaryl or heterocycle;

each **X** is independently NL, oxygen, C(Q)₂, or S(O)_z;

each **L** is independently hydrogen, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -C(O)O(C₁-C₆)alkyl, -C(O)Oaryl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, aryl, heteroaryl, heterocycle, arylO(C₁-C₆)alkyl, -CONR_eR_f, -S(O)_z(C₁-C₆)alkyl, -S(O)_zaryl, -C(O)(C₁-C₆)alkyl, arylC(O)-, -C(O)NR_g(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with up to 5 fluoro, or (C₁-C₆)alkoxy optionally substituted with up to 5 fluoro;

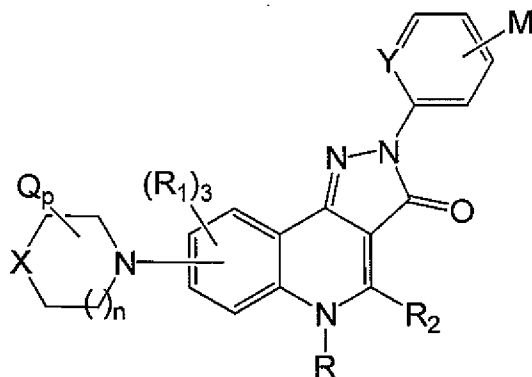
p is an integer selected from 0, 1, 2 and 3,

z is an integer selected from 0, 1, and 2; and

n is an integer selected from 0, 1, and 2.

2. The compound of claim 1, wherein **Ar** is a heteroaryl selected from the group consisting of thienyl and pyridyl, each optionally substituted with one or more **M**.

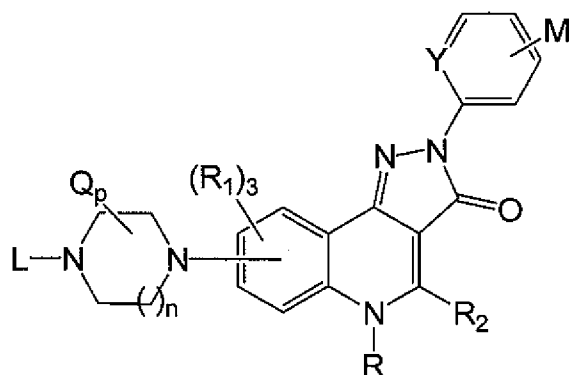
3. The compound of claim 1 that has the formula **Ia**:



(Ia)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

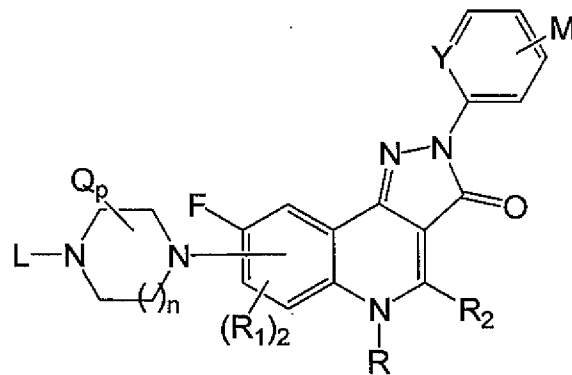
4. The compound of claim 3 that has the formula **Ib**:



(Ib)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein **Y** is **CM** or **N**.

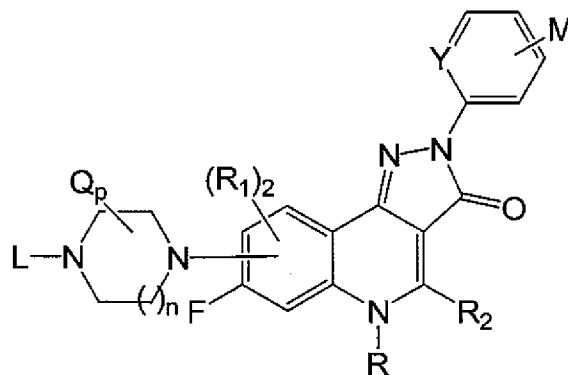
5. The compound of claim 4 that has the formula **Ic**:



(Ic)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

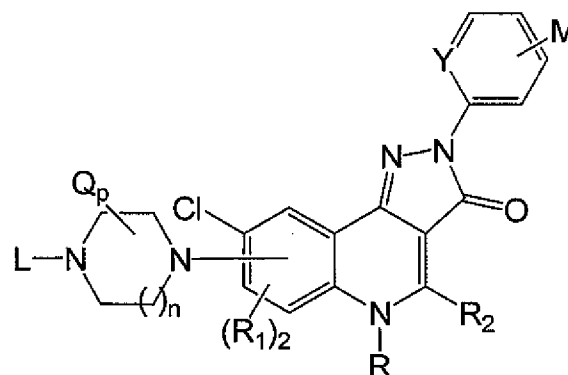
6. The compound of claim 4 that has the formula Id:



(Id)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

7. The compound of claim 4 that has the formula Ie:

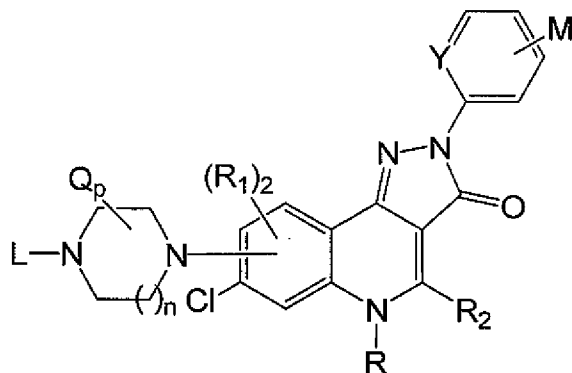


(Ie)

or a tautomer thereof, or their pharmaceutically acceptable salts,

wherein **Y** is **CM** or **N**.

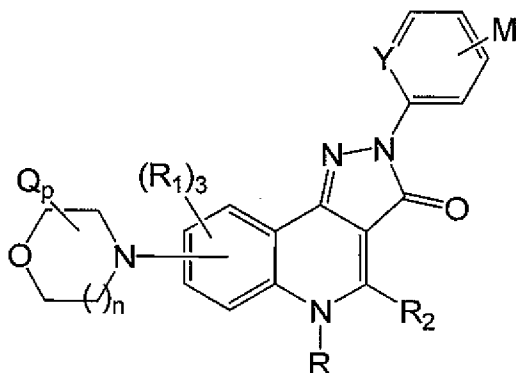
8. The compound of claim 4 that has the formula **If**:



(If)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein **Y** is **CM** or **N**.

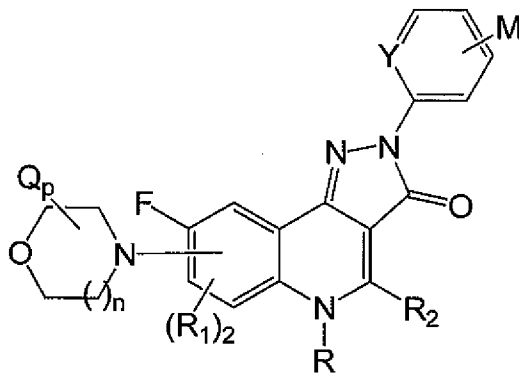
9. The compound of claim 3 that has the formula **Ig**:



(Ig)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein **Y** is **CM** or **N**.

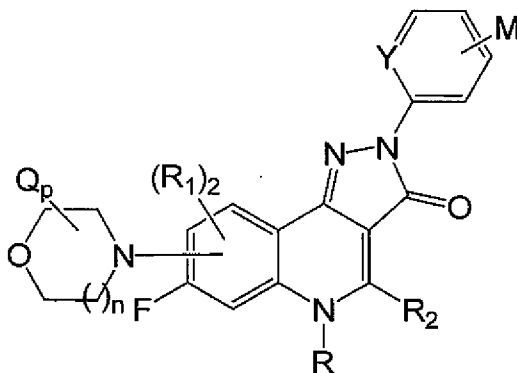
10. The compound of claim 9 that has the formula **Ih**:



(Ih)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

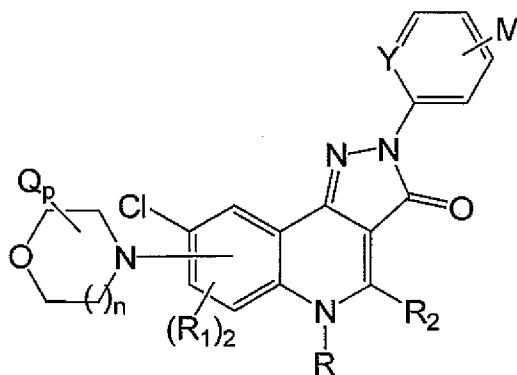
11. The compound of claim 9 that has the formula **Ii**:



(Ii)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

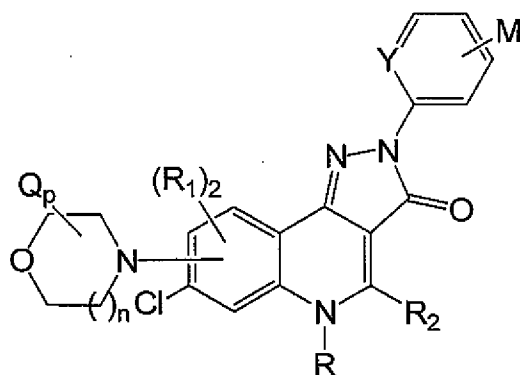
12. The compound of claim 9 that has the formula **Ij**:



(Ij)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

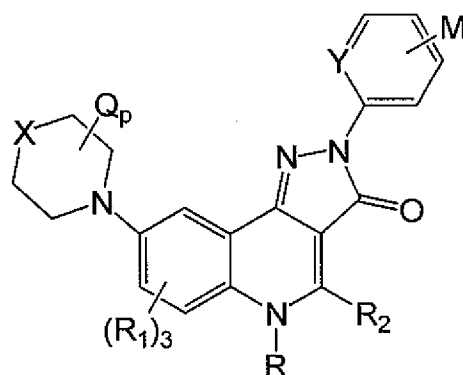
13. The compound of claim 9 that has the formula **Ik**:



(Ik)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

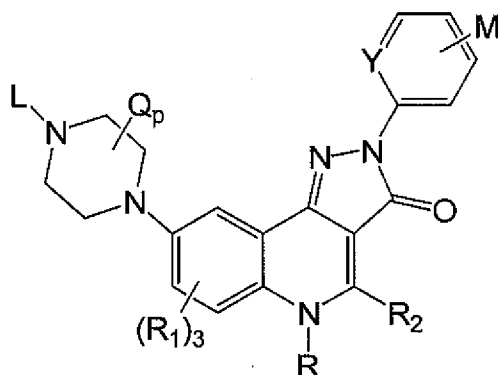
14. The compound of claim 3 that has the formula II:



(II)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

15. The compound of claim 14 that has the formula Im:

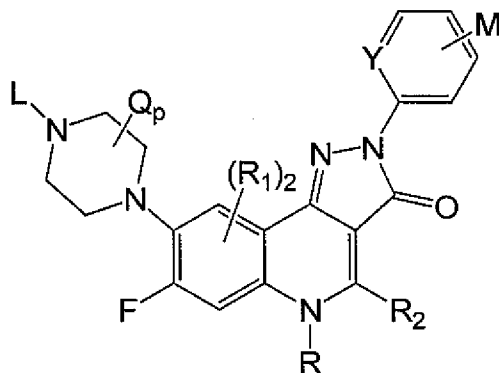


(Im)

or a tautomer thereof, or their pharmaceutically acceptable salts,

wherein Y is CM or N.

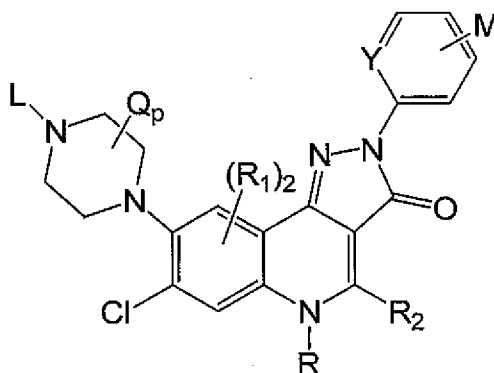
16. The compound of claim 14 that has the formula **In**:



(In)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

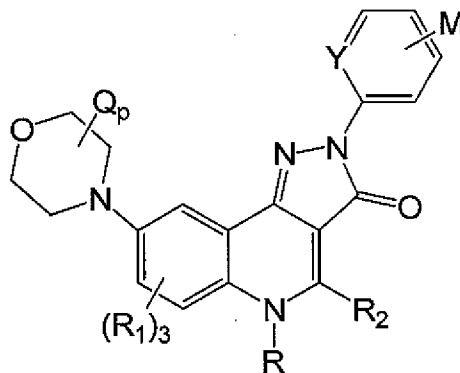
17. The compound of claim 14 that has the formula **Io**:



(Io)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

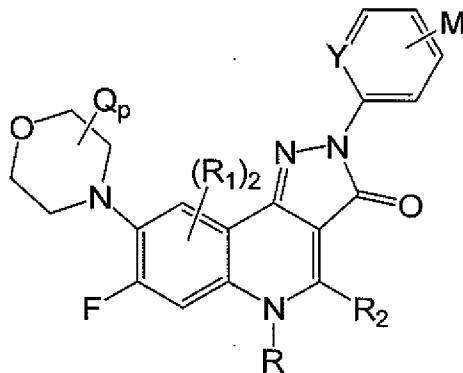
18. The compound of claim 14 that has the formula **Ip**:



(Ip)

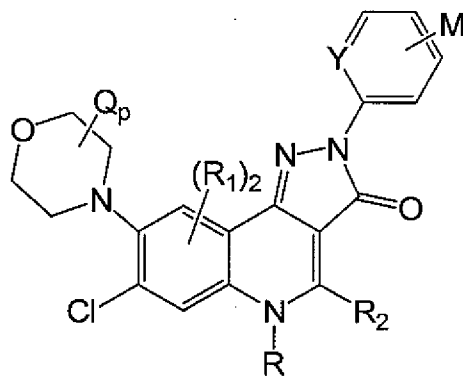
or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

19. The compound of claim 18 that has the formula **Iq**:

**(Iq)**

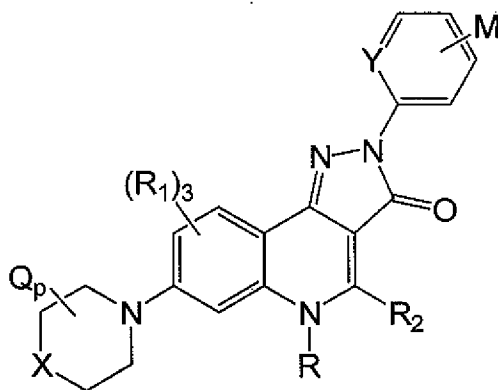
or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

20. The compound of claim 18 that has the formula **Ir**:

**(Ir)**

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

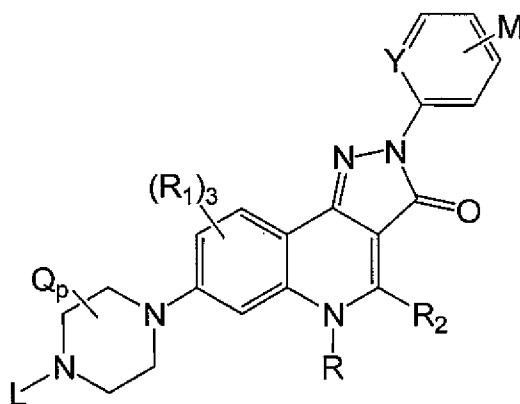
21. The compound of claim 3 that has the formula **Is**:



(Is)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

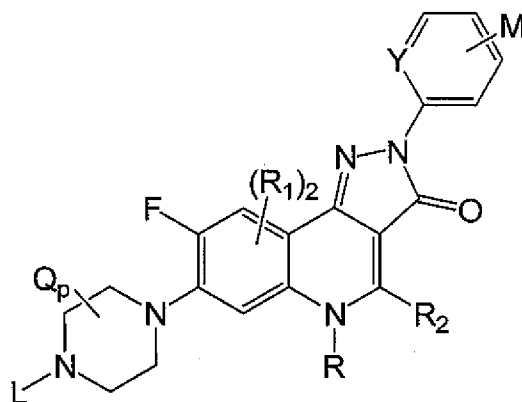
22. The compound of claim 21 that has the formula **It**:



(It)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

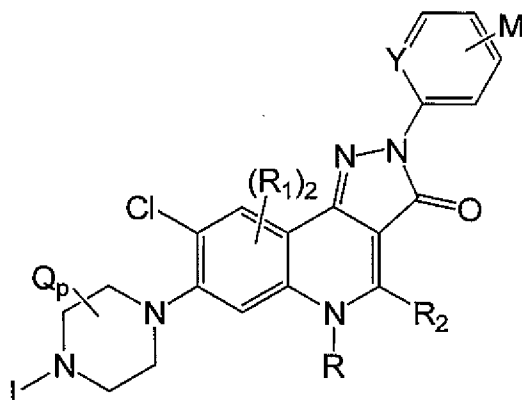
23. The compound of claim 21 that has the formula **Iu**:



(Iu)

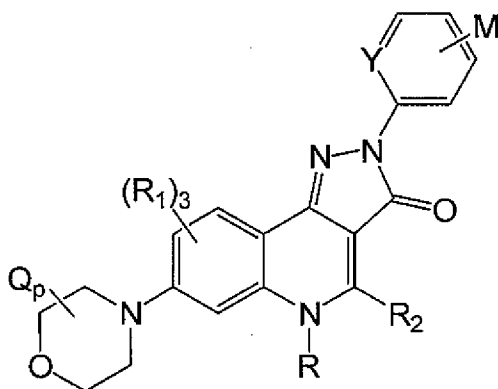
or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

24. The compound of claim 21 that has the formula **Iv**:

**(Iv)**

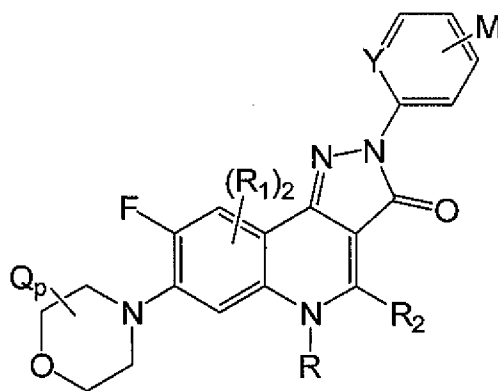
or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

25. The compound of claim 21 that has the formula **Iw**:

**(Iw)**

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

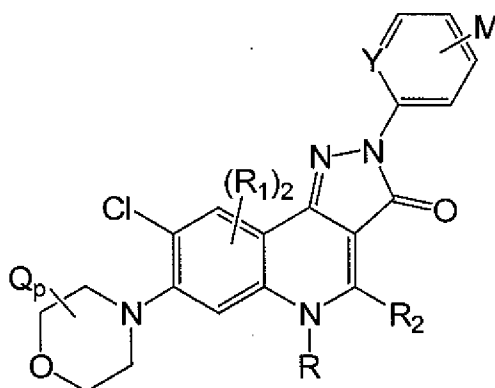
26. The compound of claim 25 that has the formula **Ix**:



(Ix)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

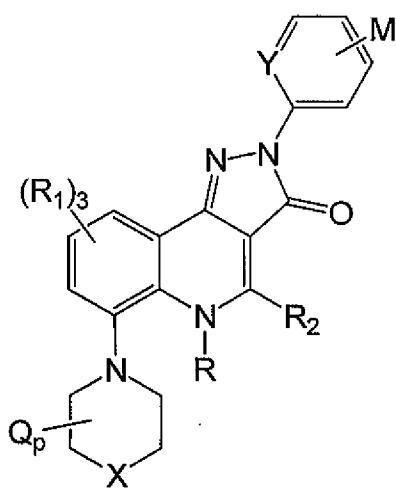
27. The compound of claim 25 that has the formula **Iy**:



(Iy)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

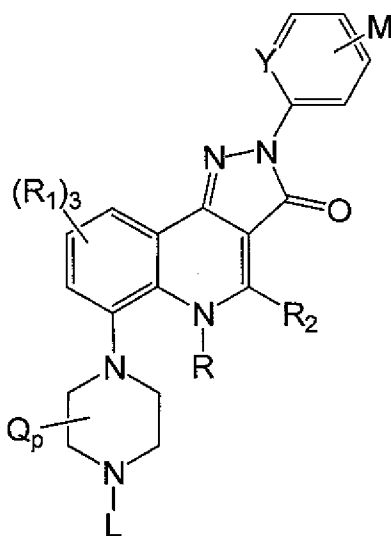
28. The compound of claim 3 that has the formula **Iz**:



(Iz)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N .

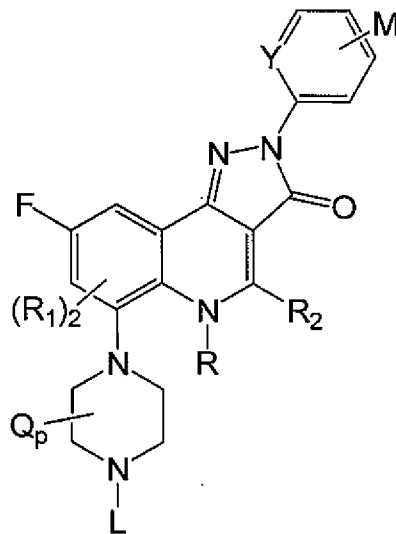
29. The compound of claim 28 that has the formula **Iaa**:



(Iaa)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N .

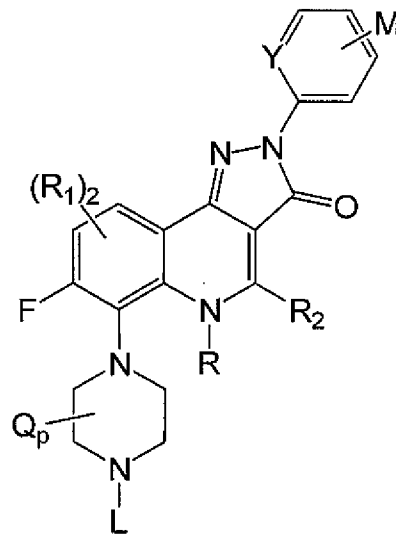
30. The compound of claim 29 that has the formula **Iab**:



(Iab)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

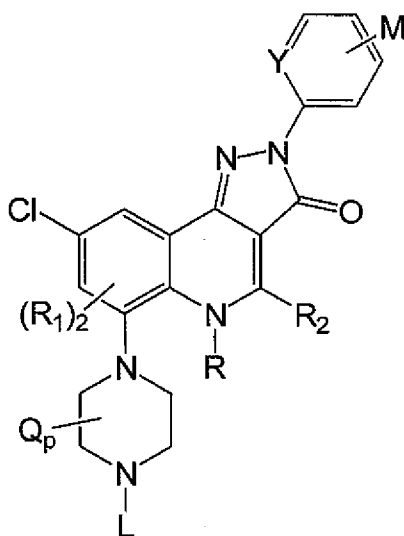
31. The compound of claim 29 that has the formula **Iac**:



(Iac)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

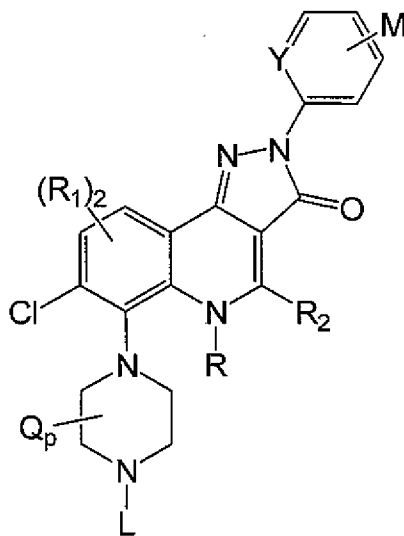
32. The compound of claim 29 that has the formula **Iad**:



(Iad)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

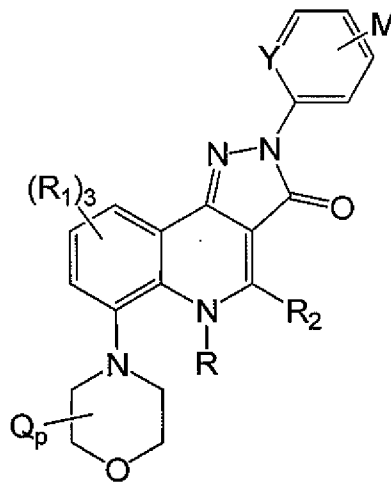
33. The compound of claim 29 that has the formula **Iae**:



(Iae)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

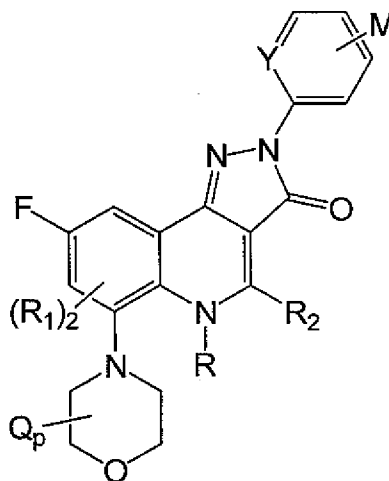
34. The compound of claim 28 that has the formula **Iaf**:



(Iaf)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

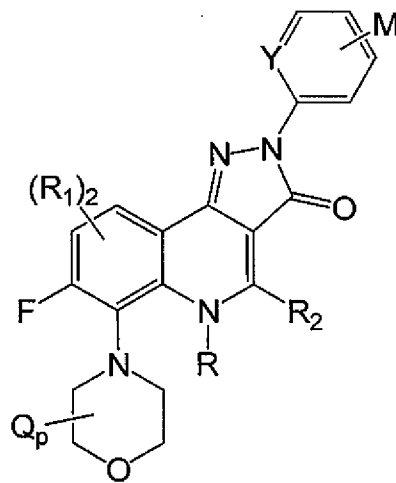
35. The compound of claim 34 that has the formula **Iag**:



(Iag)

or a tautomer thereof, or their pharmaceutically acceptable salts, wherein Y is CM or N.

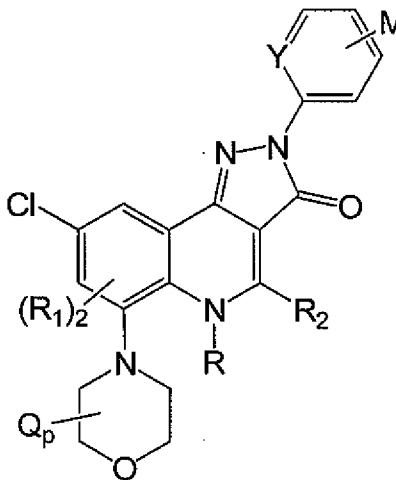
36. The compound of claim 34 that has the formula **Iah**:



(Iah)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

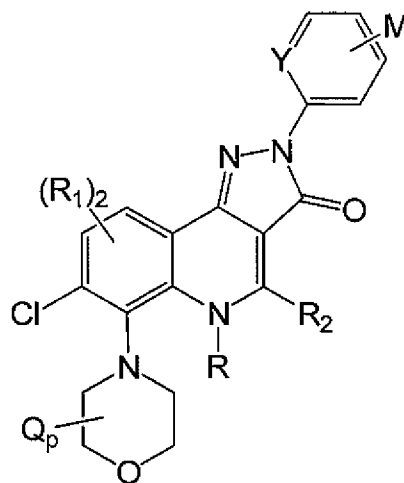
37. The compound of claim 34 that has the formula **Iaj**:



(Iaj)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

38. The compound of claim 34 that has the formula **Iak**:



(Iak)

or a tautomer thereof, or their pharmaceutically acceptable salts,
wherein Y is CM or N.

39. The compound of claim 1, having a formula selected from the group consisting of the compounds in Table 1 as described in the specification, or a tautomer thereof, or their pharmaceutically acceptable salts.

40. A pharmaceutical composition comprising:

- a) a compound of any one of Claims 1 to 39; and
- b) a pharmaceutically acceptable carrier.

41. A method of modulating one or more GABA_A subtypes in an animal comprising administering to the animal an effective amount of the compound of claim 1 or the composition of claim 40.

42. The method of claim 41 wherein the modulation is negative.

43. The method of claim 41 wherein the modulation is positive.

44. The method of claim 41 wherein the GABA_A subtypes is GABA_A α5.

45. The method of claim 44 wherein the modulation is negative.

46. The method of claim 44 wherein the modulation is positive.

47. A method of treatment of cognitive dysfunction in an animal comprising administering to the animal an effective amount of the compound of claim 1 or the composition of claim 40, under conditions wherein the cognitive dysfunction is treated.

48. The method of claim 47 wherein one or more GABA_A subtypes in the animal are negatively modulated.

49. The method of claim 48 wherein the GABA_A subtypes is GABA_A α 5.

50. The method of claim 47, wherein the animal is a mammal.

51. The method of claim 47 wherein the animal is an aged animal.

52. The method of claim 47 wherein the cognitive dysfunction is Alzheimer's disease, dementia or another neurodegenerative disease.

53. A method of treatment of a psychiatric disorder in an animal comprising administering to the animal an effective amount of the compound of claim 1 or the composition of claim 40, under conditions wherein the psychiatric disorder is treated.

54. The method of claim 53 wherein the psychiatric disorder is an anxiety disorder, sleep disorder, depression, or schizophrenia.

55. A method of increasing cognitive function in an animal comprising administering to the animal an effective amount of the compound of claim 1 or the composition of claim 40, under conditions wherein memory is increased.

56. The method of Claim 55 wherein the animal is healthy.

57. The method of Claim 55 wherein the memory is long term memory.

58. The method of Claim 55 wherein the memory is short term memory.

59. Use of a compound of claim 1 or the composition of claim 40, for the manufacture of a medicament for modulation of one or more GABA_A subtypes in an animal.

60. The use of claim 59 wherein the GABA_A subtypes is GABA_A α 5.

61. The use of claim 59 wherein the modulation is negative.

62. The use of claim 59 wherein the modulation is positive.

63. The use of claim 60 wherein the compound negatively modulates GABA_A α 5 subtype.

64. Use of a compound of claim 1 or the composition of claim 40, for the manufacture of a medicament for treatment of a cognitive dysfunction in an animal.

65. Use of a compound of claim 1 or the composition of claim 40, for the manufacture of a medicament for treatment of psychiatric disorders in an animal.

66. The use of claim 65 wherein the psychiatric disorder is an anxiety disorder, sleep disorder, depression, or schizophrenia.

67. Use of a compound of claim 1 or the composition of claim 40, for the manufacture of a medicament for treatment of disorders ameliorated by modulation of GABA_A α subunits other than α 5 in an animal.

68. The use of claim 67 wherein the modulation is positive.

69. The use of claim 67 wherein the modulation is negative.

70. Use of a compound of claim 1 or the composition of claim 40, for the manufacture of a medicament for increasing cognitive function in an animal under conditions wherein memory is increased.

71. The use of Claim 70 wherein the animal is healthy.

72. The use of Claim 70 wherein the memory is long term memory.

73. The use of Claim 70 wherein the memory is short term memory.

74. Use of a compound of claim 1 or the composition of claim 40, for the manufacture of a medicament for increasing cognitive function in an animal wherein the GABA_A α 5 subtype in the animal is negatively modulated.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/66201

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/42; A61K 31/47 (2008.04)

USPC - 514/311

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/311

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/311, 187, 253.06, 314, 406 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST(USPT,PGPB,EPAB,JPAB); Google Scholar

Search terms: Pyrazoloquinoline, pyrazolo, quinoline, morpholine, piperazine, piperidine, phenyl, cognition, memory, dysfunction, psychiatric, alzheimers, dementia, schizophrenia, Parkinsons, GABA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,334,595 A (Wentland) 02 August 1994 (02.08.1994) col 4, ln 15-44	1-40
Y	US 6,686,373 B2 (Kawamura et al.) 03 February 2004 (03.02.2004) col 2, ln 1-10, ln 48-50; col 3, ln 6, ln 55-60	1-40
A	US 4,690,930 A (Takada et al.) 01 September 1987 (01.09.1987) entire document	1-40
A	US 4,552,874 A (Mardin et al.) 12 November 1985 (12.11.1985) entire document	1-40

 Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 October 2008 (01.10.2008)

Date of mailing of the international search report

07 OCT 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/66201

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 41-74
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.