(19) (KR)
(12) (A)

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(22) ( ) 2008 06 06
(85) 2010 01 07
(86) PCT/US2008/066201
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2008 12 18
(30)
60/943,005 2007 06 08 (US)

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(72)
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92121
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(74)

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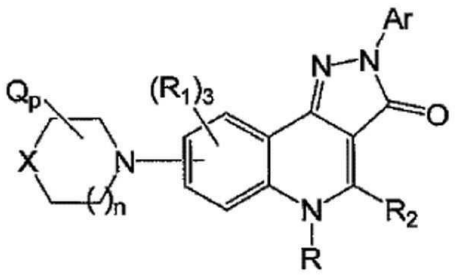
**(54)**

*(57)*

(I) , $GABA_A$ $GABA_A$
, $GABA_A$ (I)
. (I)
$GABA_A$ .

1

(I) :



(I)

( ,

R , ;

$R_1$ , , , , -CON$R_a$$R_b$, -N$R_a$$R_b$, $(C_1-C_6)$ , , ,
, $(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5
$(C_1-C_6)$ ;

$R_2$ , , , $(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5
$(C_1-C_6)$ ;

$R_a$ $R_b$ , $(C_1-C_6)$ , , , , $(C_1-C_6)$ , $-S(O)_z(C_1-C_6)$ , $-S(O)_z$ , $-C(O)(C_1-C_6)$ , $-C(O)NR_g(C_1-C_6)$ , $-C(O)NR_g$ , $-C(O)O(C_1-C_6)$ , $OC(O)-$
$C(O)-$ , $R_a$ $R_b$ $R_d$ ;
O ( ), S ( ), N$R_c$ ;

$R_c$ , $(C_2-C_6)$ , $(C_2-C_6)$ , $-C(O)O(C_1-C_6)$ , $-C(O)O$ , $(C_1-C_6)$ $(C_1-C_6)$ , $(C_1-C_6)$ , , , , $O(C_1-C_6)$ , $-C(O)NR_g(C_1-C_6)$ , $-C(O)NR_g$ , $-S(O)_z(C_1-C_6)$ , $-S(O)_z$ , $-C(O)(C_1-C_6)$ , $C(O)-$, 5
$(C_1-C_6)$ , 5 $(C_1-C_6)$ ;

$R_d$ , , , , -C(O)N$R_a$$R_b$, -N$R_a$$R_b$, $(C_1-C_6)$ , , $(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5 $(C_1-C_6)$
;

$R_e$ $R_f$ , $(C_1-C_6)$ , , , , $(C_1-C_6)$ , $(C_1-C_6)$ , $-C(O)(C_1-C_6)$ , $-S(O)_z(C_1-C_6)$ , $-S(O)_zNR_g(C_1-C_6)$ , $-S(O)_z$ , $-C(O)NR_g(C_1-C_6)$ , $-C(O)(C_1-C_6)$ , $C(O)-$, $OC(O)-$, $-C(O)O(C_1-C_6)$ ;

$R_g$ , , , , 5 $(C_1-C_6)$ ;

Ar M M ;

Q , , , , -C(O)N$R_a$$R_b$, -N$R_a$$R_b$, 5 $(C_1-C_6)$ , 5 $(C_1-C_6)$ , $R_d$ $(C_1-C_6)$ ,
$R_d$ $(C_1-C_6)$ , $R_d$ , $R_d$

($C_1$-$C_6$) ;

**M** , , $CF_3$, $CF_2H$, , , , ($C_1$-$C_6$) , ($C_1$-$C_6$) , ($C_1$-$C_6$) , -N$R_a$$R_b$, , ;

**X** N**L**, , C(**Q**)$_2$, S(O)$_z$ ;

**L** , ($C_2$-$C_6$) , ($C_2$-$C_6$) , -C(O)O($C_1$-$C_6$) , -C(O)O , ($C_1$-$C_6$) ($C_1$-$C_6$) , ($C_1$-$C_6$) , , , , O($C_1$-$C_6$) , -CON$R_e$$R_f$, -S(O)$_z$($C_1$-$C_6$) , -S(O)$_z$ , -C(O)($C_1$-$C_6$) , C(O)-, -C(O)N$R_g$($C_1$-$C_6$) , 5 ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) ;

**p** 0, 1, 2 3 ;

**z** 0, 1, 2 ;

**n** 0, 1, 2 )

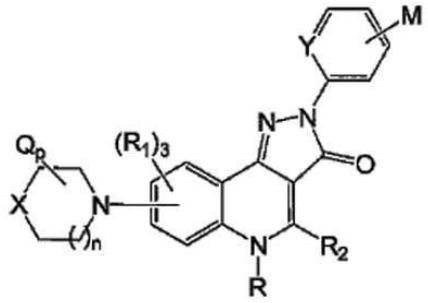
, .

**2**

1 , **Ar** **M** .

**3**

1 , **Ia**:



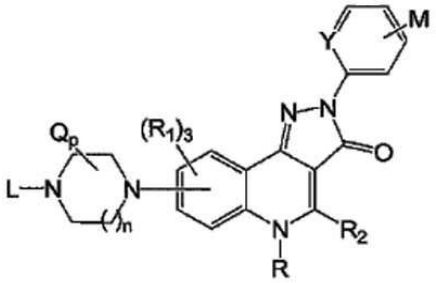
(**Ia**)

( , **Y** C**M** N )

, , .

**4**

3 , **Ib**:



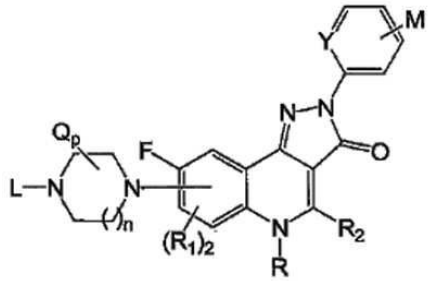
**(Ib)**

( , Y CM N )

, , .

**5**

4 , **Ic**:



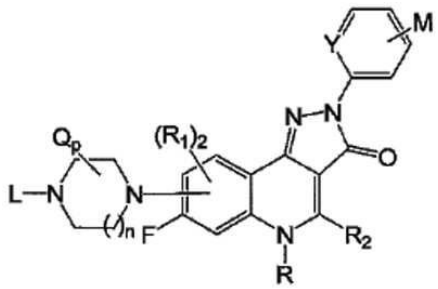
**(Ic)**

( , Y CM N )

, , .

**6**

4 , **Id**:



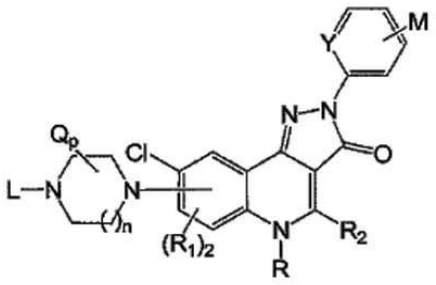
**(Id)**

( , Y CM N )

, , .

**7**

4 , **Ie**:



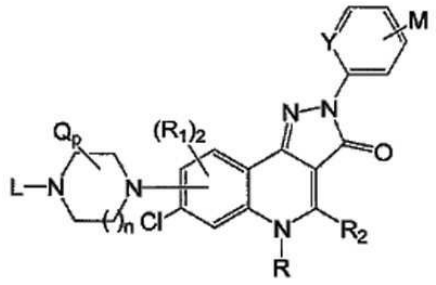
**(Ie)**

( , Y CM N )

, , .

**8**

4 , **If**:



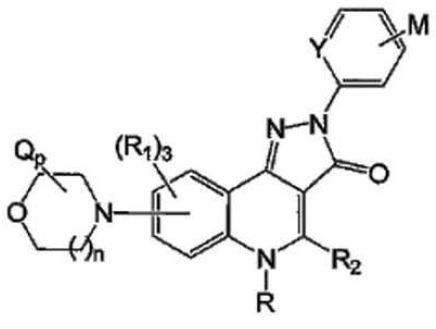
**(If)**

( , Y CM N )

, , .

**9**

3 , **Ig**:



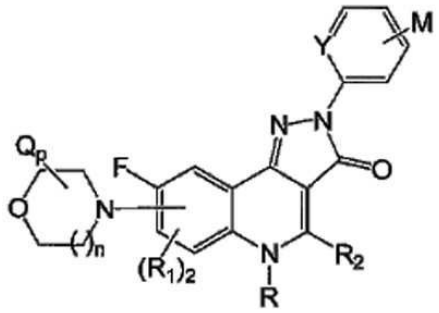
**(Ig)**

( , Y CM N )

, , .

**10**

9 , **Ih**:



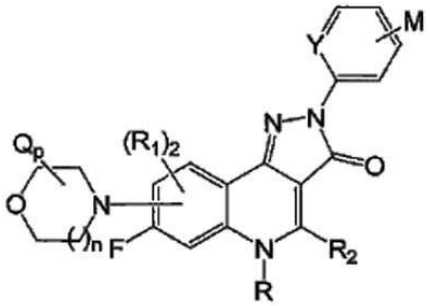
(Ih)

( , **Y** CM N )

, , .

**11**

9 , **Ii**:



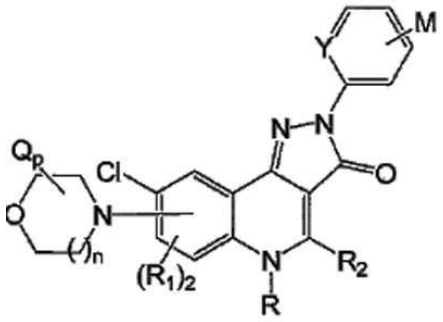
(Ii)

( , **Y** CM N )

, , .

12

9 , Ij:



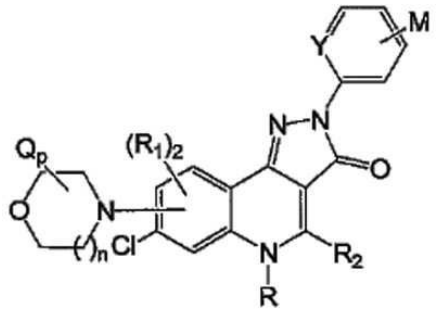
(Ij)

( , Y CM N )

, , .

13

9 , Ik:



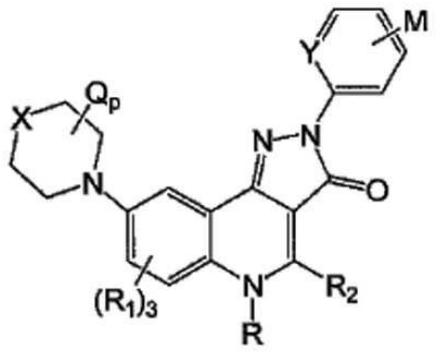
(Ik)

( , Y CM N )

, , .

14

3 , Il:



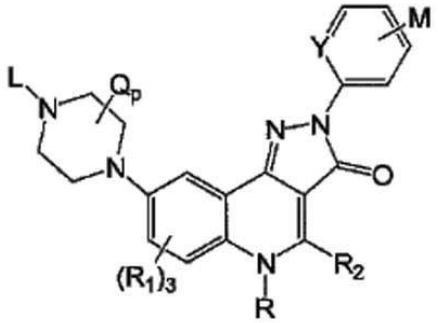
(II)

( , Y CM N )

, , .

**15**

14 , **Im**:



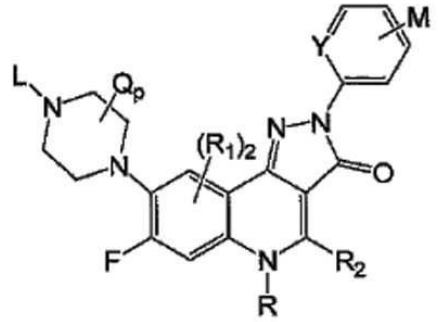
**(Im)**

( , Y CM N )

, , .

**16**

14 , **In**:



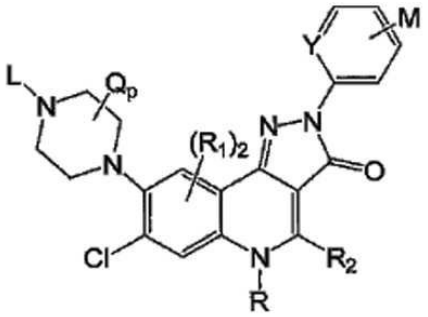
**(In)**

( , Y CM N )

, , .

17

14 , Io:



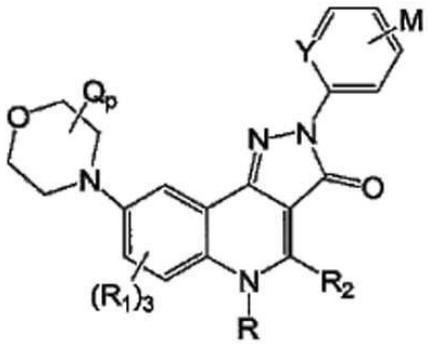
(Io)

( , Y CM N )

, , .

18

14 , Ip:



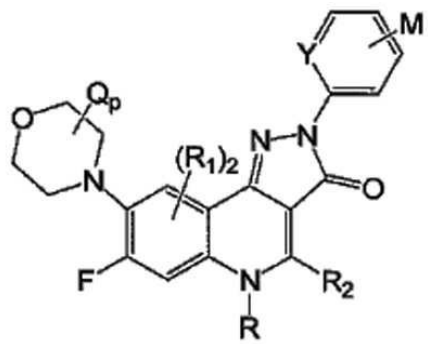
(Ip)

( , Y CM N )

, , .

19

18 , Iq:



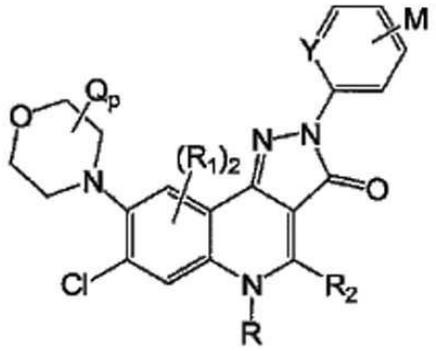
(Iq)

( , Y CM N )

, , .

20

18 , Ir:



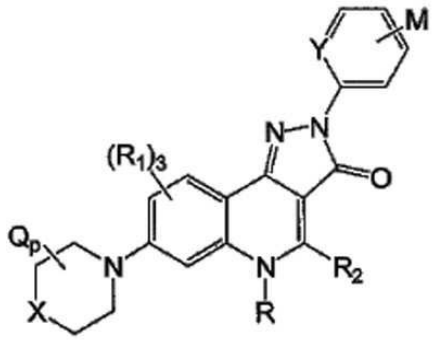
(Ir)

( , Y CM N )

, , .

21

3 , Is:



(Is)

( , Y CM N )

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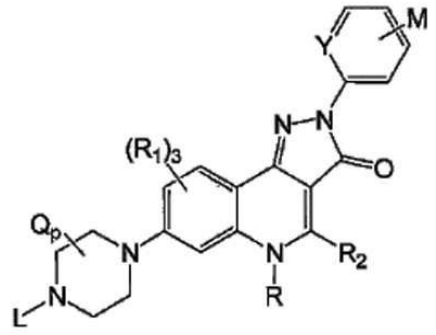
**22**

21 , **It**:



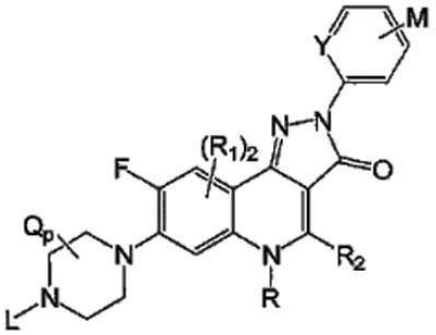
**(It)**

( , Y CM N )

, , .

**23**

21 , **Iu**:



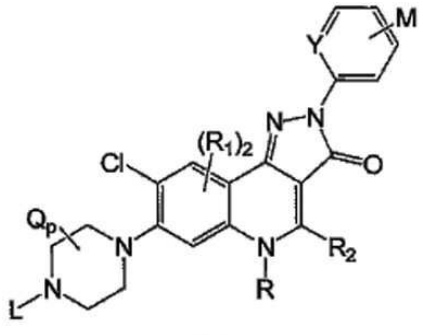
(Iu)

( , Y CM N )

, , .

**24**

21 , **Iv**:



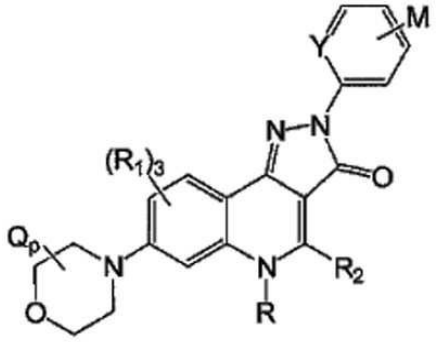
**(Iv)**

( , Y CM N )

, , .

**25**

21 , **Iw**:



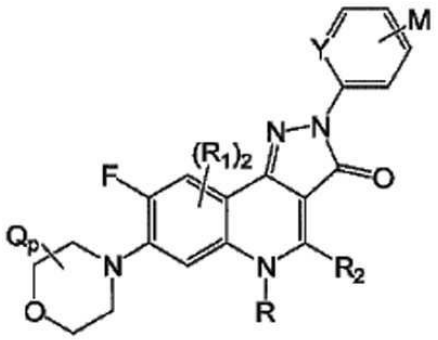
**(Iw)**

( , Y CM N )

, , .

**26**

25 , **Ix**:



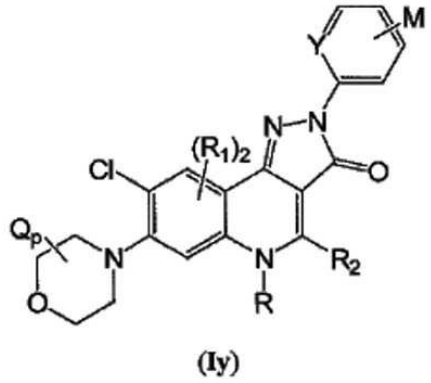
**(Ix)**

( , Y CM N )

, , .

27

25 , Iy:



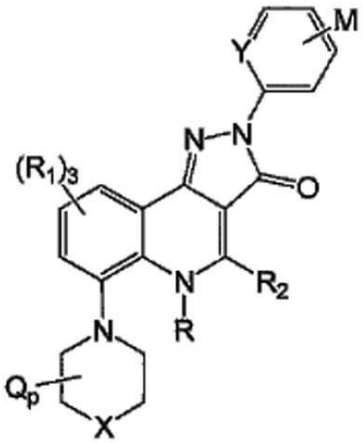
(Iy)

( , Y CM N )

, , .

28

3 , Iz:



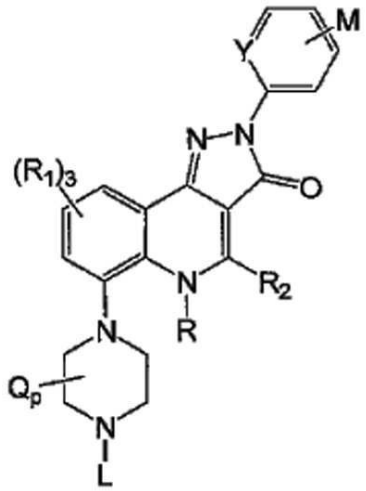
(Iz)

( , Y CM N )

, , .

**29**

28 , **Iaa**:



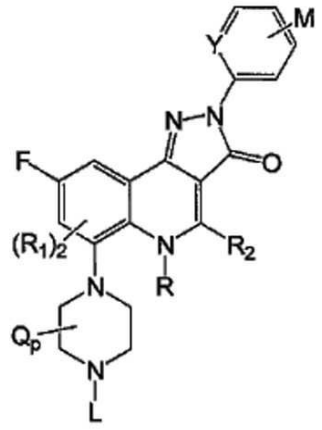
**(Iaa)**

( , Y CM N )

, , .

**30**

29 , **Iab**:



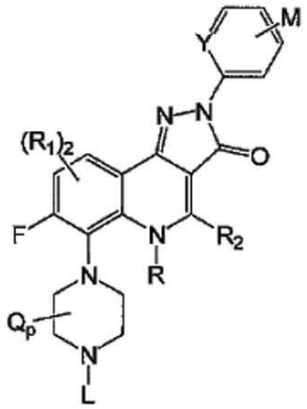
**(Iab)**

( , Y CM N )

, , .

**31**

29 , **Iac**:



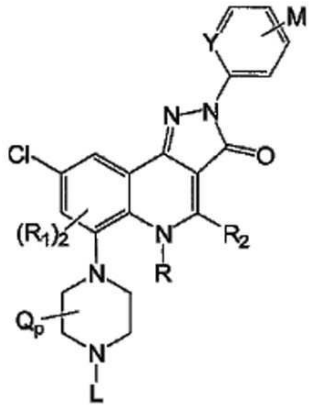
**(Iac)**

( , Y CM N )

, , .

**32**

29 , **Iad**:



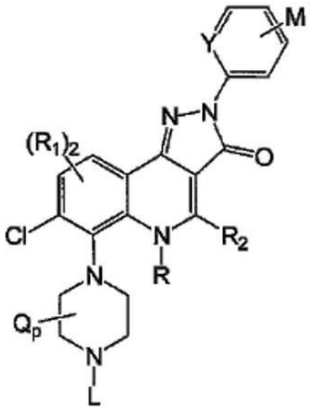
**(Iad)**

( , Y CM N )

, , .

33

29 , Iae:



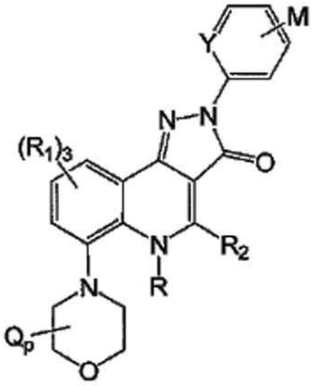
(Iae)

( , Y CM N )

, , .

34

28 , Iaf:



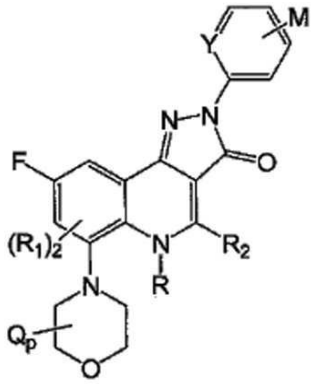
(Iaf)

( , Y CM N )

, , .

**35**

34 , **Iag**:



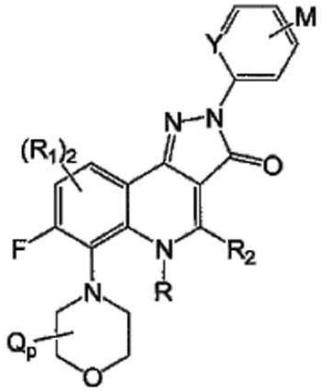
**(Iag)**

( , Y CM N )

, , .

**36**

34 , **Iah**:



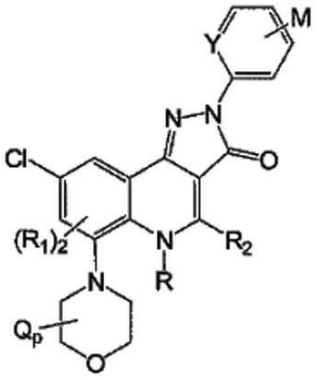
**(Iah)**

( , Y CM N )

, , .

37

34 , Iaj:



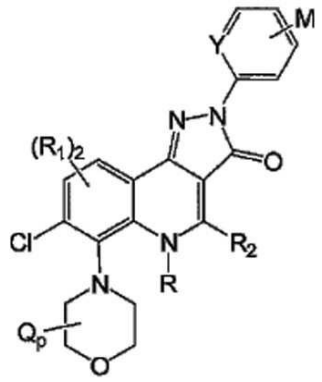
(Iaj)

( , Y CM N )

, , .

38

34 , Iak:



(Iak)

( , Y CM N )

, , .

39

1 1 ,

, .

40

a) 1 39 ;

b) .

**41**

1 40 , $GABA_A$

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**42**

41 , .

**43**

41 , .

**44**

41 , $GABA_A$ $GABA_A$ α5 .

**45**

44 , .

**46**

44 , .

**47**

1 40

, .

**48**

47 , $GABA_A$ .

**49**

48 , $GABA_A$ $GABA_A$ α5 .

**50**

47 , .

**51**

47 , .

**52**

47 , , .

**53**

1 40
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**54**

53 , , , , .

**55**

1 40 ,
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**56**

55 , .

**57**

55 , .

**58**

55 , .

**59**

$GABA_A$ , 1 40
.

**60**

59 , $GABA_A$ $GABA_A$ α5 .

**61**

59 , .

**62**

59 , .

**63**

60 , $GABA_A$ α5 .

**64**

, 1 40 .

**65**

, 1 40 .

**66**

65 , , , , .

**67**

α5 $GABA_A$ α , 1 40 .

**68**

67 , .

**69**

67 , .

**70**

, 1 40 .

**71**

70 , .

**72**

70 , .

**73**

70 , .

**74**

$GABA_A$ α5

, 1 40 .

[0001] $GABA_A$ α5 (pyrazoloquinoline) .

[0002] γ- (GABA) $GABA_A$ $GABA_B$ . $GABA_A$ - (ligand-gated ion channel) $GABA_B$ 7 G- . $GABA_A$ α, β, γ δ (subunit) . $GABA_A$ 6 α , 3 β , 3 γ 1 δ . α , β γ (pentamer) .

[0003] , $GABA_A$ 10,000 . ( ) α1β2γ2(43%), α2β2/3γ2(18%), α3βγ2/3(17%), α2βγ1(8%), α5β3γ2/3(4%), α6βγ2(2%), α6βδ(2%) α4βδ(3%) (Barnard, E.A., *et al.* (1998) *Pharmacol. Rev.* 50: 291-313, ).

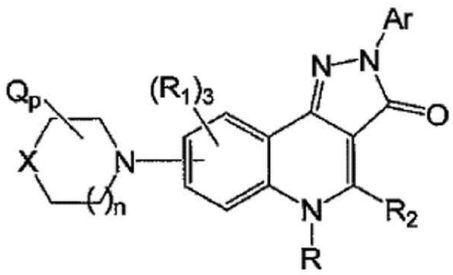
[0004] (benxodiazepine), (steroid), (barbiturate), (convulsant, ) , $GABA_A$ . GABA α/β . α/γ (BZ ) . GABA BZ- , . $GABA_A$ (agonist) (anxiolytic agent) (Muller, W.E. (1988) *Drugs of Today* 24: 649-663, ). α1 , α1β2γ2 α2β2γ2 α3β2γ2 (Rudolph, U. F., *et al.* (1999) *Nature* 401 : 796-800, ; Low, K.F., *et al.* (2000) *Science* 290: 131-134, ; McKernan, R.M., *et al.* (2000) *Nat. Neurosci.* 3: 587-592, ).

[0005] α5- (spatial navigation) . , α5 GABA . α5β γ2/3 $GABA_A$ (inverse agonism) .

(Yokoyama, N., *et al.* (1982) *J Med. Chem.* 25: 337-339, ; Takada, S., *et al.* (1988) *J Med. Chem.* 31 : 1738-1745, ; Atack, J.R., *et al.* (2006) *European Journal of Pharmacology* 548: 77-82, ). α5 α1, α2 α3 . , α5 $GABA_A$ , .

[0006]

[0007] I , $GABA_A$ $GABA_A$ α5 . I :




(I)

[0008]

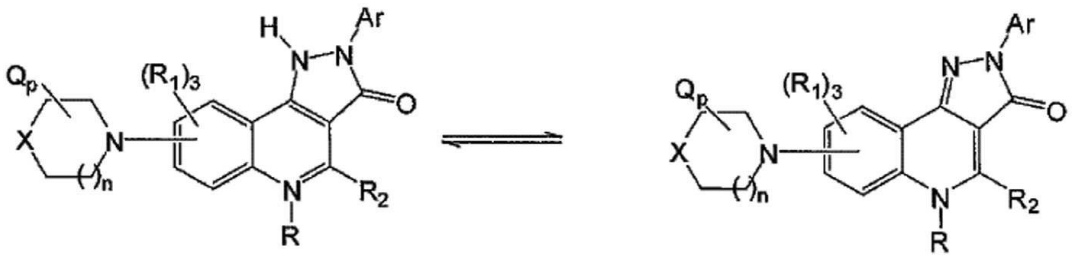
[0009] I (tautomer) .

[0010] _____, _____

[0011] , "**R**" . (I) "**R**" , "**R**" . . , . .

[0012] . , ( ) , , . .

[0013] (I) , , :



(I)

[0014]

[0015] ,

[0016] R , , ;

[0017] $R_1$ , , , , -CON$R_a$$R_b$, -N$R_a$$R_b$, $(C_1-C_6)$ , , ,
, $(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5
$(C_1-C_6)$ ;

[0018] $R_2$ , , , $(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5
$(C_1-C_6)$ ;

[0019] $R_a$ $R_b$ , $(C_1-C_6)$ , , , , $(C_1-C_6)$ , $-S(O)_z(C_1-C_6)$ , $-S(O)_z$ , $-C(O)(C_1-C_6)$ , $-C(O)NR_g(C_1-C_6)$ , $-C(O)NR_g$ , $-C(O)O(C_1-C_6)$ , OC(O)-
C(O)- , $R_a$ $R_b$ $R_d$ ;
O( ), S( ), N$R_c$ ;

[0020] $R_c$ , $(C_2-C_6)$ , $(C_2-C_6)$ , $-C(O)O(C_1-C_6)$ , -C(O)O , $(C_1-C_6)$ $(C_1-C_6)$ , $(C_1-C_6)$ , , , , $O(C_1-C_6)$ , $-C(O)NR_g(C_1-C_6)$ , $-C(O)NR_g$ , $-S(O)_z(C_1-C_6)$ , $-S(O)_z$ , $-C(O)(C_1-C_6)$ , C(O)-, 5
$(C_1-C_6)$ , 5 $(C_1-C_6)$ ;

[0021] $R_d$ , , , , $-C(O)NR_aR_b$, -N$R_a$$R_b$, $(C_1-C_6)$ , , $(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5 $(C_1-C_6)$
;

[0022] $R_e$ $R_f$ , $(C_1-C_6)$ , , , , $(C_1-C_6)$ , $(C_1-C_6)$ , $-C(O)(C_1-C_6)$ , $-S(O)_z(C_1-C_6)$ , $-S(O)_zNR_g(C_1-C_6)$ , $-S(O)_z$ , $-C(O)NR_g(C_1-C_6)$ , $-C(O)(C_1-C_6)$ , C(O)-, OC(O)-, $-C(O)O(C_1-C_6)$ ;

[0023] $R_g$ , , , , 5 $(C_1-C_6)$ ;

[0024] Ar M M ;

[0025] Q , , , , $-C(O)NR_aR_b$, -N$R_a$$R_b$, 5 $(C_1-C_6)$ , 5 $(C_1-C_6)$ , $R_d$ $(C_1-C_6)$ ,
$R_d$ $(C_1-C_6)$ , $R_d$ , $R_d$
$(C_1-C_6)$ ;

[0026] M , , $CF_3$, $CF_2H$, , , , $(C_1-C_6)$ , $(C_1-C_6)$ , $(C_1-C_6)$ , -N$R_a$$R_b$, , ;

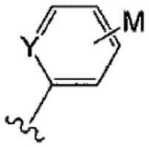
[0027] X NL, , C(Q)$_2$, S(O)$_z$ ;

[0028] L , ($C_2$-$C_6$) , ($C_2$-$C_6$) , -C(O)O($C_1$-$C_6$) , -C(O)O , ($C_1$-$C_6$) ($C_1$-$C_6$) , ($C_1$-$C_6$) , , , O($C_1$-$C_6$) , -CON$R_eR_f$, -S(O)$_z$($C_1$-$C_6$) , -S(O)$_z$ , -C(O)($C_1$-$C_6$) , C(O)-, -C(O)N$R_g$($C_1$-$C_6$) , 5 ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) ;

[0029] p 0, 1, 2 3 ;

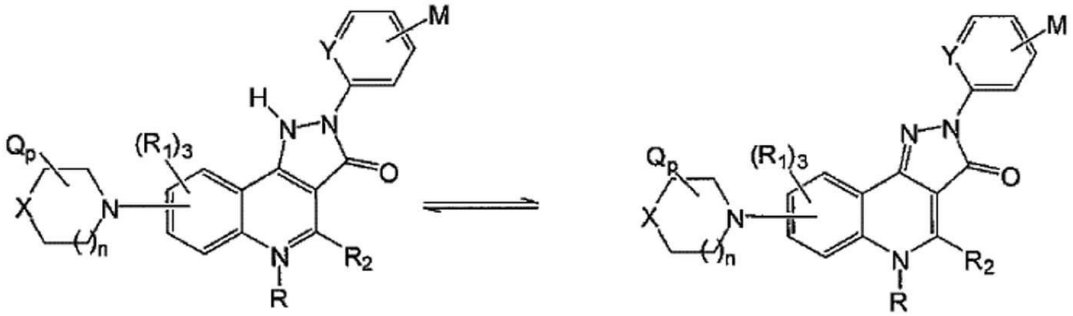
[0030] z 0, 1, 2 ;

[0031] n 0, 1, 2 .



[0032] , Ar ( , Y CM N ) .

[0033] , Ia , :

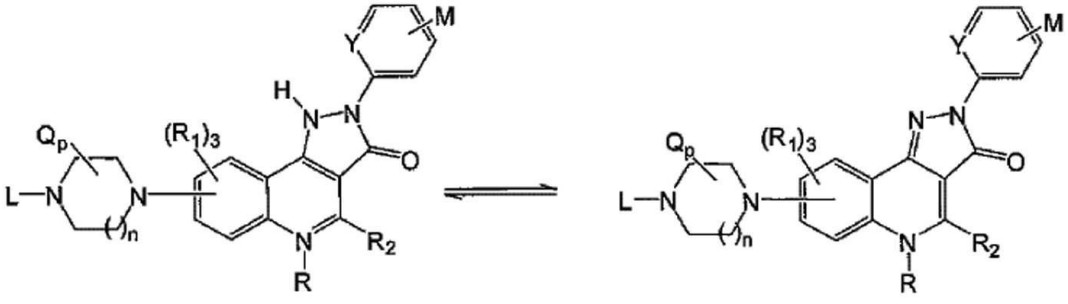


(Ia)

[0034]

[0035] Y CM N .

[0036] , Ib , :

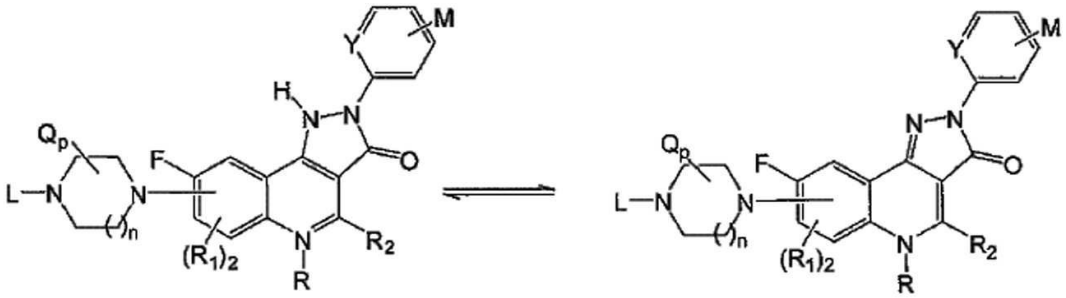


(Ib)

[0037]

[0038] Y CM N .

[0039] , Ic :

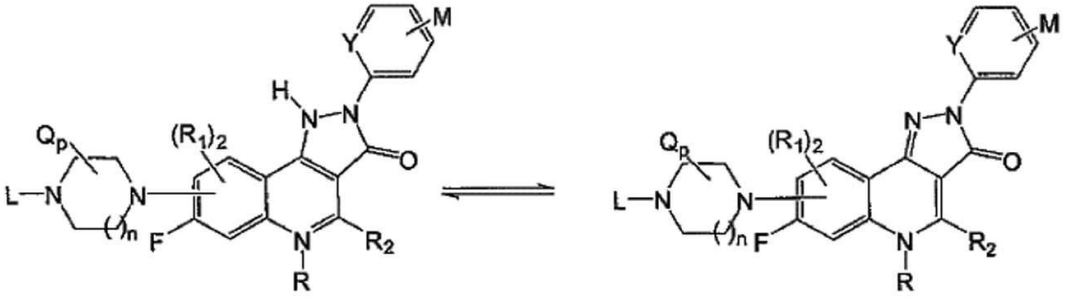


(Ic)

[0040]

[0041] Y CM N .

[0042] , Id , :

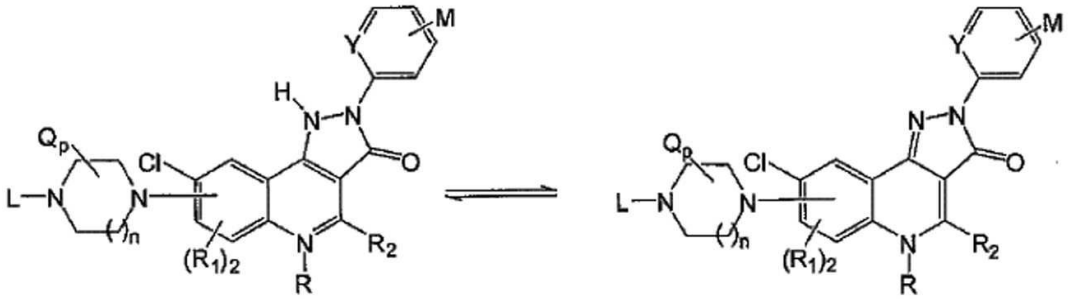


(Id)

[0043]

[0044] Y CM N .

[0045] , Ie , :

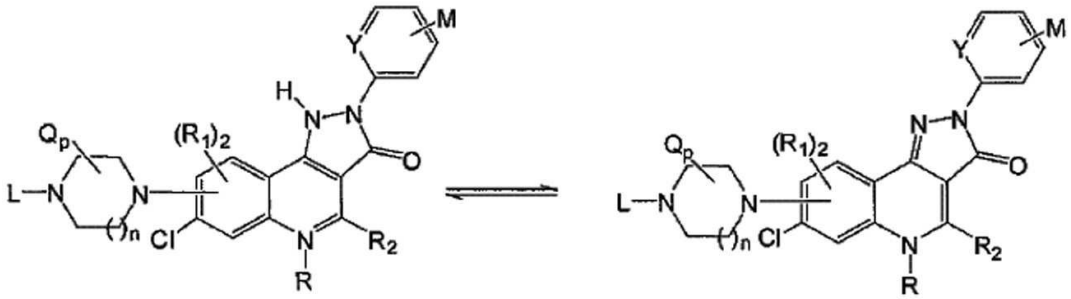


(Ie)

[0046]

[0047] Y CM N .

[0048] , If , :

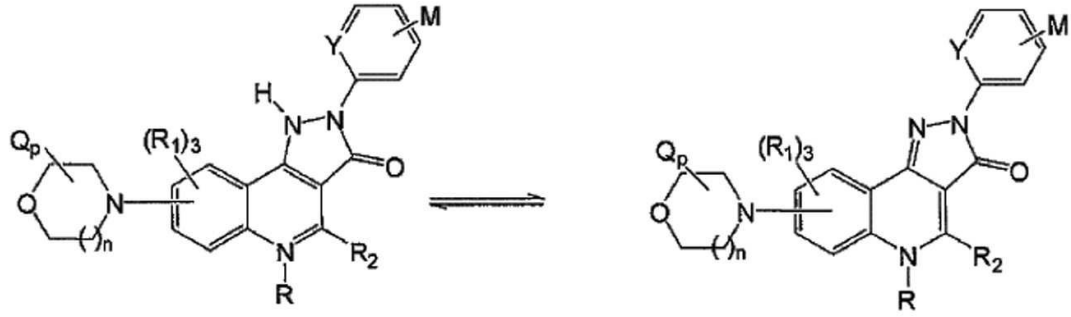


(If)

[0049]

[0050] Y CM N .

[0051] , Ig , :

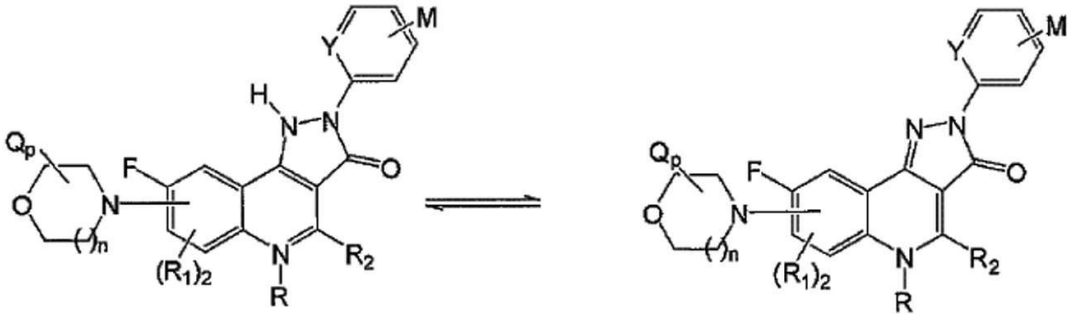


(Ig)

[0052]

[0053] Y CM N .

[0054] , Ih :

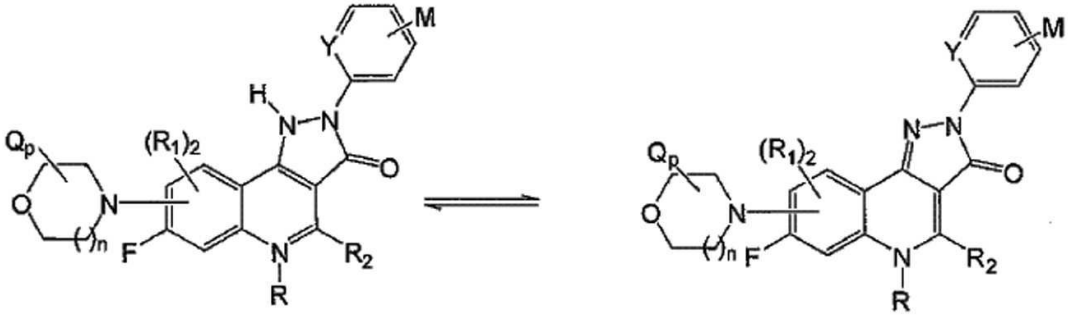


(Ih)

[0055]

[0056] Y CM N .

[0057] , Ii , :

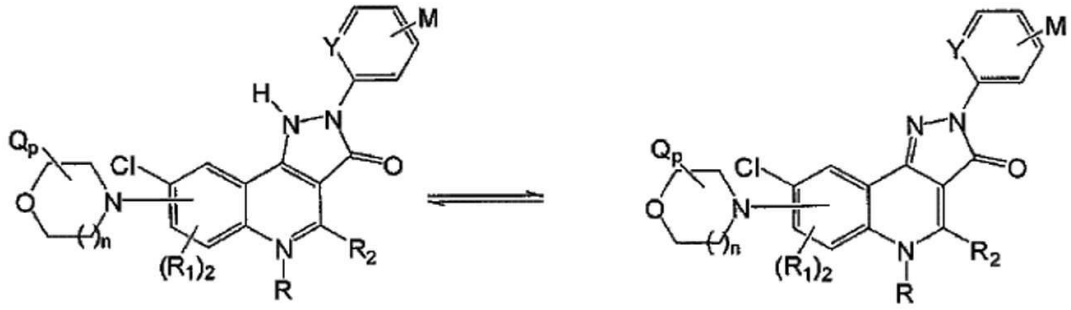


(Ii)

[0058]

[0059] Y CM N .

[0060] , Ij , :

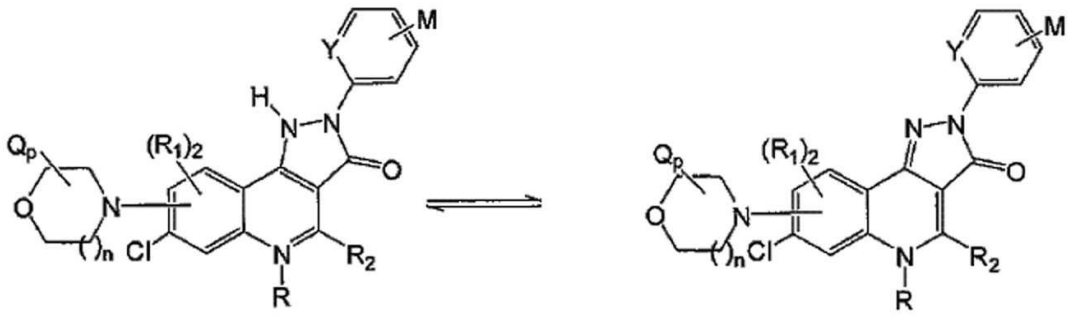


(Ij)

[0061]

[0062] Y CM N .

[0063] , Ik , :

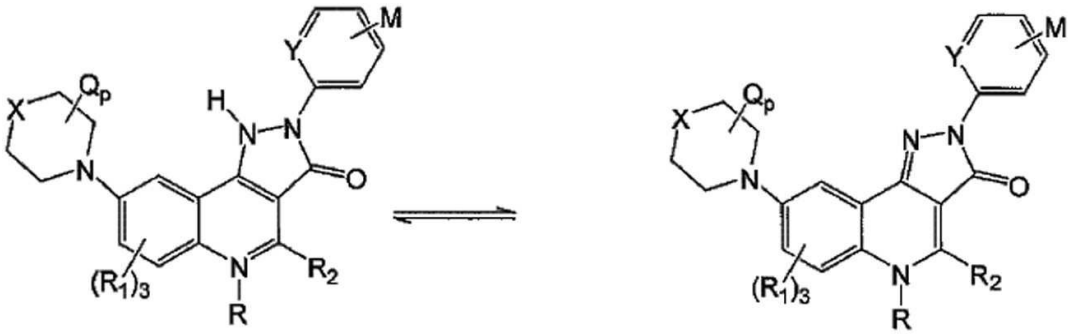


(Ik)

[0064]

[0065] Y CM N .

[0066] , Il , :

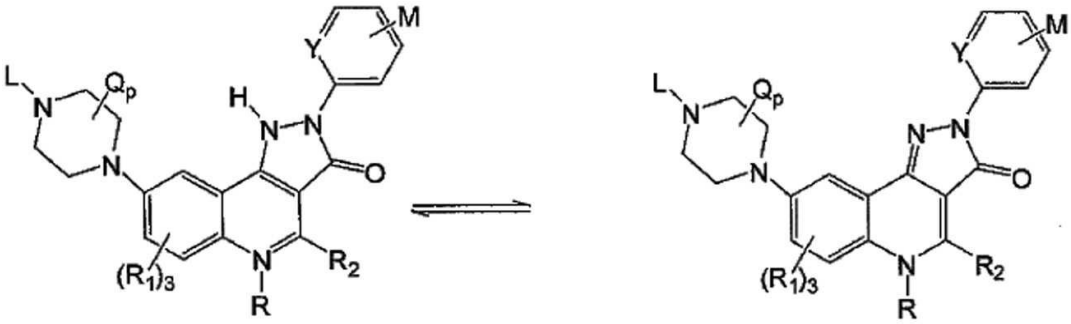


(II)

[0067]

[0068] Y CM N .

[0069] , Im , :

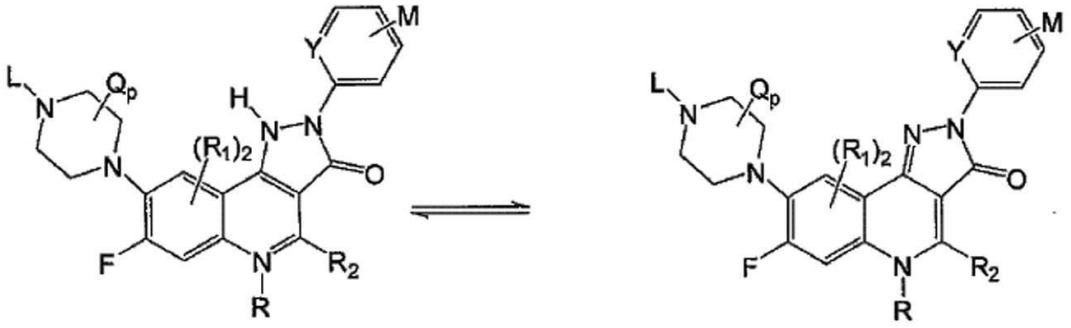


(Im)

[0070]

[0071] Y CM N .

[0072] , In , :

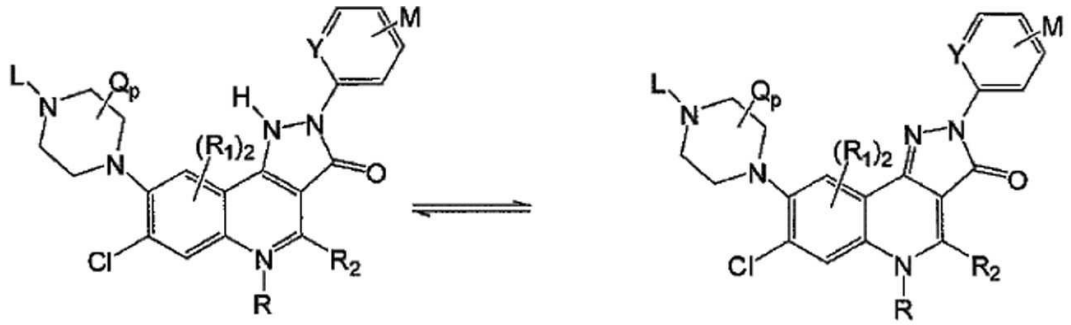


(In)

[0073]

[0074] Y CM N .

[0075] , Io , :

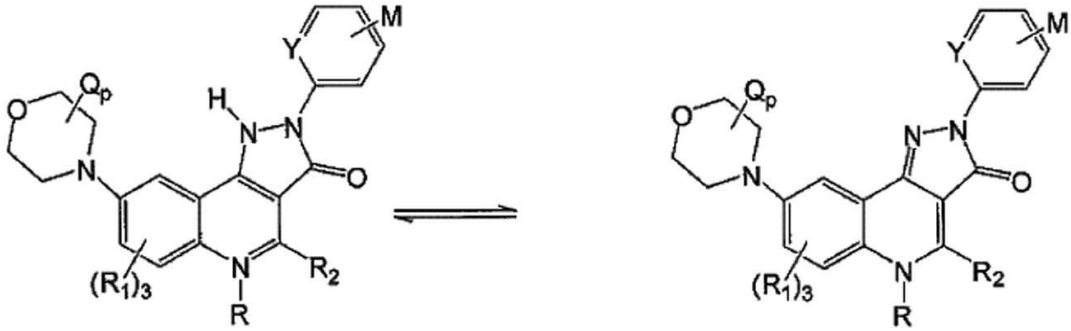


(Io)

[0076]

[0077] Y CM N .

[0078] , Ip , :

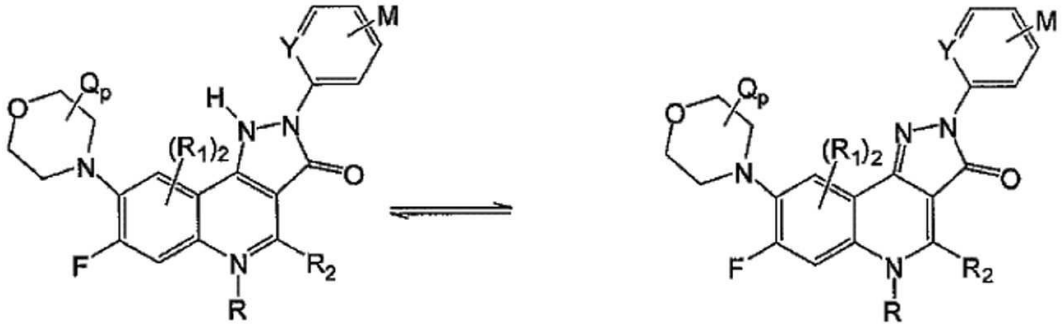


(Ip)

[0079]

[0080] Y CM N .

[0081] , Iq , :

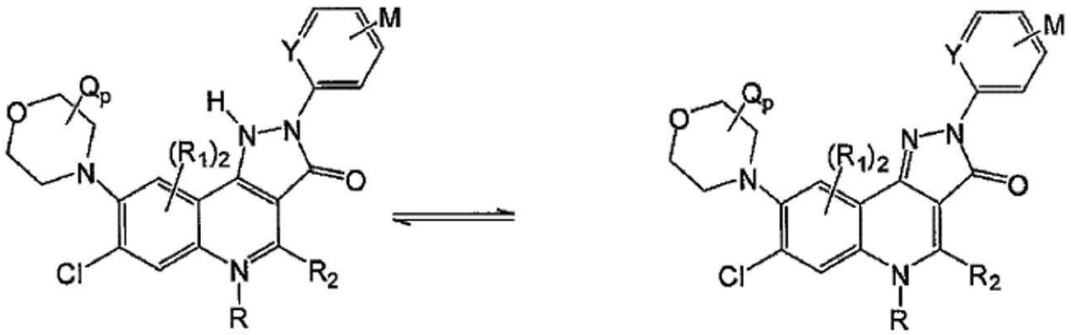


(Iq)

[0082]

[0083] Y CM N .

[0084] , Ir , :

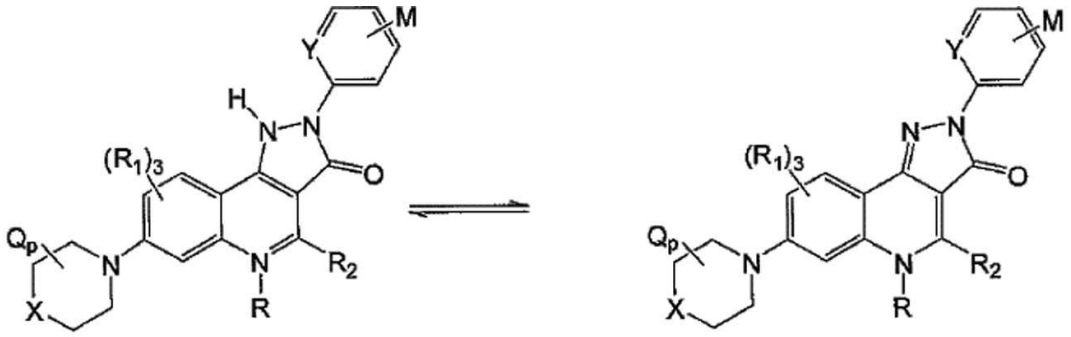


(Ir)

[0085]

[0086] Y CM N .

[0087] , Is , :

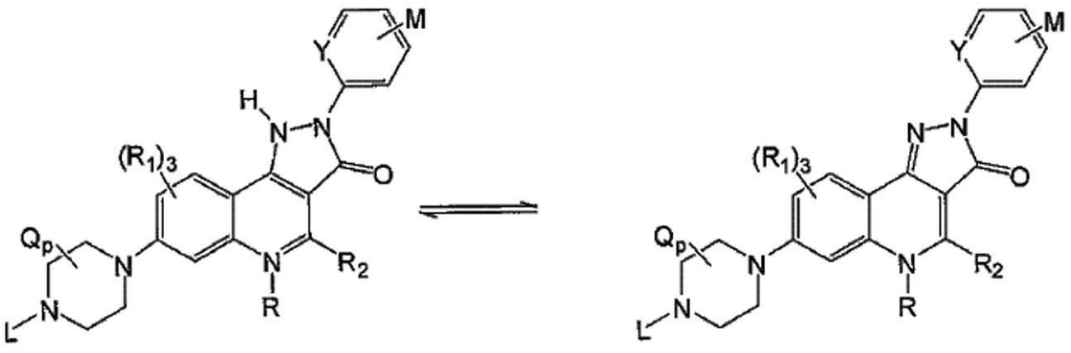


(Is)

[0088]

[0089] Y CM N .

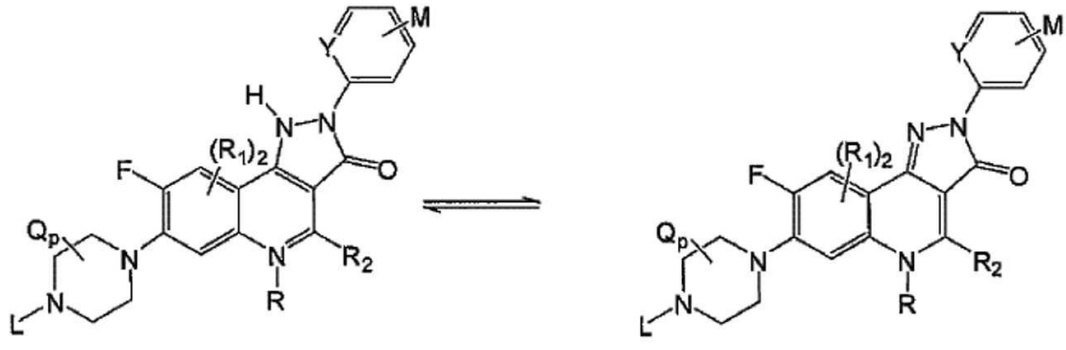
[0090] , It , :



[0091] (It)

[0092] Y CM N .

[0093] , Iu , :

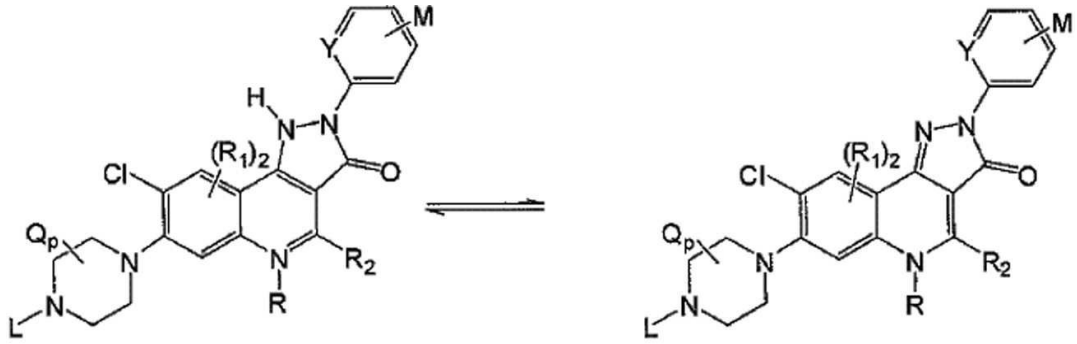


(Iu)

[0094]

[0095] Y CM N .

[0096] , Iv , :

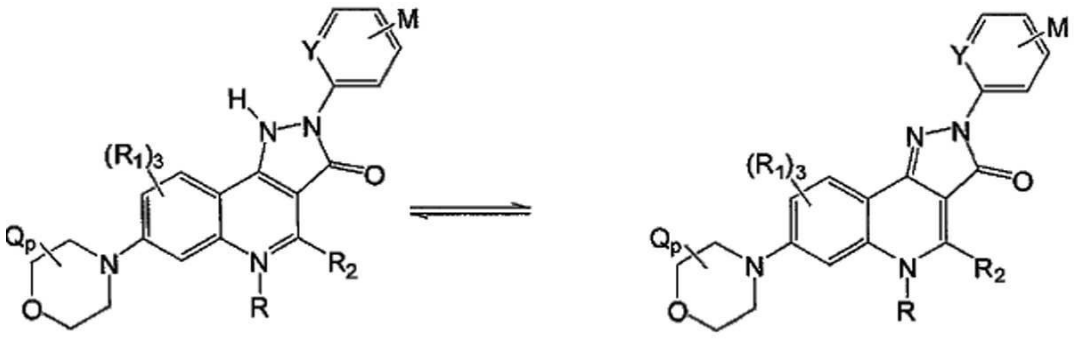


(Iv)

[0097]

[0098] Y CM N .

[0099] , Iw , :

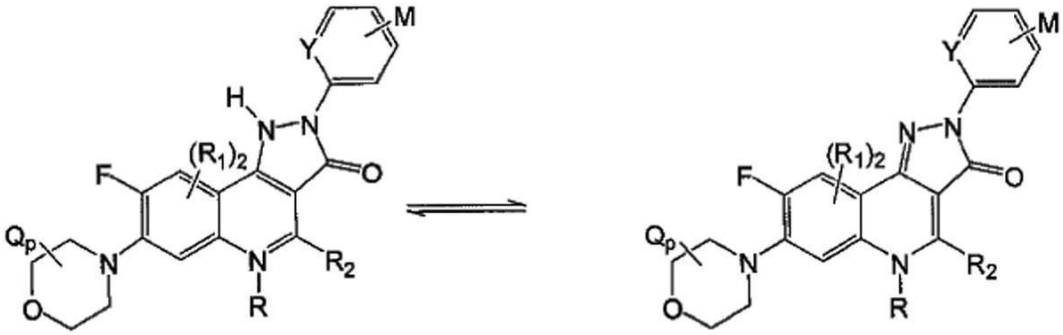


(Iw)

[0100]

[0101] Y CM N .

[0102] , Ix , :

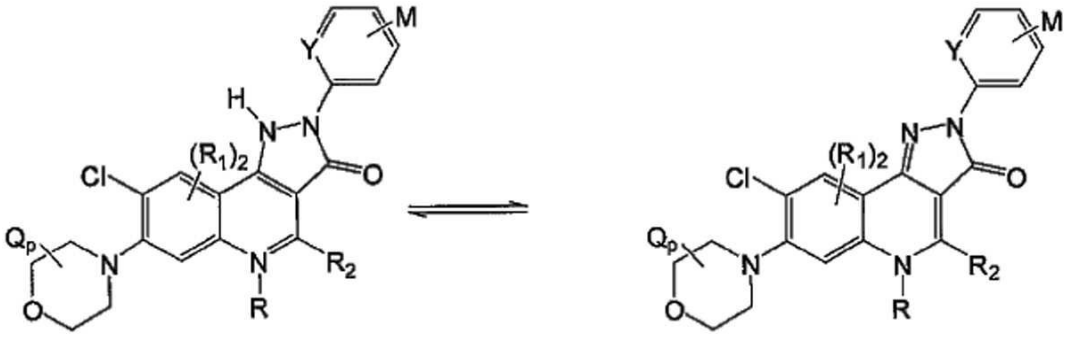


(Ix)

[0103]

[0104] Y CM N .

[0105] , Iy , :

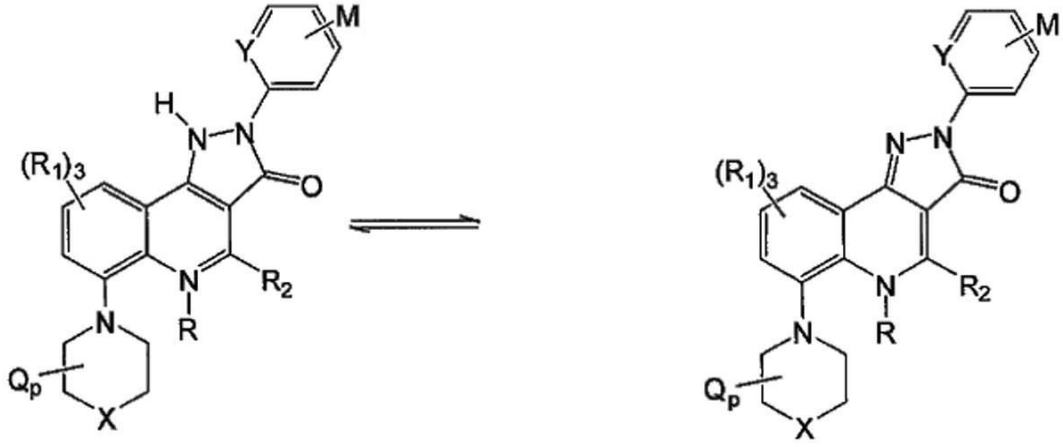


(Iy)

[0106]

[0107] Y CM N .

[0108] , Iz , :

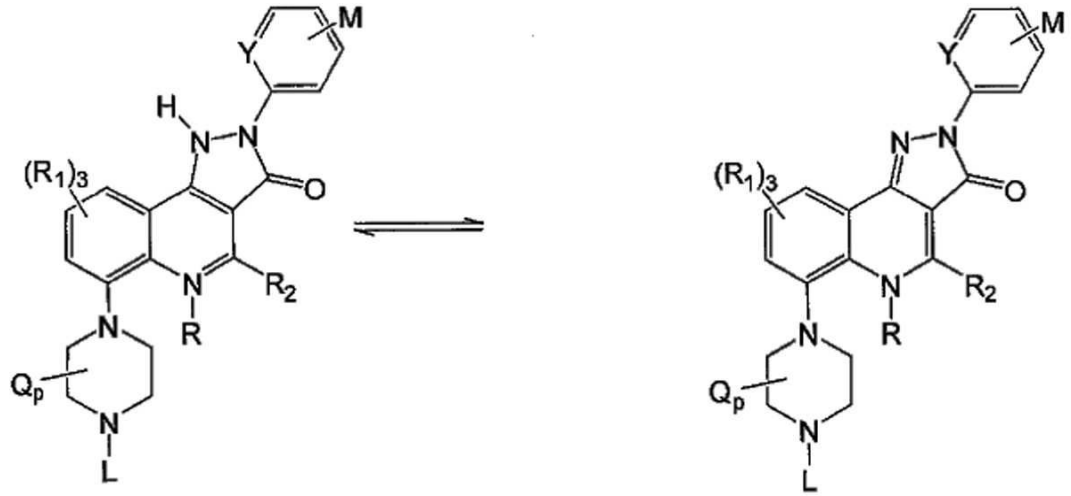


(Iz)

[0109]

[0110] Y CM N .

[0111] , Iaa , :

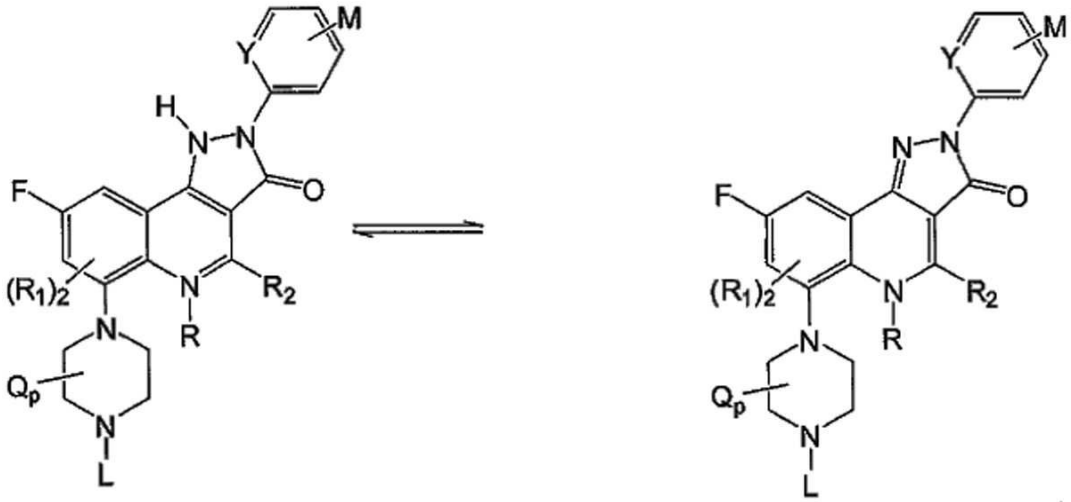


(Iaa)

[0112]

[0113] Y CM N .

[0114] , lab , :

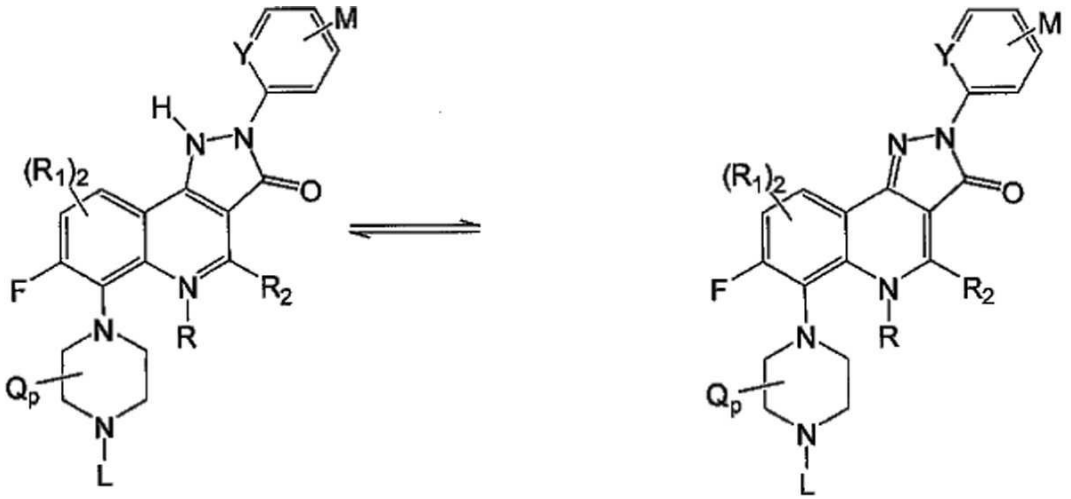


(Iab)

[0115]

[0116] Y CM N .

[0117] , lac , :

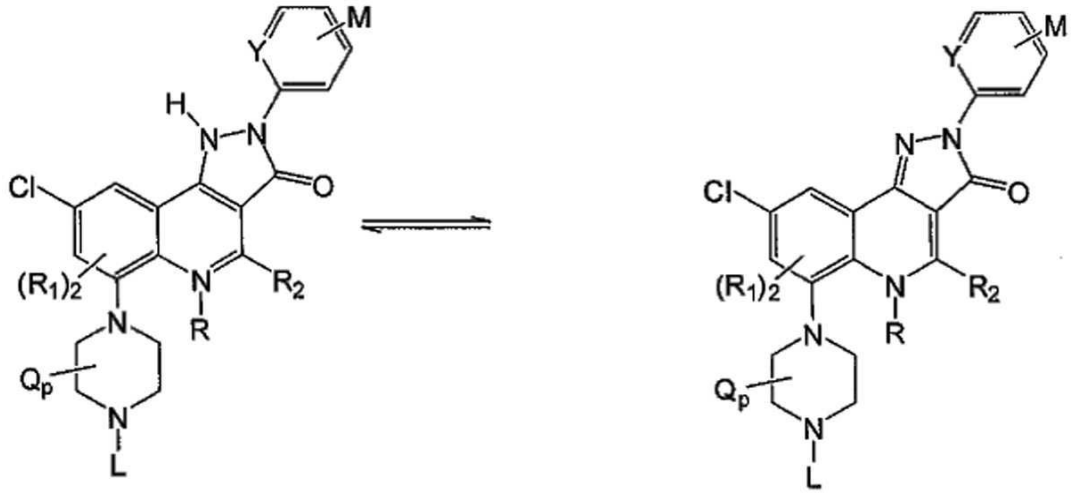


(Iac)

[0118]

[0119] Y CM N .

[0120] , lad , :

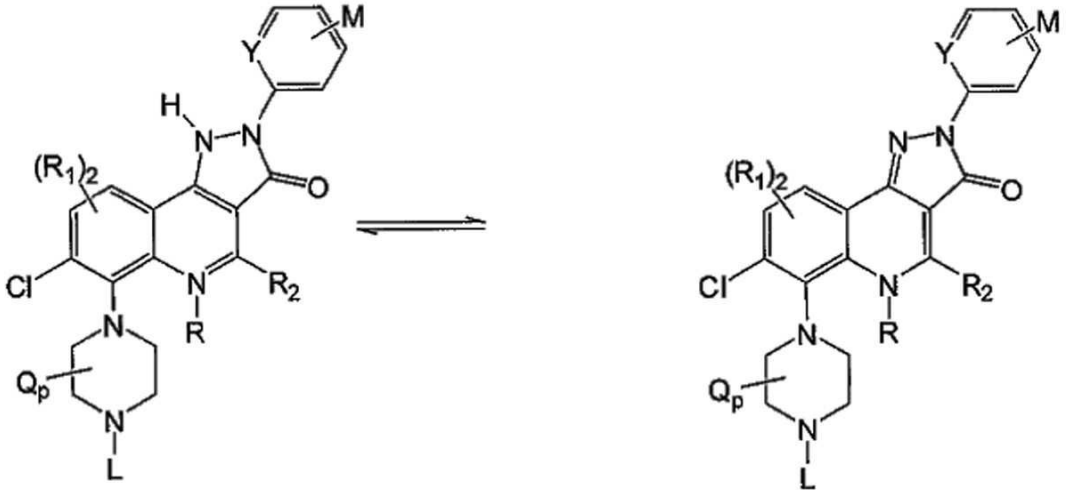


(Iad)

[0121]

[0122] Y CM N .

[0123] , Iae , :

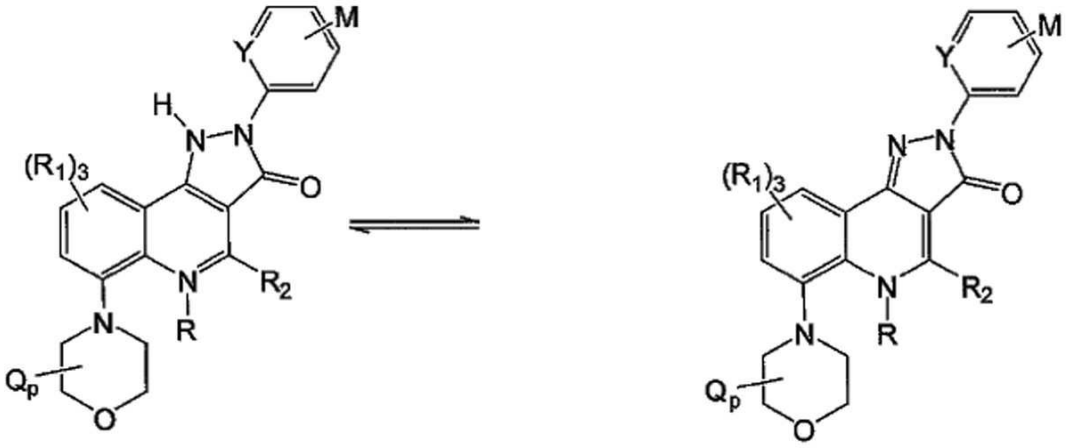


(Iae)

[0124]

[0125] Y CM N .

[0126] , Iaf , :

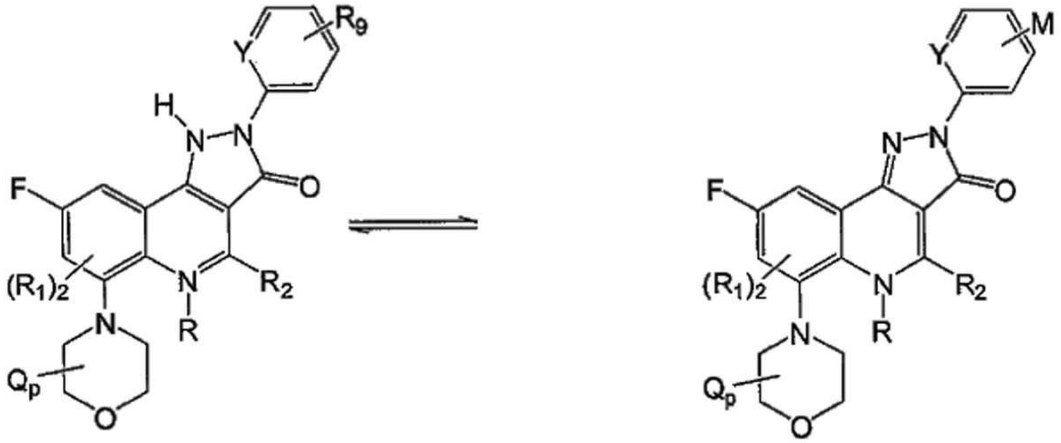


(Iaf)

[0127]

[0128] Y CM N .

[0129] , lag , :

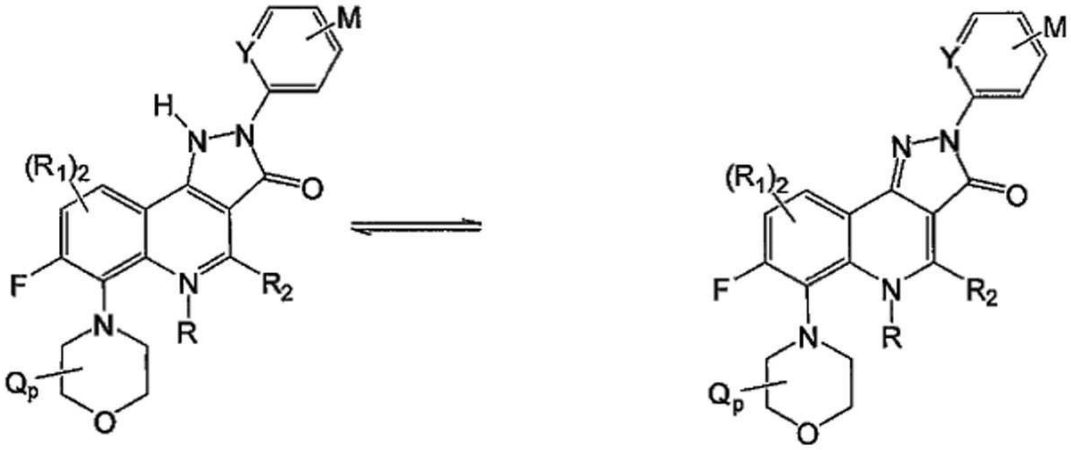


(Iag)

[0130]

[0131] Y CM N .

[0132] , Iah , :

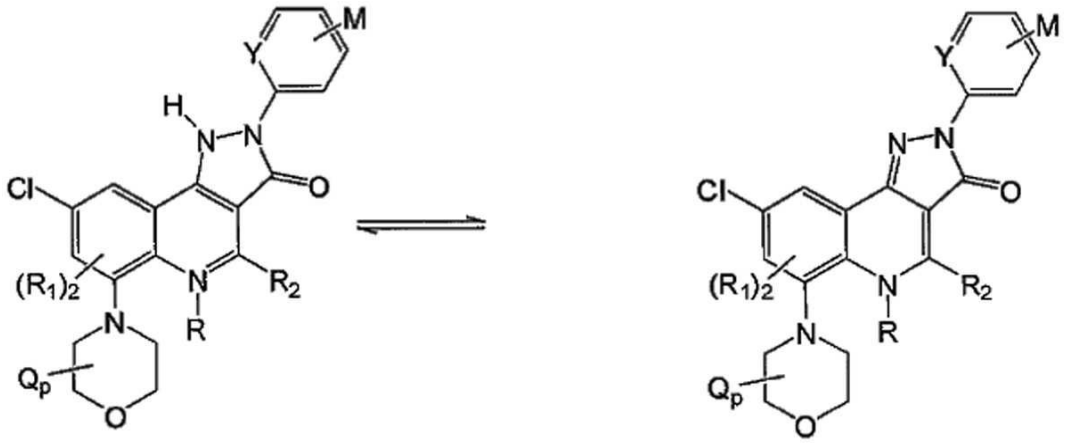


(Iah)

[0133]

[0134] Y CM N .

[0135] , Iaj , :

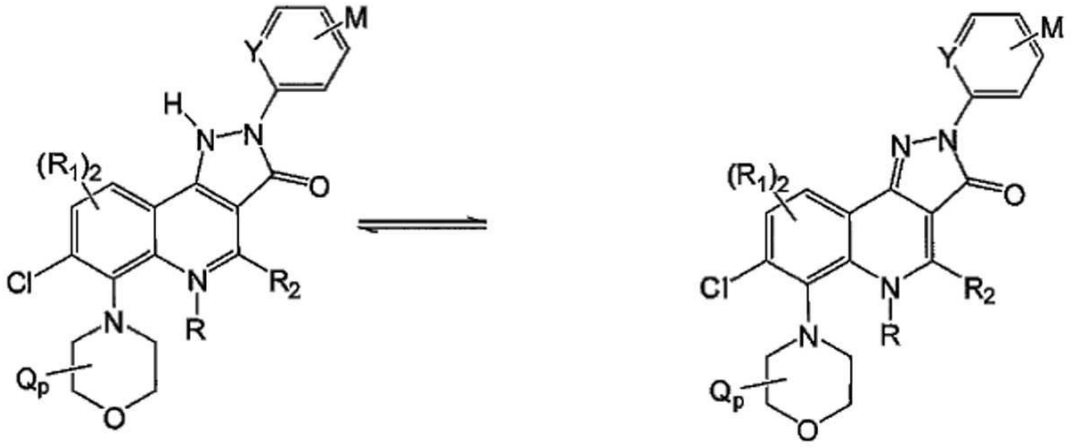


(Iaj)

[0136]

[0137] Y CM N .

[0138] , Iak , :

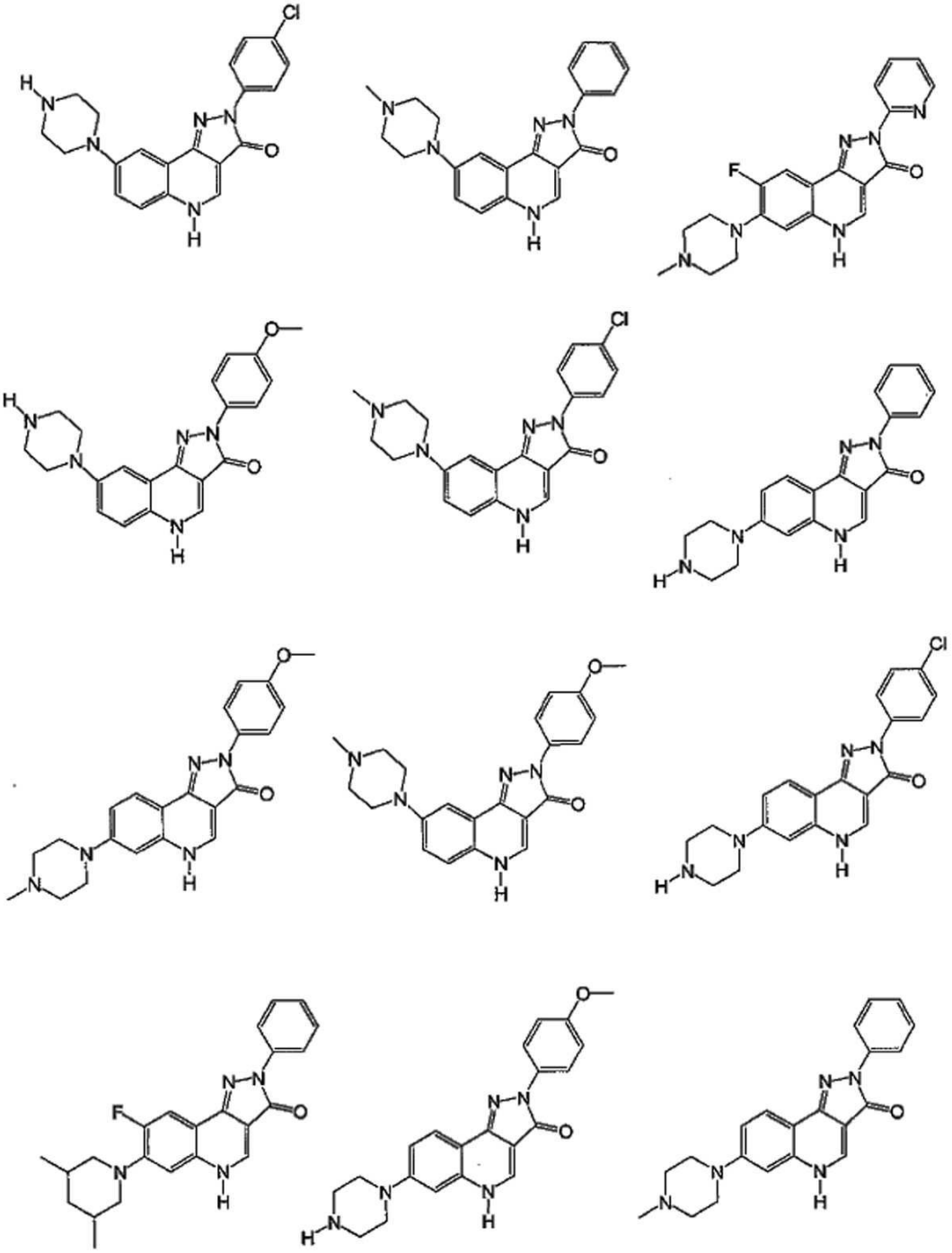


(Iak)

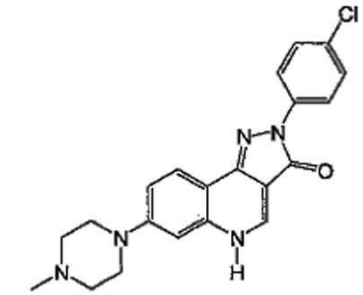
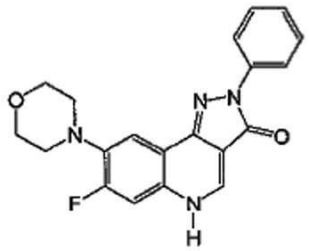
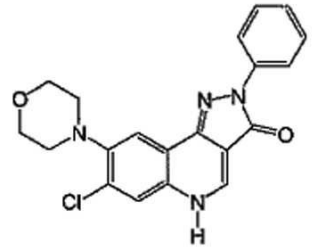
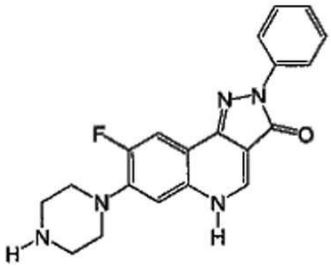
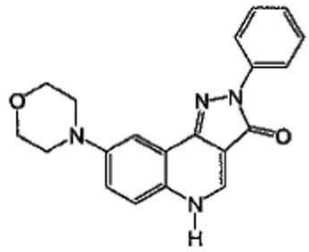
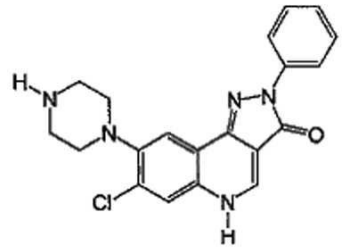
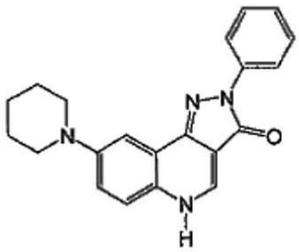
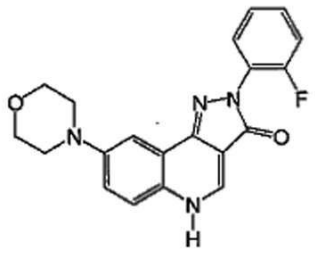
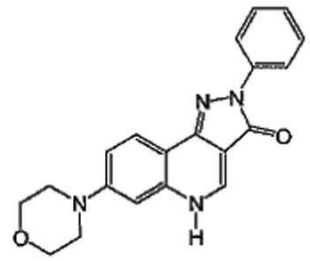
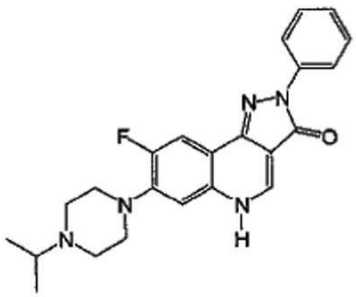
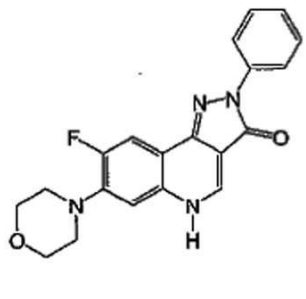
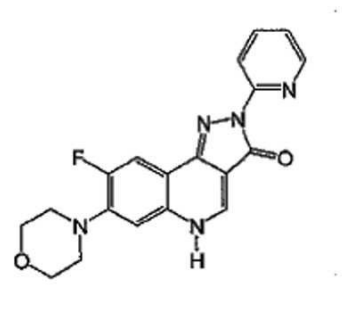
[0139]

[0140] Y CM N .

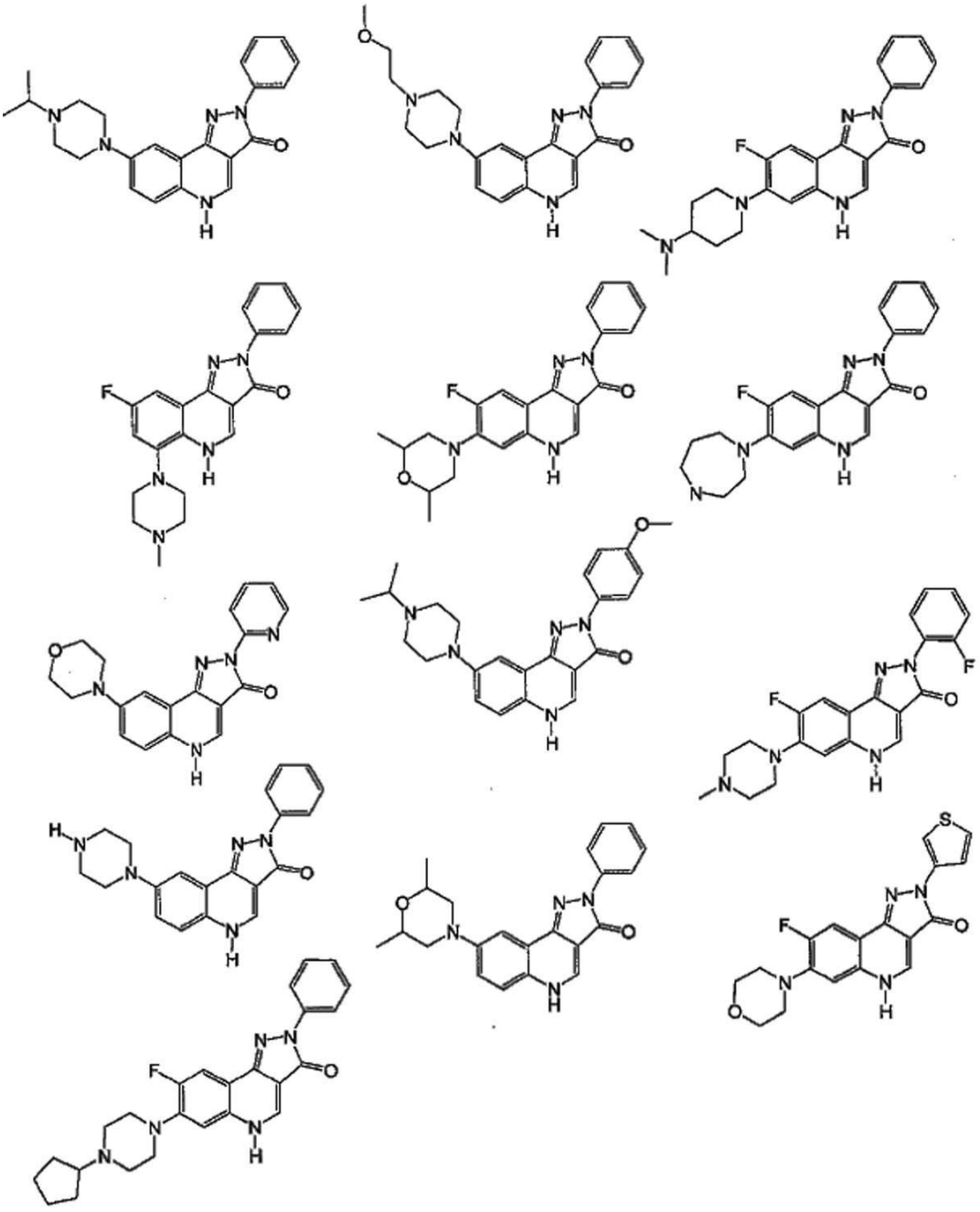
[0141] , :



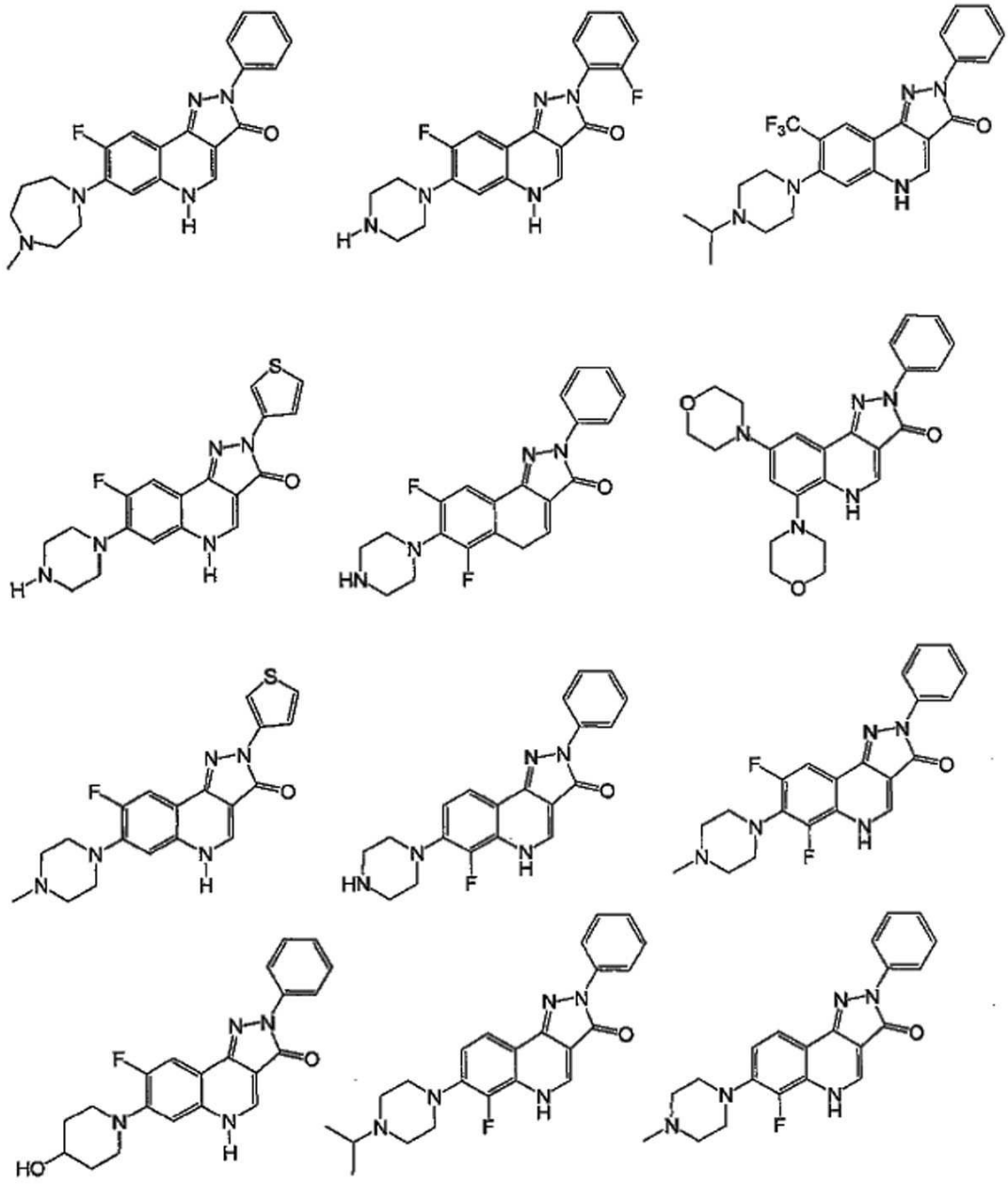
[0142]

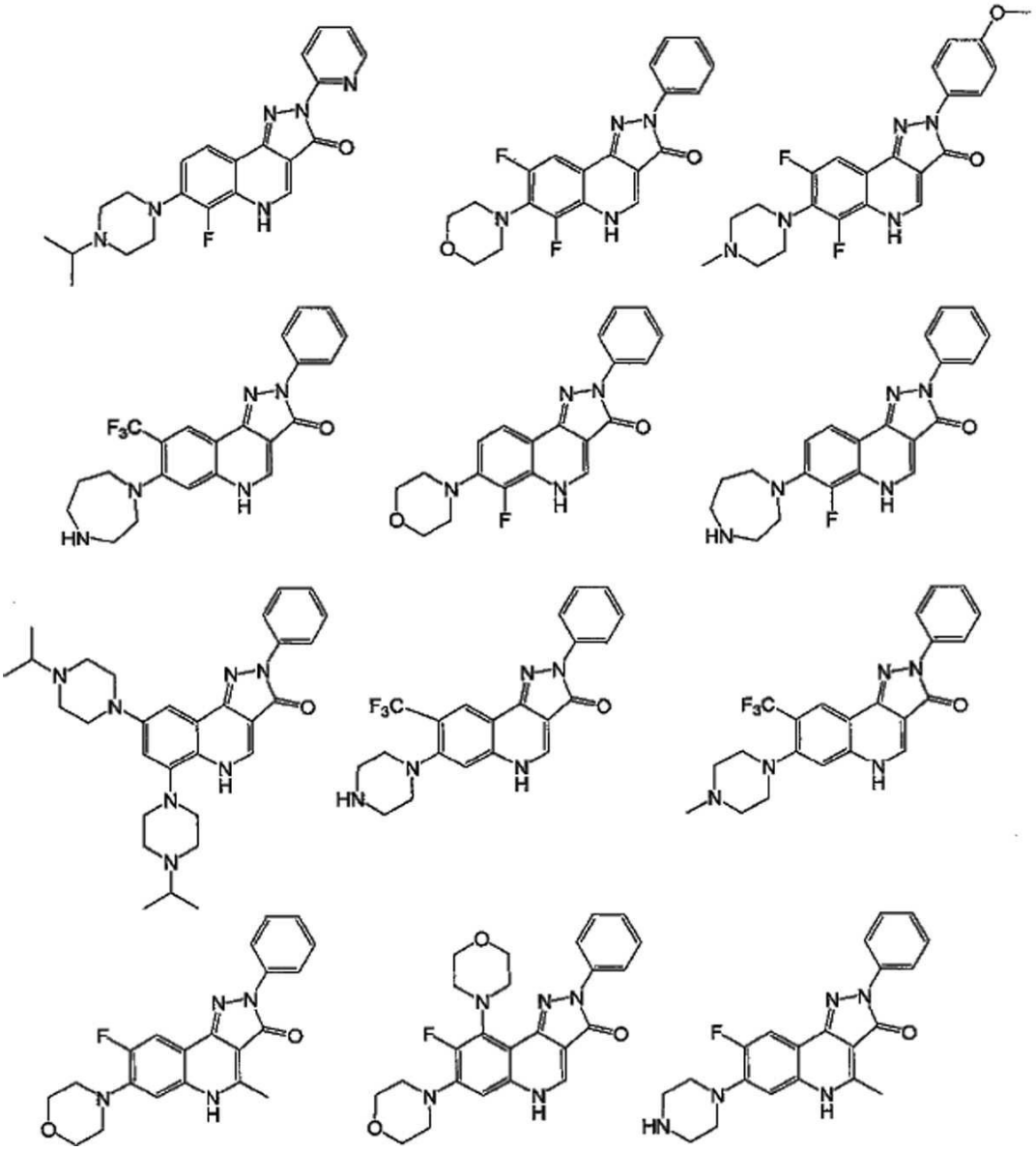
[0143]



[0144]



[0145]



[0146]

[0147] , .

[0148] :

[0149] a) ;

[0150] b) .

[0151] (I) , , , GABA$_A$ :

(I)

[0152]

[0153] R , , ;

[0154] $R_1$ , , , , -CON$R_a$$R_b$, -N$R_a$$R_b$, ($C_1$-$C_6$) , , , , ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) ;

[0155] $R_2$ , , , ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) ;

[0156] $R_a$ $R_b$ , ($C_1$-$C_6$) , , , , ($C_1$-$C_6$) , -S(O)$_z$($C_1$-$C_6$) , -S(O)$_z$ , -C(O)($C_1$-$C_6$) , -C(O)N$R_g$($C_1$-$C_6$) , -C(O)N$R_g$ , -C(O)O($C_1$-$C_6$) , OC(O)-C(O)- , $R_a$ $R_b$ $R_d$ ; O ( ), S ( ), N$R_c$ ;

[0157] $R_c$ , ($C_2$-$C_6$) , ($C_2$-$C_6$) , -C(O)O($C_1$-$C_6$) , -C(O)O , ($C_1$-$C_6$) ($C_1$-$C_6$) , ($C_1$-$C_6$) , , , , O($C_1$-$C_6$) , -C(O)N$R_g$($C_1$-$C_6$) , -C(O)N$R_g$ , -S(O)$_z$($C_1$-$C_6$) , -S(O)$_z$ , -C(O)($C_1$-$C_6$) , C(O)-, 5 ($C_1$-$C_6$) , 5 (C1-$C_6$) ;

[0158] $R_d$ , , , , -C(O)N$R_a$$R_b$, -N$R_a$$R_b$, ($C_1$-$C_6$) , , ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) ;

[0159] $R_e$ $R_f$ , ($C_1$-$C_6$) , , , , ($C_1$-$C_6$) , ($C_1$-$C_6$) , -C(O)($C_1$-$C_6$) , -S(O)$_z$($C_1$-$C_6$) , -S(O)$_z$N$R_g$($C_1$-$C_6$) , -S(O)$_z$ , -C(O)N$R_g$($C_1$-$C_6$) , -C(O)($C_1$-$C_6$) , C(O)-, OC(O)-, -C(O)O($C_1$-$C_6$) ;

[0160] $R_g$ , , , , 5 ($C_1$-$C_6$) ;

[0161] Ar M M ;

[0162] Q , , , , -C(O)N$R_a$$R_b$, -N$R_a$$R_b$, 5 ($C_1$-$C_6$) , 5 ($C_1$-$C_6$) , $R_d$ ($C_1$-$C_6$) , $R_d$ ($C_1$-$C_6$) , $R_d$ , $R_d$ ($C_1$-$C_6$) ;

[0163] M , , $CF_3$, $CF_2H$, , , , ($C_1$-$C_6$) , ($C_1$-$C_6$) , ($C_1$-$C_6$) , -N$R_a$$R_b$, , ;

[0164] X NL, , C(Q)$_2$, S(O)$_z$ ;

[0165] **L** , $(C_2-C_6)$ , $(C_2-C_6)$ , $-C(O)O(C_1-C_6)$ , $-C(O)O$ , $(C_1-C_6)$ $(C_1-C_6)$ , $(C_1-C_6)$ , , , , $O(C_1-C_6)$ , $-CONR_eR_f$, $-S(O)_z(C_1-C_6)$ , $-S(O)_z$ , $-C(O)(C_1-C_6)$ , $C(O)-$, $-C(O)NR_g(C_1-C_6)$ , 5 $(C_1-C_6)$ , 5 $(C_1-C_6)$ ;

[0166] **p** 0, 1, 2 3 ;

[0167] **z** 0, 1, 2 ;

[0168] **n** 0, 1, 2 .

[0169] , . , . , $GABA_A$ $GABA_A$ α5 . , . , .

[0170] (**I**) , , , . , . , , .

[0171] (**I**) , , .

[0172] $GABA_A$ , (**I**) , , . , . , $GABA_A$ $GABA_A$ α5 . , . , .

[0173] , (**I**) , , . , . , . , .

[0174] , (**I**) , , . , , , , .

[0175] α5 $GABA_A$ α , (I) , , . , . , .

[0176] , MCI, AAMI, , , , (Pick) , (Huntington) , .

[0177] CNS α5 (inverse agonist) .

[0178] (**I**) , , . , . , . , .

[0179] $GABA_A$ α5

, (I) , ,

. , . ,

. , .

[0180] _____

[0181] ____

[0182] , :

[0183] Ac

[0184] aq.

[0185] Bu n-

[0186] cat.

[0187] CDI 1,1'-

[0188]

[0189] Dowtherm® ( )

[0190] DBN 1,5- [4.3.0] -5-

[0191] DBU 1,8- [5.4.0] -7-

[0192] DIEA

[0193] DMA

[0194] DMF N,N'-

[0195] DMSO

[0196] Et

[0197] g ( )

[0198] h ( )

[0199] HPLC

[0200] iPr isopr

[0201] LCMS -

[0202] Me

[0203] MeOH

[0204] mL ( )

[0205] Pd/C

[0206] ppt

[0207] Rt

[0208] TEA

[0209] Tert,t 3

[0210] μL ( )

[0211] " " , , , .

[0212] , " " .
" " . " " 2
- , " " 2
- . , ,
. , sec- , t- , .
, , , , , , ,
. , , , ,
.

[0213] " " --O-- ( )
. , , , , , n- , sec- , t-
, .

[0214] " " 2 20 1
, 1- , 2- , 2- -1- , 1- , 2- ,
.

[0215] " " 2 20 1
, 1- , 1- , 2- , .

[0216] " " (homocyclic)
. , " " , , 2 ,
9 10 -
, . " "
, , , , , , , ,
.

[0217] " " " "
, , , .
, , . " " . ,
" " , ,
. , ,
, ,
. 4, 5, 6, 7, 8 . 6 3
, , , , , 5 ,
1 2 , , , ,
. 8 12 .

[0218] " " ,
. , .
, , , , , , , ,
, , .
" " - .

[0219] " " , , .

[0220] " " , , , .
-NH , -$NH_2$, -N $_2$, -N , -NH , -N
.

[0221] " " .
, , , .

[0222] " " .
, , .

[0223] " " --O-- .

[0224] " " --S--
. , , , , , n- , sec- , t-
.

[0225] " " C=O ( , ) .

[0226] " " =0 ( , ) . , " "
.

[0227] " " " " " " , " " " "
. , ,
. .

[0228] , (species)
(unpaired electron) . , ,
. , . " "
" " .

[0229] , -
.

[0230] . (enantiomer)
.
, . .
, , - -
. - - , - - .
, ,
.

[0231] (polymorph), , , (conformer), ,
. .
( ) .
. . ,
( ) .
. ,
.

[0232] " " , , ( , ) .

[0233] " ," " (host)," " ," " " , , ,
, , ,
.

[0234] ---

[0235] , (**I**) **Ia** **Iak** .

[0236] , , ;
.

[0237] **Ar** , 4- , 4- , 2- , 2- .

[0238] **X** , , .

[0239] **n** 1 .

[0240] **L** , , , 2- .

[0241] **Q** , .

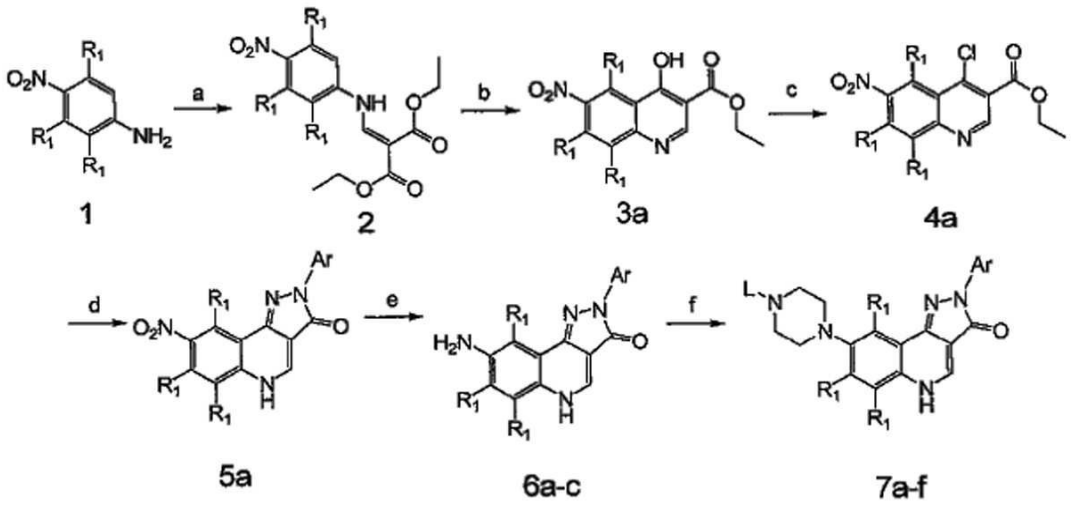
[0242] _____

[0243] (**I**) ,
.

[0244] (**I**) 1 7
. 1 , **3** 4- -6-
**1** 2-( ) . 3
4- -6- **4** . **5** **4**
. 8- N- ( )
N- ( ) . 2 14
.

[0245] (tautomerization) (sigmatropic rerrangement)
.

[0246] **1: 8-( -1- )-**



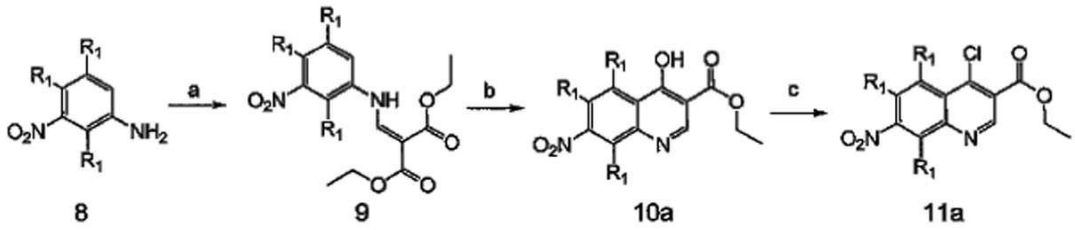

[0247]

[0248] a) 1 2-( ) , 125 , 3 , b) $Ph_2O$, , 30 3 , c) 4
, cat. DMF, $CHCl_3$, , 3 , d) 2 , 2 , o-
, , 12 , e) $SnCl_2$, , , 12 , f) ( )NL · HCl, , ,
72 .

[0249] **1** 8-( -1- )- .
**1** 4- - 2-( ) -
**2** 4- - . **2** **3a**
, (**b**) , Dowtherm®
. **3** **4a** -

DMF . (c)
, $P(O)Cl_3$, $PCl_5$, , ,
. (c)
, , 1,2- , .
**4a** - **5a** -
. (d) ,
: (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU),
1,5- [4.3.0] -5- (DBN), N- .
(d) o- , , ,
. **5a** **6a-c** .
$SnCl_2$, $Fe/H_2$, , $Pt/H_2$, $PtO_2/H_2$ .
**6a-c** ( ) **7a-f** .
(f) o- , , , ,
. (f) ( ) ( )
.

[0250] **2: 7-( -1- )-**



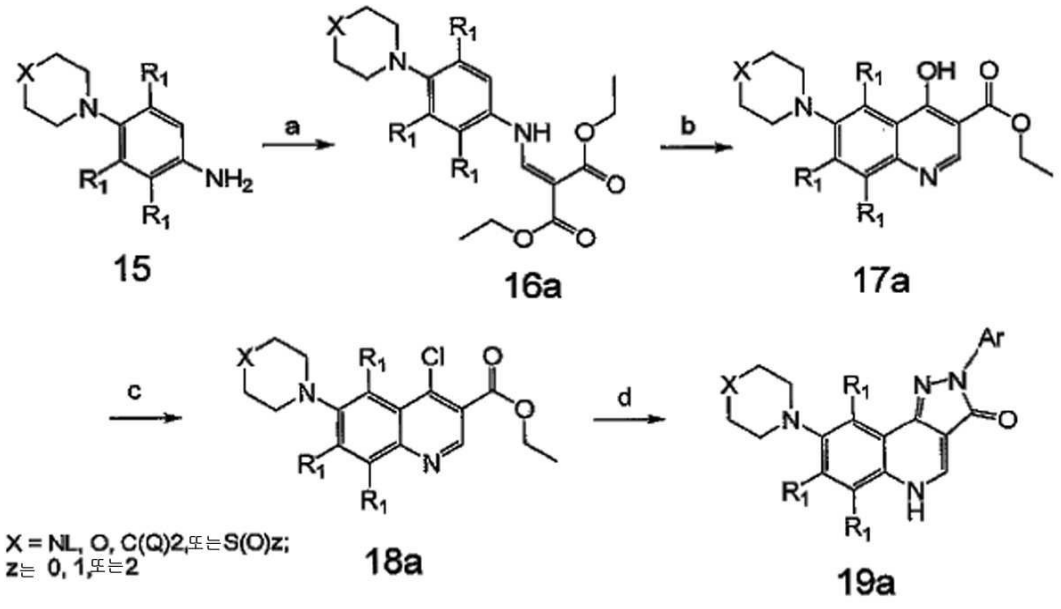

[0251]

[0252] a) 1 2-( ) , 125 , 3 ; b) $Ph_2O$, , 30 3 ; c) 4
, cat. DMF, $CH_2Cl_2$, , 3 ; d) 2 , 2 , o-
, , 12 ; e) $SnCl_2$, , , 12 ; f) ( )NL-HCl, , , 72 .

[0253] **2** 7-( -1- )- .
**8** 3- - 2-( ) -
9 3- - . **9** **10a**
. (b) , Dowtherm®
, . **10a** **11a**
- DMF .
(c) , $P(O)Cl_3$, $PCl_5$, ,
, , . (c)
, , 1,2- ,
. **11a** - **12a-c** - . (d)
(TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (d)

o- , , , .
**12a-c** **13a-c** . $SnCl_2$, $Fe/H_2$, , $Pt/H_2$, $PtO_2/H_2$ . **13a-c** ( ) **14a-f** . (**f**) o- , , , , . (**f**) ( ) ( ) .

[0254] **3: 8-( -1- )- 8-( -1- )-**

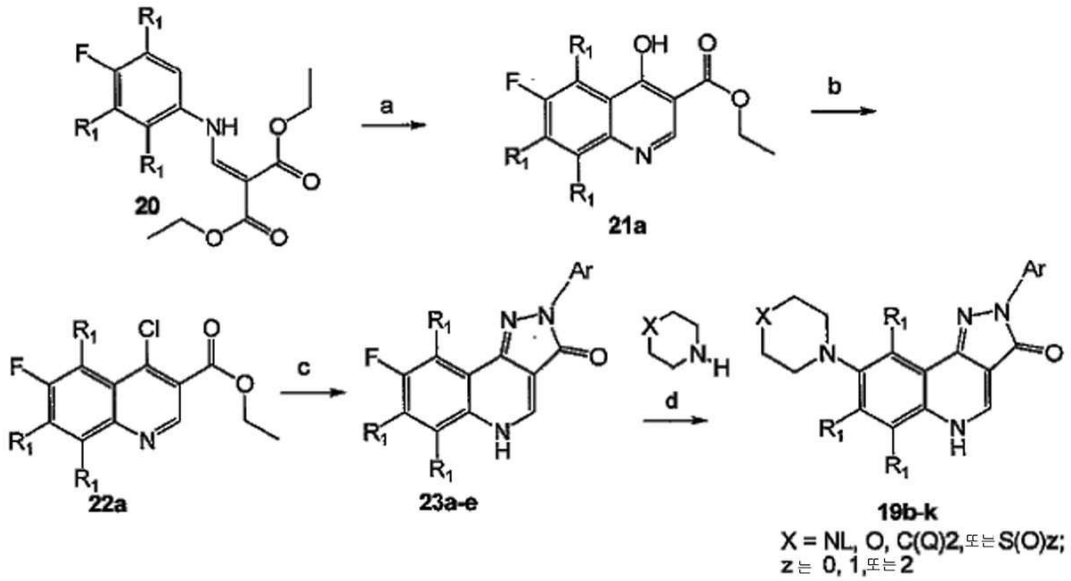



[0255]

[0256] a) 1 2-( ) , 125 , 3 ; b) $Ph_2O$, , 30 3 ; c) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; d) 2 , 2 , o- , , 12 .

[0257] **3** 8-( -1- )- 8-( -1- )- . **15** 4- - - 2-( ) - **16a** 4- - - . 16a **17a** - - . (**b**) , Dowtherm® , . **17a** - DMF . (**c**) , $P(O)Cl_3$, $PCl_5$, , , , . (**c**) , , 1,2- , . **18a** - **19a** - . (**d**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (**d**) o- , , , .

[0258] **4: 8-( -1- ), 8-( -1- ), 8-( -- )-**

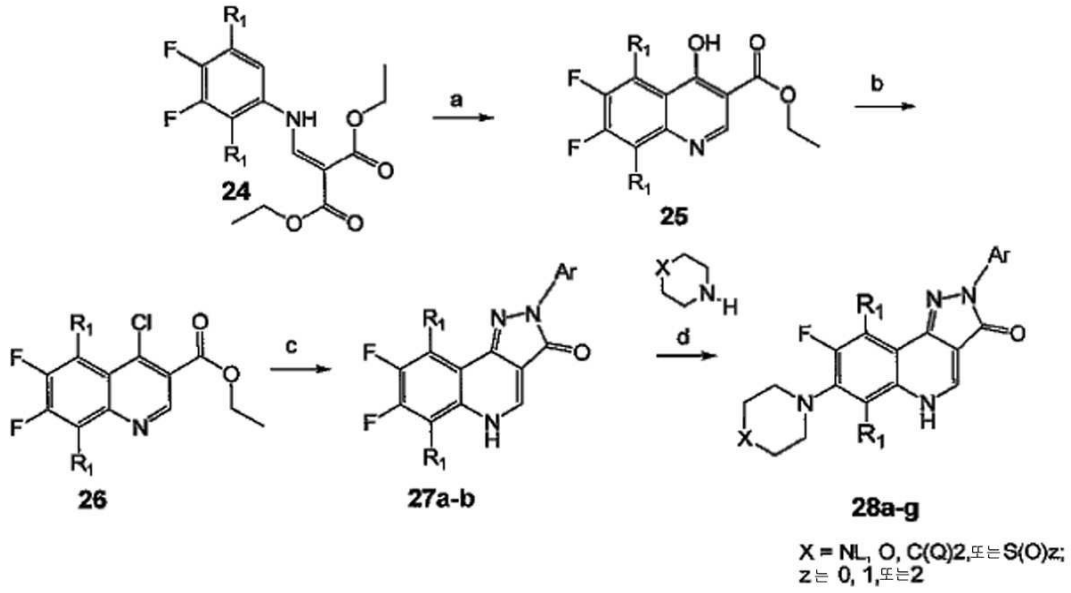



[0259]

[0260] a) $Ph_2O$, , 30 3 ; b) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; c) 2 , 2 , o- , , 12 , 175 , 12 ; d) 175 , 72

[0261] **4** 8-( -1- ), 8-( -1- ), 8-( -1- )- . **20** **17a** - . (**a**) , Dowtherm® . 21a **22a** - - DMF . (**b**) , $P(O)Cl_3$, $PCl_5$, , , . (**b**) , , 1,2- , . **22a** - **23a-e** - . (**c**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (**c**) o- , , , . **23a-e** **19b-k** . (**d**) .

[0262] **5: 7-( -1- ), 8-( -1- ), 8-( -1- )-**

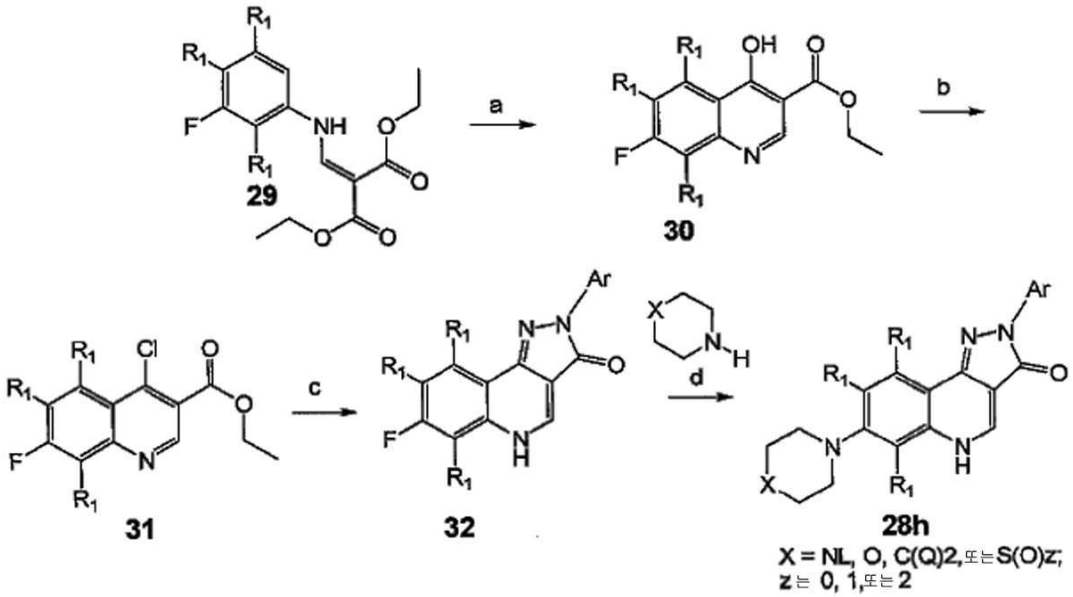



[0263]

[0264] a) $Ph_2O$, , 30 3 ; b) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; c) 2 , 2 , o- , , 12 , 175 , 12 ; d) 175 , 72

[0265] **5** 7-( -1- ), 8-( -1- ), 8-( -1- )- . **24** **25** - . (**a**) , Dowtherm® . **25** **26** - - DMF . (**b**) , $P(O)Cl_3$, $PCl_5$, , , . (**b**) , , 1,2- , . **26** - **27a-b** - . (**c**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- o- , , , . **27a-b** **28a-g** . (**d**) .

[0266] **6: 7-( -1- ), 8-( -1- ), 8-( -1- )-**

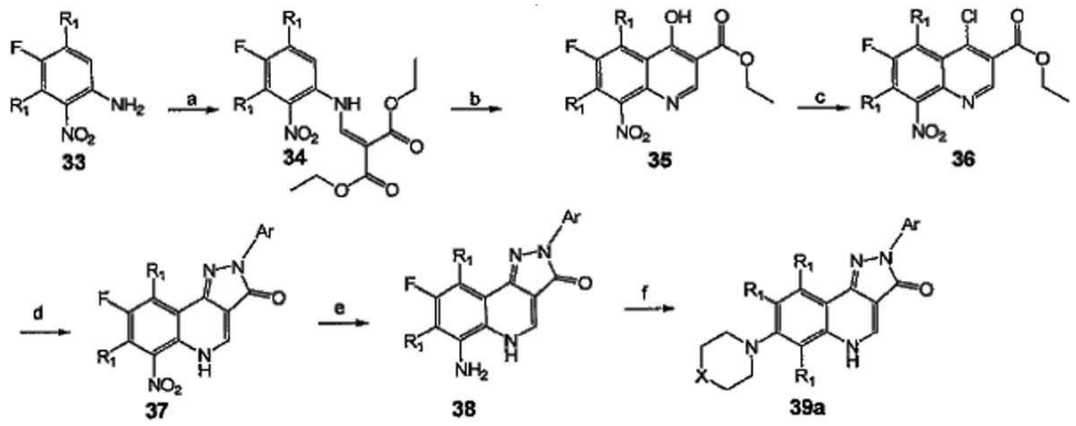



[0267]

[0268] a) $Ph_2O_5$, , 30 3 ; b) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; c) 2 , 2 , o- , , 12 , 175 , 12 ; d) 175 , 72

[0269] **6** 7-( -1- ), 8-( -1- ), 8-( -1- )- . **29** **30** - . (**a**) , Dowtherm® . **30** **31** - - DMF . (**b**) , $P(O)Cl_3$, $PCl_5$, , , . (**b**) , , 1,2- , . **31** - **32** - . (**c**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- o- , , , . (**c**) . **32** **28h** . (**d**) .

[0270] **7: 6-**

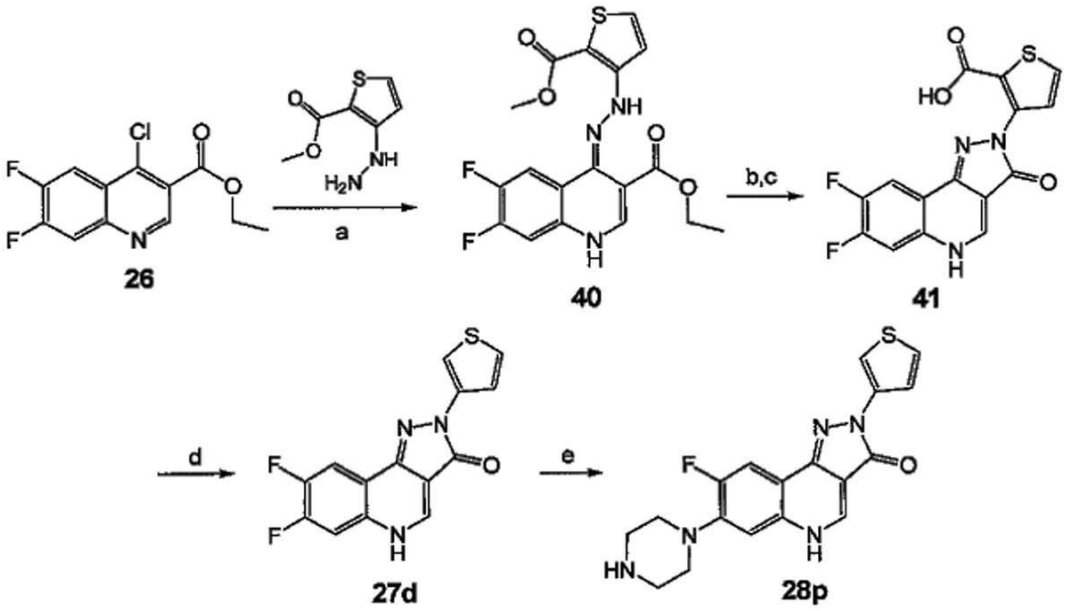


[0271]

[0272] a) 1 2-( ) , 125 , 3 , b) $Ph_2O$, , 30 3 , c) 4 , cat. DMF, $CH_2Cl_2$, , 3 , d) 2 , 2 , o- , , 12 , e) $SnCl_2$, , , 12 , f) ( )N-L-HCl, , , 72 .

[0273] **7** 6- . **33** 2- - 2-( ) - **34** 2- - . **34** **35** . (**b**) , Dowtherm® . **35** **36** - DMF . (**c**) , $P(O)Cl_3$, $PCl_5$, , , . (**c**) , , 1,2- , . **36** - **37** - . (**d**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (**d**) o- , , , . **37** **38** . $SnCl_2$, $Fe/H_2$, , $Pt/H_2$, $PtO_2/H_2$ . **38** ( ) **39a** . (**f**) o- , , , . (**f**) ( ) ( ) .

[0274] **8: 2- -**



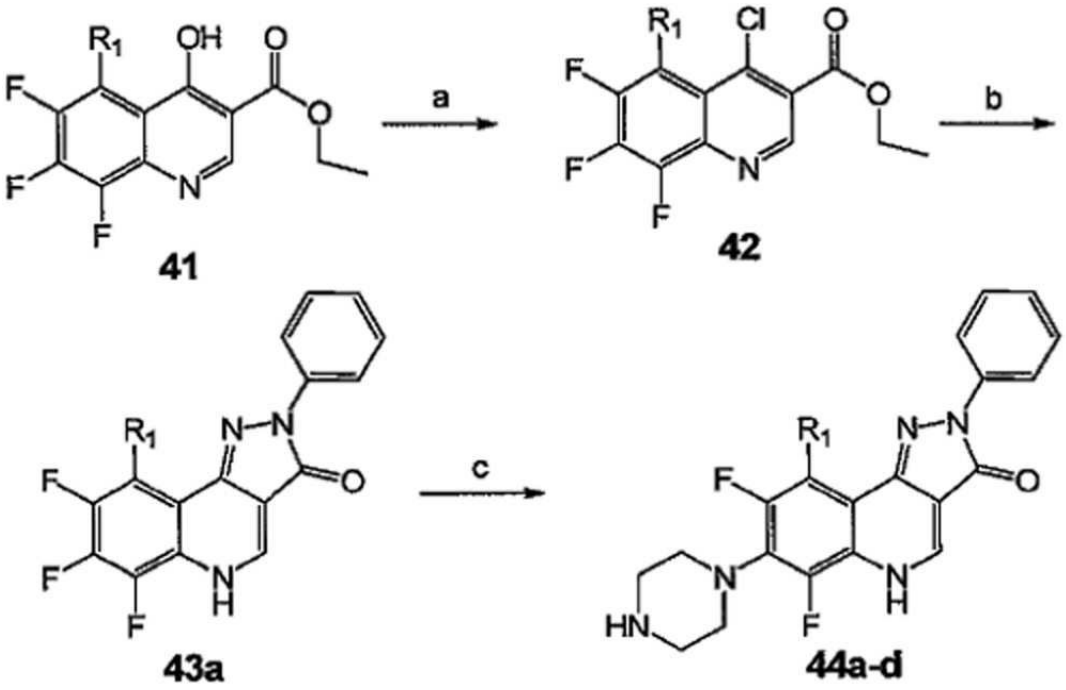

[0275]

[0276] a) NaOH/ , b) NaOH, , c) NaOH, , d) Cu, , e) , 175 , 72

[0277] **8** 2- - .

**26** - 3- -2- **40** . (**a**) NaOH, MeOH NaOH . **40** **41** . **40** **41** NaOH, MeOH NaOH . **41** (decarboxylation) **27d** . **27d** **28p** . (**e**) .

[0278] **9: 6,8- -7-( -1- )-**

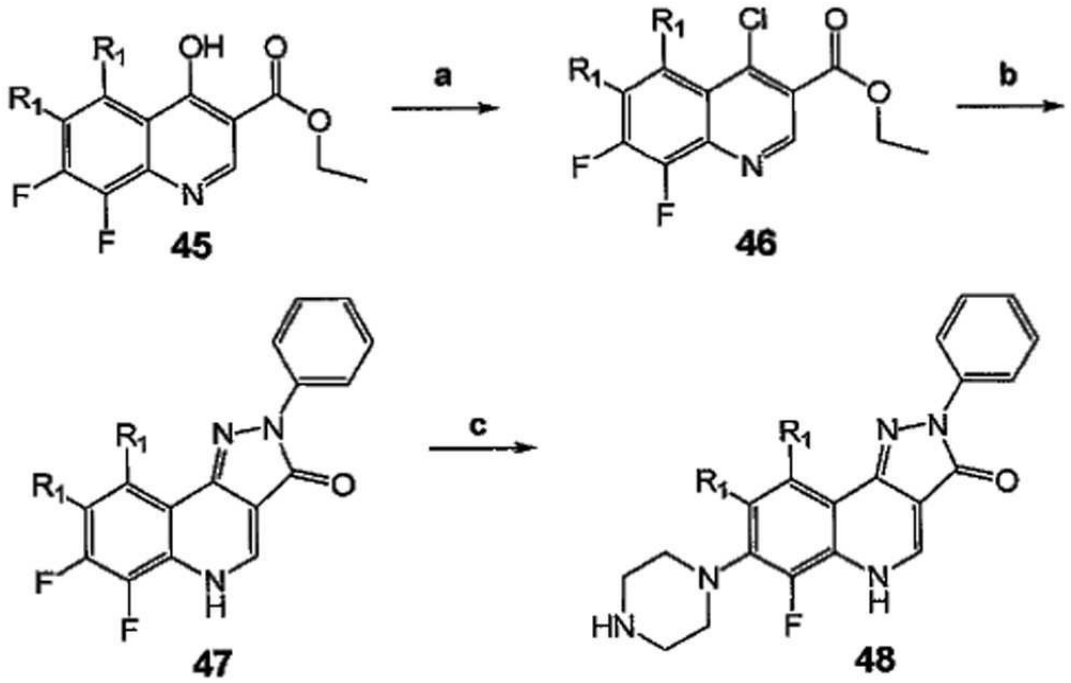



[0279]

[0280] a) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; b) 2 , 2 , o- , , 12 , 175 , 12 ; c) 175 , 72

[0281] **9** 6,8- -7-( -1- )- . **41** **42** - - DMF . (**a**) , $P(O)Cl_3$, $PCl_5$, , , . (**a**) , , 1,2- , . **42** - **43a** - . (**b**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (**b**) o- , , , . **43a** **44a-d** . (**c**) .

[0282] **10: 6- -7-( -1- )-**

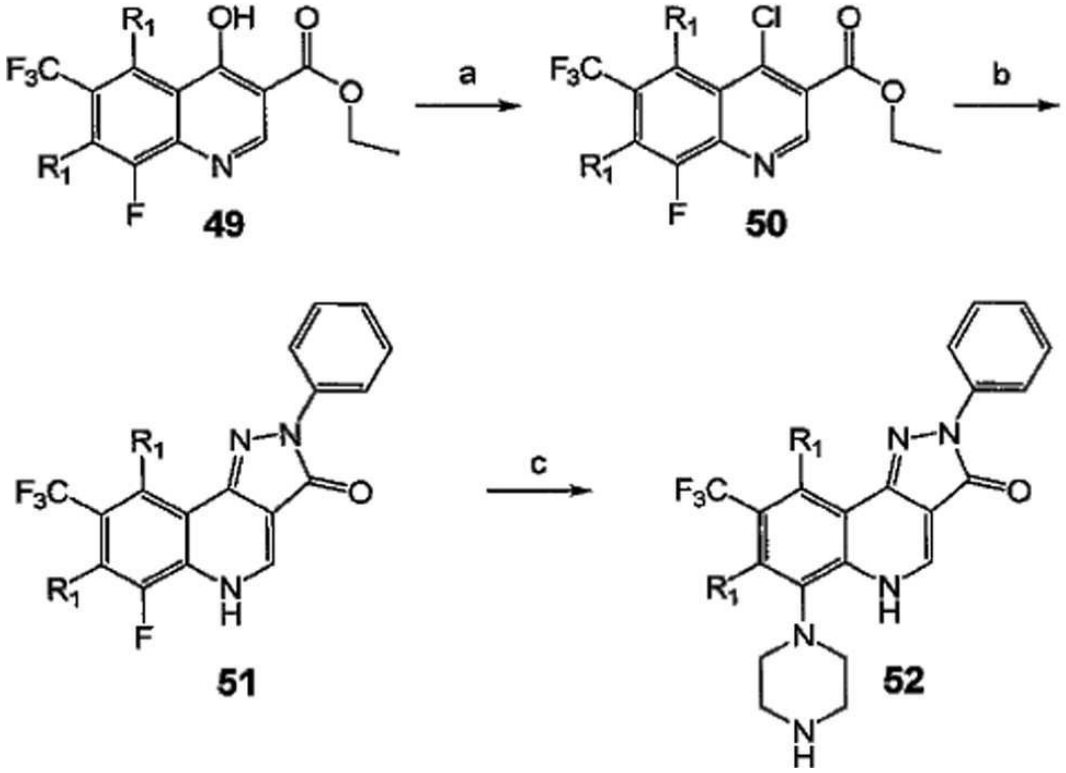



[0283]

[0284] a) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; b) 2 , 2 , o- , , 12 , 175 , 12 ; c) 175 , 72

[0285] **10** 6- -7-( -1- )- . **45** **46** - - DMF . (**a**) , $P(O)Cl_3$, $PCl_5$, , , . (**a**) , , 1,2- , . **46** - - **43a** - . (**b**) (TEA), (DIEA), 1,8- [5.4.0] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (**b**) o- , , , . **43a** **44a-d** . (**c**) .

[0286] **11: 6-( -1- )-8- -**

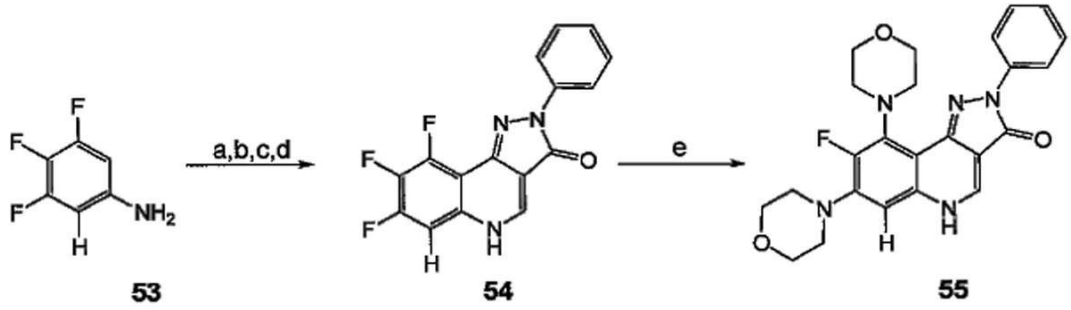



[0287]

[0288] a) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; b) 2 , 2 , o- , , 12 , 175 , 12 ; c) 175 , 72

[0289] **11** 6-( -1- )-8- - . **49** **50** - - DMF . (**a**) , $P(O)Cl_3$, $PCl_5$, , , . (**a**) , , 1,2- , . **50** - - 51 - . (**b**) (TEA), (DIEA), 1,8- [5.4.0] - 7- (DBU), 1,5- [4.3.0] -5- (DBN), N- . (**b**) o- , , , . **51** **52** . (**c**) .

[0290] **12: 7,9- ( -1- )-8- -**

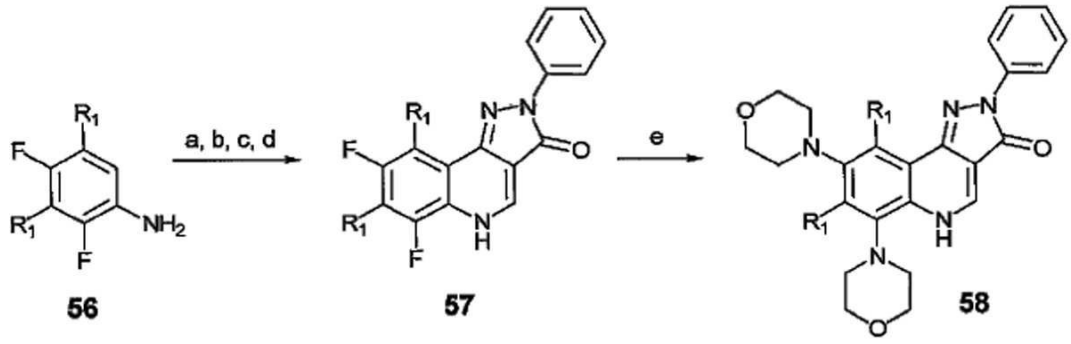



[0291]

[0292] a) 1 2-( ) , 125 , 3 ; b) $Ph_2O$, , 30 3 ; c) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; d) 2 , 2 , o- , , 12 ; e) 5 , 175 .

[0293] **12** 7,9- ( -1- )-8- - . **53** **54** - - - **a, b, c, d** . **55** **55** - - . (**e**) .

[0294] **13: 6,8- ( -1- )-**

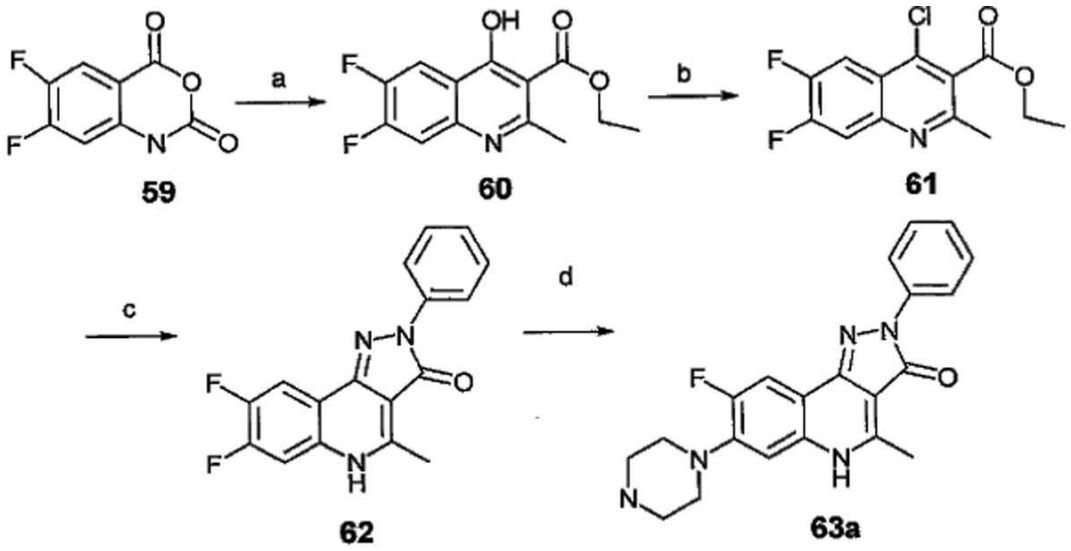



[0295]

[0296] a) 1 2-( ) , 125 , 3 ; b) $Ph_2O_5$, , 30 3 ; c) 4 , cat. DMF, $CH_2Cl_2$, , 3 ; d) 2 , 2 , o- , , 12 ; e) 5 , 175 .

[0297] **13** 6,8- ( -1- )- . **53** **57** - - - **a, b, c, d** . **57** **58** - - . (**e**) .

[0298] **14: 8- -4- -7- -1- -**



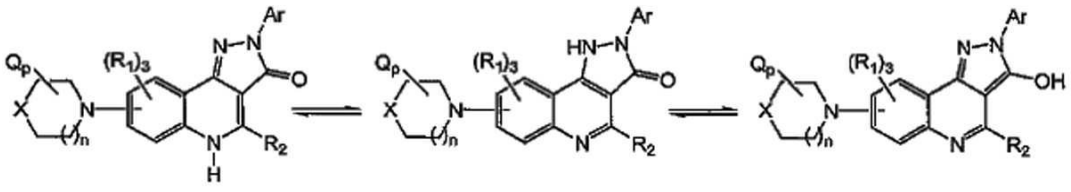

[0299]

[0300] a) 10 , 1.1 NaH, DMA, 125 , 10 ; b) $POCl_3$, 0.5 ; c) 2 , 2 , o- , , 12 ; d) 5 , 125 , 72 .

[0301] **14** 8- -4- -7- -1- - . **59** - **60** . (**a**) DMA, DMF, NMP . (**a**) , , , . **60** **61** - - . (**b**) , $P(O)Cl_3$, $PCl_5$, , , . **61** - - **62** - . (**c**) (TEA), (DIEA), 1,8- [5A] -7- (DBU), 1,5- [4.3.0] -5- (DBN), N- o- , , , . **62** **63a** . (**d**) .

[0302] (**I**) , (I) , , (enantiomer) .

[0303] (**I**) , (tautomer) , , . , (**I**) :




[0304]

[0305] (**I**) . (**I**)

.

[0306]

, . ,

, , , , ,

, , , , , , , α-

α- . , , ,

, , , .

[0307] ,

.

( : , ) ( : ) .

[0308] I , , ( , ,

) , .

[0309] , (assimilable edible carrier)

, .

,

. , , ,

, (troches), , , , (wafers)

. 0.1 % .

, (dosage form) 2 60 %

.

.

[0310] , , , : , ,

; ; ,

(disintegrating agent); ; , ,

, , (oil of wintergreen) .

, ,

.

. , , , , (shellac)

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, , . ,

. , .

[0311] , .

. ,

, , .

, .

[0312] ,

(extemporaneous preparation)

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. , ,

.

[0313] . , , .

[0314] , , . , .

[0315] , , , . , - / , . . , .

[0316] , , , , , (paste), , .

[0317] I . .

[0318] , , , .

[0319] , (dose) 0.15 100 mg/kg, 1 kg , 0.75 50 mg 1 75 mg, 1 90 mg/, 1 60 mg .

[0320] 1 1000 mg, 10 750 mg, 5 500 mg .

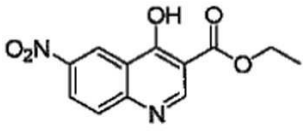
[0321] , 0.5 75 μM, 1 50 μM, 2 30 μM . , 0.05 5% 1-100 mg (bolus) . 0.01-5.0 mg/kg/hr 0.4-15 mg/kg .

[0322] , 1 2, 3, 4 (subdose) . , .

[0323] , (AAMI), (MCI), , (schizophrenia), (dementia)(HIV , , , , (Pick's disease), - ) (CNS) .

[0324] 1-7 , .

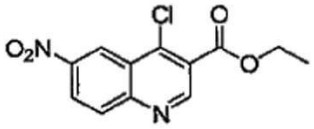
[0325]



**3a**

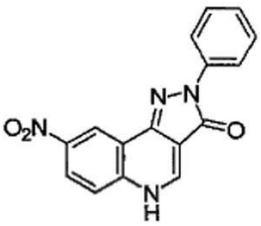
[0326]

[0327] 1: 4- -6- - -3- (**3a**): 4- , 3 120 . 2-(4- )- - . Dowtherm A® , 1 . 80 , (ligroin) . , 30 80% . $^1$H-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 ($MH^+$).



[0328]

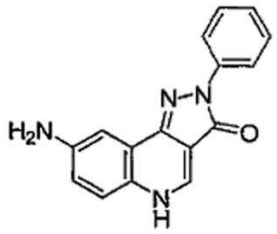
[0329] 2: 4- -6- - -3- (**4a**): **3a** 4 , , 0.1 . 3 , 5 M 4 . , 100 mL , , , . , . $^1$H-NMR ($CDCl_3$) δ (ppm): 1.48 (3H, t, J = 7.08 Hz), 4,55 (2H, q, J = 7.08 Hz), 8.31 (1H, d, J = 9.27 Hz), 8.62 (1H, m), 9.36 (2H, m). m/z 281.7 ($MH^+$).



**5a**

[0330]

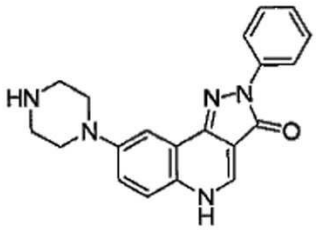
[0331] 3: 8- -2- -2,5- - -[4,3-c] -3- (**5a**): **4a**, . , 12 135 . , 85% . $^1$H-NMR (DMSO-d6) δ (ppm): 7.19 (1H, tt, J = 7.32, 1.22 Hz), 7.42 (2H, t, J = 7.56 Hz), 7.84 (1H, d, J = 9.03 Hz), 8.16 (2H, dd, J = 8.30, 1.22 Hz), 8.82 (1H, s), 8.89 (1H, d, J = 2.44 Hz). m/z 307.3 ($MH^+$).



[0332] **6a**

[0333] 4: 8- -2- -2,5- - -[4,3-c] -3- (**6a**): **5a** Pd . 20 psi . , , 8- -2- -2,5- - -(4,3-c) -3- 87% . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

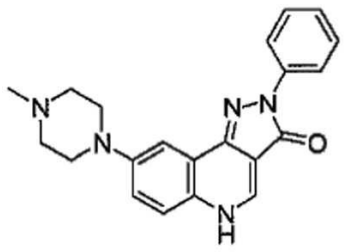
[0334] 1



[0335] **7a**

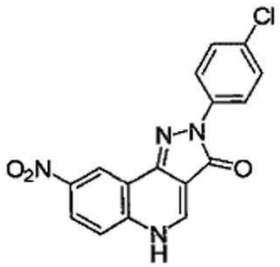
[0336] 5: 2- -8- -1- -2,5- - [4,3-c] -3- (**7a**): **6a** ( ) , 175 60 . , , 75% . $^1$H-NMR (DMSO-d6) δ (ppm); 3.25 (4H, br), 3.52 (4H, br), 7.12 (1H, t, J = 7.47 Hz), 7.39 (3H, m), 7.45 (1H, m), 7.68 (1H, m), 8.22 (2H, dd, J = 8.55, 0.98 Hz), 8.60 (1H, d, J = 5.86 Hz), 9.12 (1H, br). m/z 346.4 ($MH^+$).

[0337] 2



[0338] **7b**

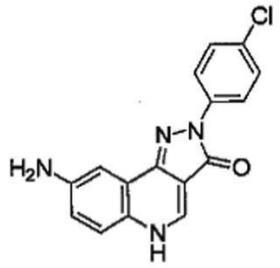
[0339] 8-(4- -1- )-2- -2,5- - [4,3-c] -3- (**7b**): , 1- **7a** . $^1$H-NMR (DMSO-d6) δ (ppm): 3.25 (4H, br), 3.41 (3H, s), 3.52 (4H, br), 7.12 (1H, t, J = 7.47 Hz), 7.39 (3H, m), 7.45 (1H, m), 7.68 (1H, m), 8.22 (2H, dd, J = 8.55, 0.98 Hz), 8.60 (1H, d, J = 5.86 Hz), 9.12 (1H, br). m/z 346.4 ($MH^+$). m/z 360.4 ($MH^+$).



**5b**

[0340]

[0341] 2-(4'- )-8- -2,5- - -[4,3-c] -3- (**5b**): , **5a** 4- . $^1$H-NMR (DMSO-d6) 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, d, J = 8.91, 2.38 Hz), 8.88 (1H, s), 8.91 (1H, d, J = 2.67 Hz). m/z 341.8 ($MH^+$).

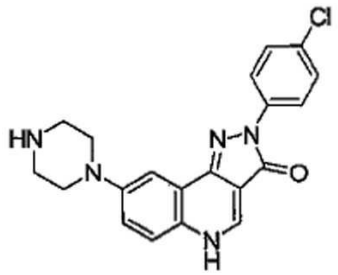


**6b**

[0342]

[0343] 8- -2-(4- )-2,5- - -[4,3-c] -3- (**6b**): , **5b** **6a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0344] 3

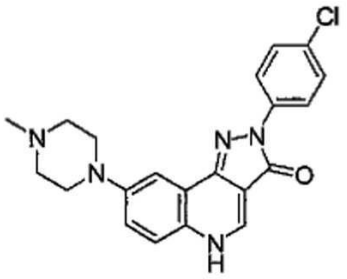


**7c**

[0345]

[0346] 2-(4'- )-8- -1- -2,5- - [4,3-c] -3- (**7c**): , **7a** **6b** . $^1$H-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 ($MH^+$).

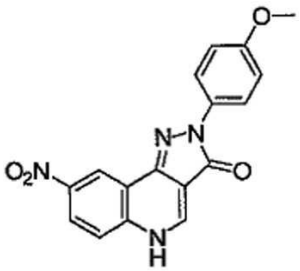
[0347] 4



7d

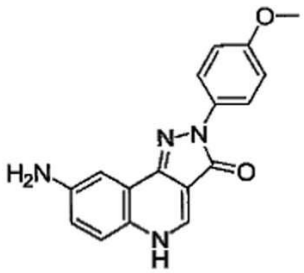
[0348]

[0349] 2-(4'- )-8-(4- -1- )-2,5- - [4,3-c] -3- (**7d**): **7a** **6b** 1- - . $^1$H-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 ($MH^+$).



[0350]

[0351] 2-(4'- )-8- -2,5- - -[4,3-c] -3- (**5c**): , **5a** 4- . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

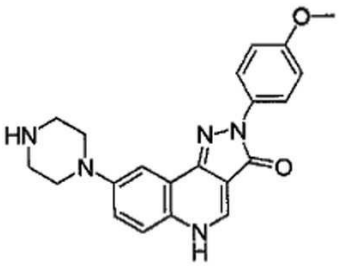


6c

[0352]

[0353] 8- -2-(4'- )-2,5- - -[4,3-c] -3- (**6c**): , **6a** **5c** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0354] 5

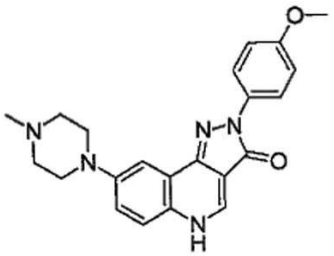


7e

[0355]

[0356] 2-(4'- )-8- -1- -2,5- - [4,3-c] -3- (**7e**): , **7a** **6c** . $^1$H-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 ($MH^+$).

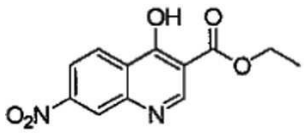
[0357] 6



7f

[0358]

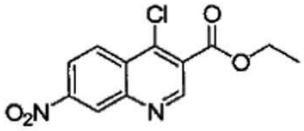
[0359] 2-(4'- )-8-(4- -1- )-2,5- - [4,3-c] -3- (**7f**): , **7a** **6c** 1- . $^1$H-NMR (DMSO-d6) δ (ppm): 3.25 (4H, br), 3.45 (3H, s), 3.50 (4H, br), 3.75 (3H, s), 7.00 (1H, d, J = 9.06 Hz), 7.40 (1H, m), 7.48 (1H, br), 7.68 (1H, d, J = 9.06 Hz), 7.92 (1H, d, J = 8.79 Hz), 8.05 (2H, d, J = 8.79 Hz), 8.56 (1H, br), 9.12 (1H, br). m/z 390.4 ($MH^+$).



10a

[0360]

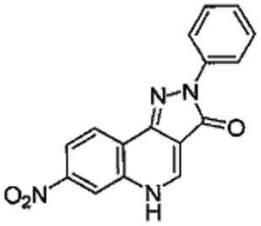
[0361] 4- -7- - -3- (**10a**): , **1** 4- 3- . $^1$H-NMR (DMSO-d6) δ (ppm): 1.24 (3H, t, J = 7.14 Hz), 4.18 (2H, q, J = 7.14 Hz), 8.10 (1H, dd, J = 9.06, 2.19 Hz), 8.32 (1H, d, J = 8.79 Hz), 8.48 (1H, d, J = 2.19 Hz), 8.71 (1H, d, J = 5.76 Hz). m/z 263.3 ($MH^+$).



**11a**

[0362]

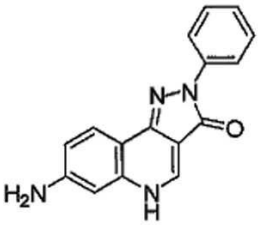
[0363] 4- -7- - -3- (**11a**): , **2** **10a** .. $^{1}$H-NMR ($CDCl_3$) δ (ppm): 1.46 (3H, t, J = 7.14 Hz), 4.54 (2H, q, J = 7.14 Hz), 8.47 (1H, dd, J = 9.34, 2.20 Hz), 8.60 (1H, d, J = 9.07 Hz), 9.02 (1H, d, J = 2.19 Hz), 9.32 (1H, s). m/z 281.7 ($MH^+$).



**12a**

[0364]

[0365] 7- -2- -2,5- - -[4,3-c] -3- (**12a**): , **3** **11a** . $^{1}$H-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 307.3 ($MH^+$).

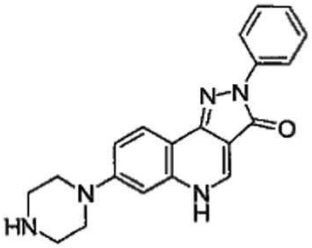


**13a**

[0366]

[0367] 7- -2- -2,5- - -[4,3-c] -3- (**13a**): , **4** **12a** . $^{1}$H-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 ($MH^+$).

[0368] 7

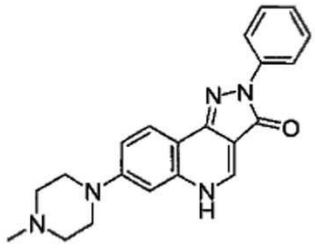


14a

[0369]

[0370] 2- -7- -1- -2,5- - [4,3-c] -3- (**14**a): , **5** **13a** . $^1$H-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 ($MH^+$).

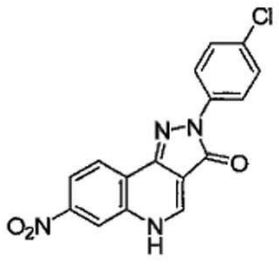
[0371] 8



14b

[0372]

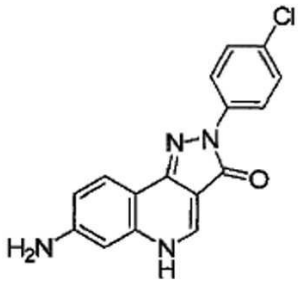
[0373] 7-(4- -1- )-2- -2,5- - [4,3-c] -3- (**14b**): , **5** **13a** 1- . $^1$H-NMR ($CD_3OD$) δ (ppm): 2.44 (3H, s), 2.74 (4H, brm), 3.44 (4H, brm), 7.03 (1H, d, J = 2.20 Hz), 7.27 (1H, ddd, J = 7.41, 1.64, 1.10 Hz), 7.35 (1H, dd, J = 9.07, 2.47 Hz), 7.65 (2H, m), 7.99 (2H, m), 8.17 (1H, d, J = 9.07 Hz), 8.53 (1H, s). m/z 360.4 ($MH^+$).



12b

[0374]

[0375] 2-(4'- )-7- -2,5- - -4,3-c] -3- (**12b**): , **12a** **11a** 4- . $^1$H-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 ($MH^+$).

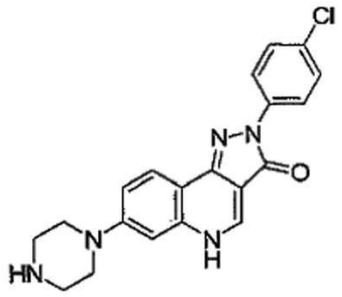


**13b**

[0376]

[0377] 7- -2-(4'- )-2,5- - -[4,5-c] -3- (**13b**): , **4** **12b** . $^1$H-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 311.8 ($MH^+$).

[0378] 9

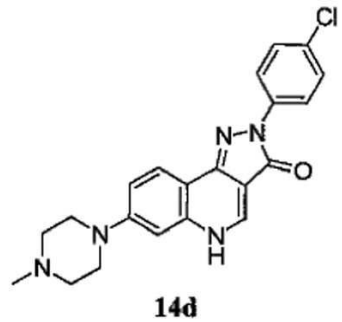


**14c**

[0379]

[0380] 2-(4'- )-7- -1- -2,5- - [4,3-c] -3- (**14c**): , **14a** **13b** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0381] 10

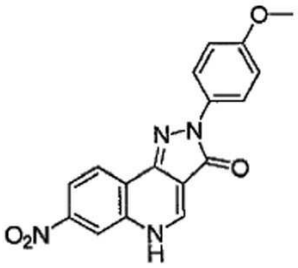


**14d**

[0382]

[0383] 2-(4- )-7-(4- -1- )-2,5- - [4,3-c] -3- (**14d**): , **14a** **13b** 1- . $^1$H-NMR ($CD_3OD$) δ (ppm):

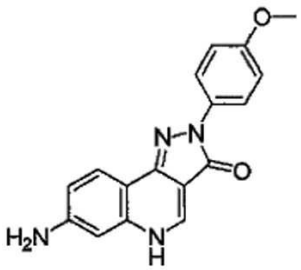
2.39 (3H, s), 2.67 (4H, brm), 3.40 (4H, brm), 7.01 (1H, d, J = 2.47 Hz), 7.34 (1H, dd, J = 9.07, 2.47 Hz), 7.46 (2H, dd, J = 6.87, 2.20 Hz), 8.09 (2H, dd, J = 7.14, 1.92 Hz), 8.19 (1H, d, J = 9.07 Hz), 8.51 (1H, s). m/z 394.9 ($MH^+$).



**12c**

[0384]

[0385] 2-(4'- )-7- -2,5- - -(4,3-c) -3- (**12c**): , **12a** **11a** 4- . $^1$H-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 ($MH^+$).

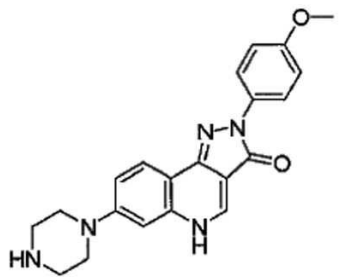


**13c**

[0386]

[0387] 7- -2-(4'- )-2,5- - -[4,3-c] -3- (**13c**): , **13a** **12c** . $^1$H-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 ($MH^+$).

[0388] 11



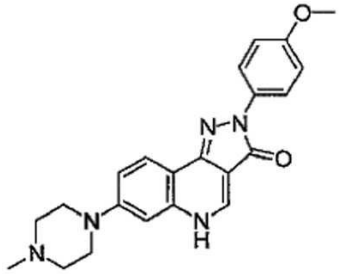
**14e**

[0389]

[0390] 2-(4- )-7- -1- -2,5- - [4,3-c] -3- (**14e**): , **14a** **13c** . $^1$H-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 ($MH^+$).

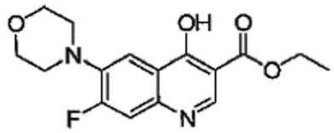
[0391] 12



**14f**

[0392]

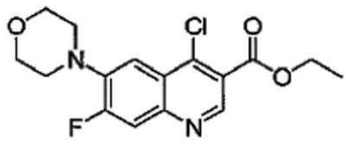
[0393] 2-(4- )-7-(4- -1- )-2,5- - [4,3-c] -3- (**14f**): , **14a** **13c** 1- . $^1$H-NMR ($CD_3OD$) δ (ppm): 2.32 (3H, s), 2.67 (4H, brm), 3.40 (4H, brm), 3.85 (3H, s), 6.88 (2H, m), 7.02 (1H, d, J = 2.47 Hz), 7.31 (1H, dd, J = 9.06, 2.20 Hz), 7.66 (2H, m), 8.16 (1H, d, J = 9.06 Hz), 8.52 (1H, s). m/z 390.4 ($MH^+$).



**17a**

[0394]

[0395] 7- -4- -6- - -3- (**17a**): , **1** 4- 3- -4- . $^1$H-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 ($MH^+$).

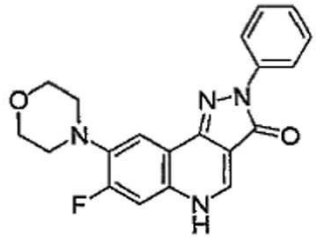


**18a**

[0396]

[0397] 4- -7- -6- - -3- (**18a**): , **2** **3a** **17a** . $^1$H-NMR ($CDCl_3$) 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 ($MH^+$).

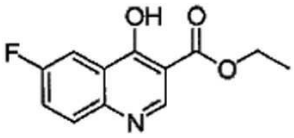
[0398] 13



19a

[0399]

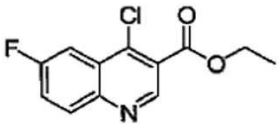
[0400] 1- -8- -4- -2- -2,5- - [4,3-c] -3- (**19a**): **3** **5a** **18a** . $^1$H-NMR (DMSO-d6) δ (ppm): 3.15 (4H, m), 3.80 (4H, m), 7.16 (1H, tt, J = 7.32, 1.22 Hz), 7.40 (3H, m), 7.64 (1H, d, J = 9.03 Hz), 8.20 (2H, dd, J = 8.79, 1.22 Hz), 8.75 (1H, br), 12.65 (1H, br). m/z 364.4 ($MH^+$).



21a

[0401]

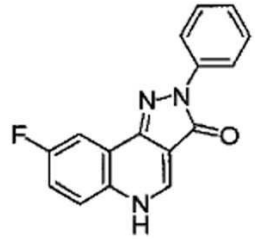
[0402] 4- -6- - -3- (**21a**): , **1** 4- 4- . $^1$H-NMR (DMSO-d6) δ (ppm): 1.15 (3H, t, J = 7.080 Hz), 4.1 (2H, q, J = 7.08 Hz), 7.61 (1H, dd, J = 8.30, 2.93 Hz), 7.68 (1H, dd, J = 9.03, 4.63 Hz), 7.80 (1H, dd, J = 9.27, 2.93 Hz), 8.56 (1H, s). m/z 237.3 ($MH^+$).



22a

[0403]

[0404] 4- -6- - -3- (**22a**): , **2** **3** **21a** . $^1$H-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 ($MH^+$).

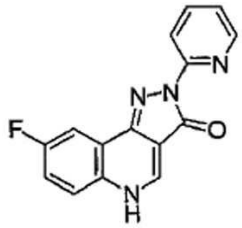


23a

[0405]

[0406] 8- -2- -2,5- - -[4,3-c] -3- (**23a**): **3**

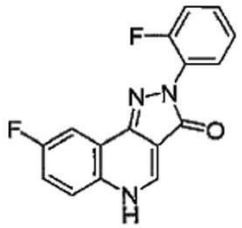
**4a** **22a** . $^1$H-NMR (DMSO-d6) δ (ppm): 7.16 (1H, t, J = 13.67 Hz), 7.41 (2H, t, J = 7.56 Hz), 7.55 (1H, dt, J = 8.54, 2.93 Hz), 7.77 (1H, dd, J = 9.27, 4.88 Hz), 7.90 (1H, dd, J = 9.27, 2.93 Hz), 8.18 (2H, dd, J = 7.58, 1.95 Hz), 8.73 (1H, s). m/z 280.2 ($MH^+$).



**23b**

[0407]

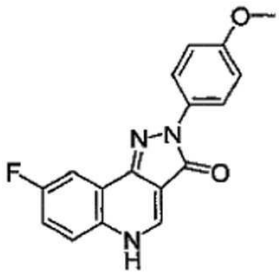
[0408] 8- -2-(2'- )-2,5- - -[4,3-c] -3- (**23b**): , **23a** -2- . $^1$H-NMR (DMSO-d6) δ (ppm): 7.24 (1H, ddd, J = 7.42, 4.95, 1.10 Hz), 7.57 (1H, dt, J = 9.06, 3.02 Hz), 7.76 (1H, dd, J = 9.34, 4.95 Hz), 7.88 (2H, m), 8.18 (1H, brd, J = 8.24 Hz), 8.49 (1H, ddd, J = 4.95, 2.75, 1.10 Hz), 8.76 (1H, s). m/z 281.3 ($MH^+$).



**23c**

[0409]

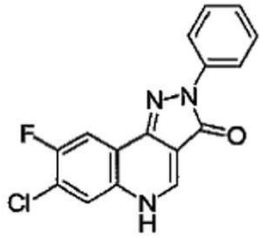
[0410] 8- -2-(2'- )-2,5- - -[4,3-c] -3- (**23c**): , **23a** 2- . $^1$H-NMR (DMSO-d6) δ (ppm): 7.37 (3H, m), 7.52 (2H, m), 7.81 (2H, m), 8.74 (1H, s). m/z 298.3 ($MH^+$).



**23d**

[0411]

[0412] 8- -2-(4'- )-2,5- - -[4,3-c] -3- (**23d**): , **23a** 4- . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

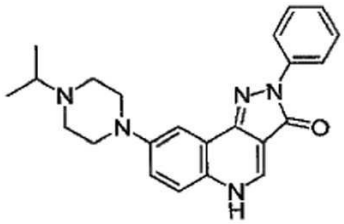


**23e**

[0413]

[0414] 7- -8- -2- -2,5- - -[4,3-c] -3- (**23e**): , **23a** -4,7- -6- - -3- . $^1$H-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 ($MH^+$).

[0415] 14

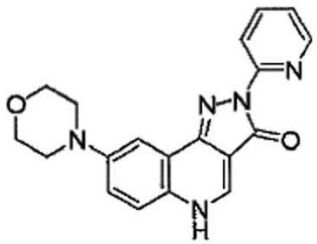


**19b**

[0416]

[0417] 8-(4- -1- )-2- -2,5- - [4,3-c] -3- (**19b**): **23a** 175 72 N- . , , 84% . $^1$H-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 ($MH^+$).

[0418] 15

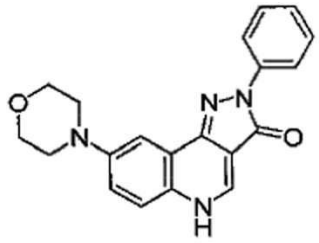


**19c**

[0419]

[0420] 8- -4- -2- -2- -2,5- - [4,3-c] -3- (**19c**): , **19b** **23b** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0421] 16

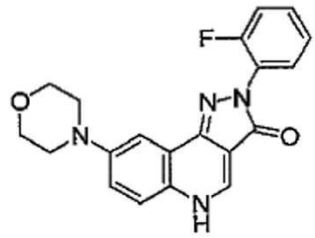


**19d**

[0422]

[0423] 8- -4- -2- -2,5- - [4,3-c] -3- (**19d**): , **19b** **23a** . $^1$H-NMR (DMSO-d6) 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, d, J = 8.24, 1.65 Hz), 8.57 (1H, s). m/z 347.4 ($MH^+$).

[0424] 17

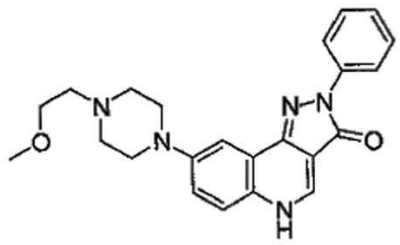


**19e**

[0425]

[0426] 2-(2- )-8- -4- -2,5- - [4,3-c] -3- (**19e**): , **19b** **23c** . $^1$H-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 ($MH^+$).

[0427] 18

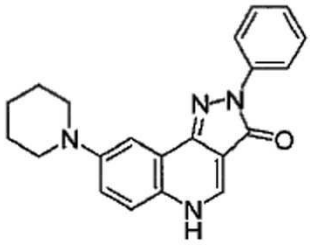


**19f**

[0428]

[0429] 8-[4-(2- )- -1- ]-2- -2,5- - [4,3-c] -3- (**19f**): , **19b** 1- . $^1$H-NMR (DMSO-d6) 6 (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 ($MH^+$).

[0430] 19

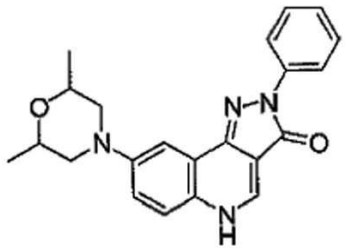


19g

[0431]

[0432] 2- -8- -1- -2,5- - [4,3-c] -3- (**19g**): , **19b** **23a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0433] 20

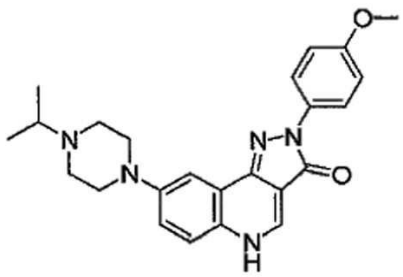


19h

[0434]

[0435] 8-(2,6- -4- )-2- -2,5- - [4,3-c] -3- (**19h**): , **19b** 2,6- . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0436] 21



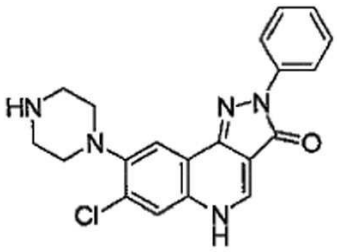
19i

[0437]

[0438] 8-(4- -1- )-2-(4- )-2,5- - [4,3-c] -3- (**19i**): , **19b** **23d** . $^1$H-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 ($MH^+$).

[0439] 22

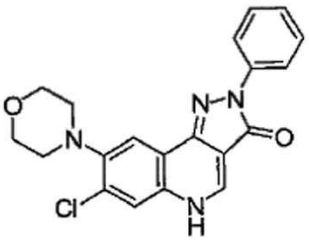


**19j**

[0440]

[0441] 7- -2- -8- -1- -2,5- - [4,3-c] -3- (**19j**): , **19b** **23e** . $^1$H-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 ($MH^+$).

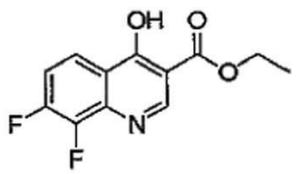
[0442] 23



**19k**

[0443]

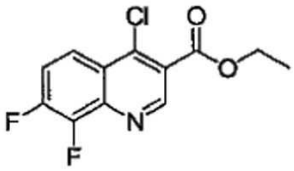
[0444] 7- -8- -4- -2- -2,5- - [4,3-c] -3- (**19k**): **19b** **23e** . $^1$H-NMR (DMSO-d6) δ (ppm): 3.08 (4H, br), 3.78 (4H, br), 7.18 (1H, tt, J = 7,32, 1.32 Hz), 7.43 (2H, t, J = 7.56 Hz), 7.78 (2H, d, J = 2.44 Hz), 8.21 (2H, dd, J = 8.54, 1.22 Hz), 8.71 (1H, s). m/z 381.8 ($MH^+$).



**25a**

[0445]

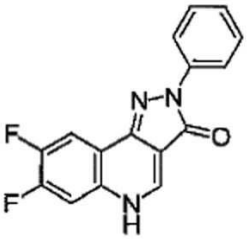
[0446] 7,8- -4- - -3- (**25a**): , 1 4- 3,4- . $^1$H-NMR (DMSO-d6) δ (ppm): 1.15 (3H, t, J = 7.08 Hz), 4.1 (2H, $q_3$ J = 7.08 Hz), 7.61 (1H, dd, J = 8.30, 2.93 Hz), 7.68 (1H, d, J = 4.63, 9.03 Hz), 7.80 (1H, dd, J = 9.27, 2.93 Hz), 8.56 (1H, s). m/z 254.2 ($MH^+$).



**26a**

[0447]

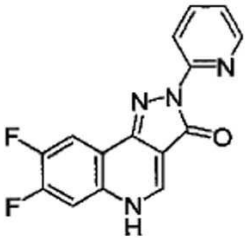
[0448] 4- -7,8- - -3- (**26a**): , **2** **3** **25a** . $^{1}$H-NMR ($CDCl_3$) δ (ppm): 1.47 (3H, t, J = 7.08 Hz), 4.56 (2H, q, J = 7.08 Hz), 7.72 (1H, d, J = 8.79 Hz), 8.39 (1H, d, J = 8.78 Hz), 9.23 (1H, s). m/z 272.7 ($MH^+$).



**27a**

[0449]

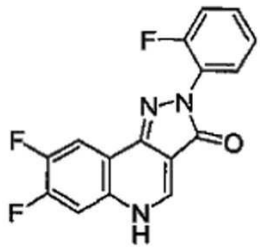
[0450] 7,8- -2- -2,5- - -[4,3-c] -3- (**27a**): , **4a** **26a** . $^{1}$H-NMR (DMSO-d6) δ (ppm): 7.18 (1H, t, J = 7.82 Hz), 7.43 (2H, dd, J = 8.30, 7.33 Hz), 7.75 (1H, dd, J = 11.22, 7.32 Hz), 8.18, 3H, m), 8.90 (1H, s). m/z 298.3 ($MH^+$).



**27b**

[0451]

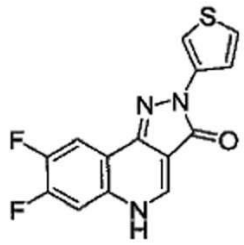
[0452] 7,8- -2-(2'- )-2,5- - -[4,3-c] -3- (**27b**): , **23b** **26** . $^{1}$H-NMR (DMSO-d6) δ (ppm): 7.31 (1H, t, J = 7.86 Hz), 7.73 (1H, dd, J = 11.26, 7.14 Hz), 8.01 (1H, dt, J = 8.79, 1.65 Hz), 8.16 (1H, t, J = 8.24 Hz), 8.24 (1H, d, J = 8.24 Hz), 8.50 (1H, d, J = 3.85 Hz), 8.82 (1H, s). m/z 299.3 ($MH^+$).



27c

[0453]

[0454] 7,8- -2-(2'- )-2,5- - -[4,3-c] -3- (**27c**): , **23b** **26** 2- -HCl . $^1$H-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 ($MH^+$).

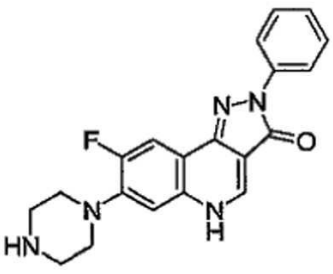


27d

[0455]

[0456] 7,8- -2-( -3- )-2,5- - -[4,3-c] -3- (**27d**): 1.05 3- -2- 3c . 1.5 , , , , , . , 30 1N , , . , , , . 1N , 1 , , . , 190 1 . , 1N , , . , **41** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0457] 24

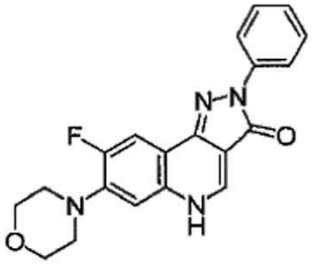


28a

[0458]

[0459] 8- -2- -7- -1- -2,5- - [4,3-c] -3- (**28a**): , **19b** **27a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0460] 25

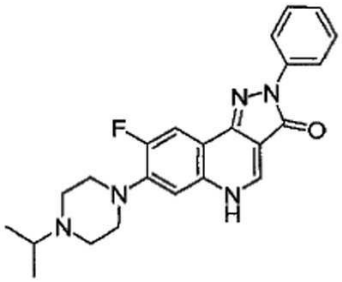


**28b**

[0461]

[0462] 8- -7- -4- -2- -2,5- - [4,3-c] -3- (**28b**): , **28a** **27a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0463] 26

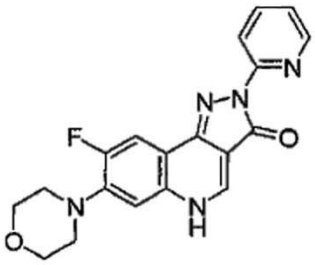


**28c**

[0464]

[0465] 8- -7-(4- -1- )-2- -2,5- - [4,3-c] -3- (**28c**): , **28a** **27a** 1- . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0466] 27



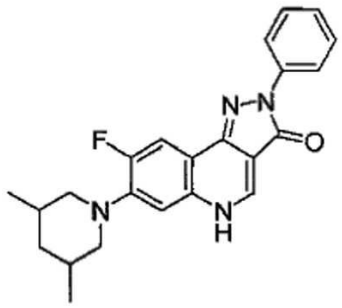
**28d**

[0467]

[0468] 8- -7-( -4- )-2- -2- -2,5- - [4,3-c] -3- (**28d**):

**28a** **27b** . $^{1}$H-NMR (DMSO-d6) 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 ($MH^+$).

[0469] 28



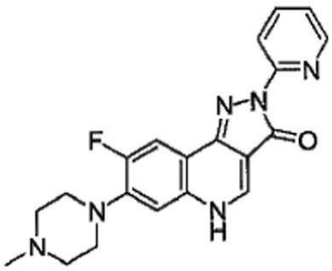
**28e**

[0470]

[0471] 7-(3,5- -1- )-8- -2- -2,5- - [4,3-c] -3- (**28e**):

, **28a** **27a** 3,5- . $^{1}$H-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 ($MH^+$).

[0472] 29



**28f**

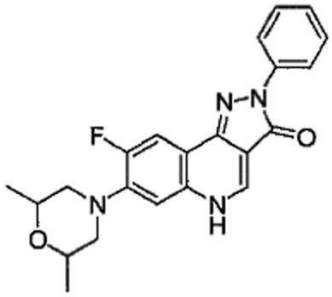
[0473]

[0474] 8- -7-(4- -1- )-2- -2- -2,5- - [4,3-c] -3- (**28f**):

**28a** **27b** 1- . $^{1}$H-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 ($MH^+$).

[0475] 30



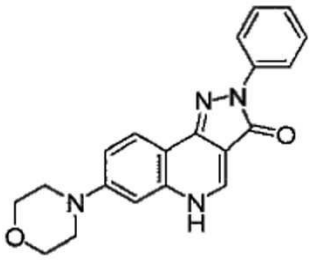
**28g**

[0476]

[0477] 7-(2,6- -4- )-8- -2- -2,5- - [4,3-c] -3- (**28g**):

, **28a** **27a** 2,6- , $^1$H-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 ($MH^+$).

[0478] 31



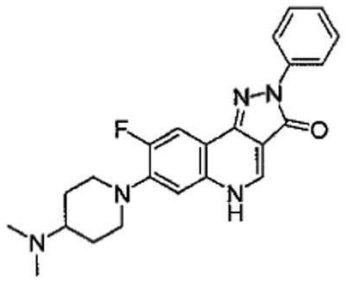
**28h**

[0479]

[0480] 7- -4- -2- -2,5- - [4,3-c] -3- (**28h**): **3**

**4a** -4- -7- -3- . $^1$H-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 ($MH^+$).

[0481] 32



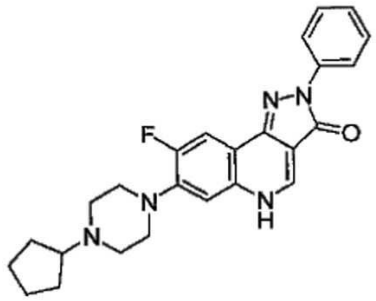
**28i**

[0482]

[0483] 7-(4- -1- )-8- -2- -2,5- - [4,3-c] -3- (**28i**):

, **28a** **27a** 4- . $^1$H-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 ($MH^+$).

[0484] 33



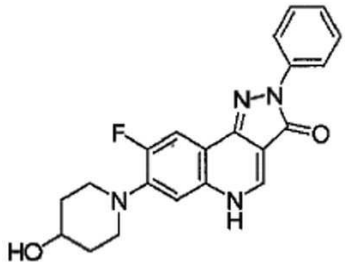
**28j**

[0485]

[0486] 7-(4- -1- )-8- -2- -2,5- - [4,3-c] -3- (**28j**):

, **28a** **27a** 1- . $^1$H-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 ($MH^+$).

[0487] 34



**28k**

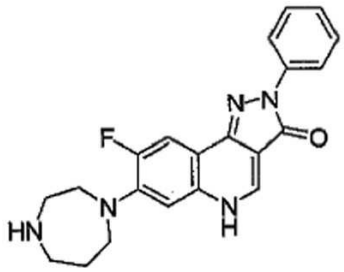
[0488]

[0489] 8- -7-(4- -1- )-2- -2,5- - [4,3-c] -3- (**28k**):

, **28a** **27a** 4- . $^1$H-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 ($MH^+$).

[0490] 35

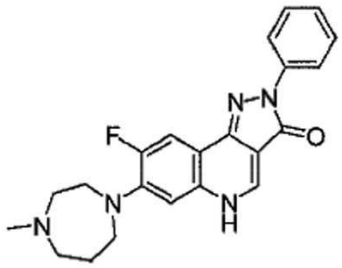


**28l**

[0491]

[0492] 8- -7-( [1,4]- -1- )-2- -2,5- - [4,3-c] -3- (**28l**): , **28a** **27a** . $^1$H-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 ($MH^+$).

[0493] 36

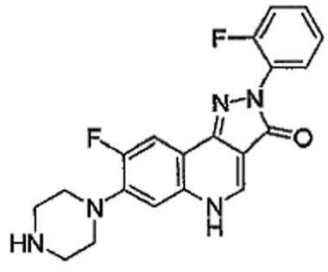


**28m**

[0494]

[0495] 8- -7-(4- [1,4]- -1- )-2- -2,5- - [4,3-c] -3- (**28m**): , **28a** **27a** 1- [1,4]- . $^1$H-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 ($MH^+$).

[0496] 37



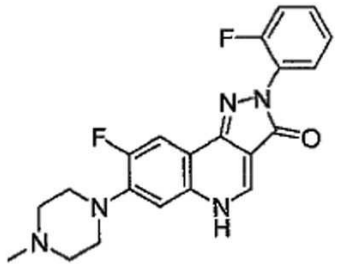
**28n**

[0497]

[0498] 8- -2-(2- )-7-( -1- )-2,5- - [4,3-c] -3- (**28n**):

, **28a** **27c** . $^1$H-NMR ($CD_3OD$) 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

[0499] 38



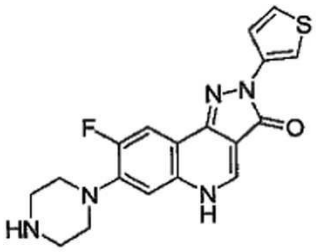
**28o**

[0500]

[0501] 8- -2-(2- )-7-(4- -1- )-2,5- - [4,3-c] -3- (**28o**):

, **28a** **27c** 1- . $^1$H-NMR ($CD_3OD$) 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

[0502] 39



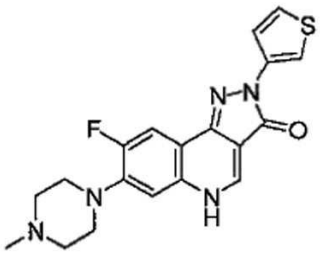
**28p**

[0503]

[0504] 8- -7-( -1- )-2-( -3- )-2,5- - [4,3-c] -3- (**28p**):

, **28a** **27d** . $^1$H-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

[0505] 40



**28q**

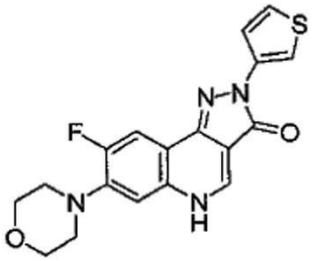
[0506]

[0507] 8- -7-(4- -1- )-2-( -3- )-2,5- - [4,3-c] -3- (**28q**):

, **28a** **27d** 1- . $^1$H-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

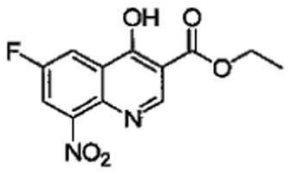
[0508] 41



**28r**

[0509]

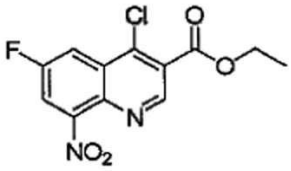
[0510] 8- -7-( -4- )-2-( -3- )-2,5- - [4,3-c] -3- (**28r**): , **28a** **27d** . $^1$H-NMR (DMSO-d6) δ (ppm): 3.11 (4H, brm), 3.79 (4H, brm), 7.21 (1H, m), 7.58 (1H, m), 7.79 (3H, m), 8.67 (1H, m). m/z 371.2



**35**

[0511]

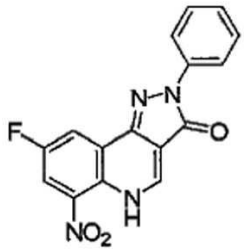
[0512] 6- -4- -8- - -3- (**35**): , 1 4- 4- -2- . $^1$H-NMR (DMSO-d6) δ (ppm): 1.26 (3H, t, J = 7.14 Hz), 4.20 (2H, q, J = 7.15 Hz), 8.31 (1H, dd, J = 8.24, 3.02 Hz), 8.57 (1H, brs), 8.64 (1H, d, J = 8.24, 3.02 Hz). m/z 281.3 ($MH^+$).



**36**

[0513]

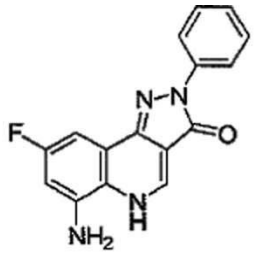
[0514] 4- -6- -8- - -3- (36): , **2** **35** . $^1$H-NMR ($CDCl_3$) δ (ppm): 1.46 (3H, t, J = 7.14 Hz), 4.55 (2H, q, J = 7.14 Hz), 7.94 (1H, dd, J = 7.14, 2.75 Hz), 8.29 (1H, dd, J = 8.79, 2.74 Hz), 9.27 (1H, s). m/z 299.7 ($MH^+$).



**37**

[0515]

[0516] 8- -6- -2- -2,5- -[4,3-c] -3- (**37**): **3** **36** . m/z 325.3 ($MH^+$).

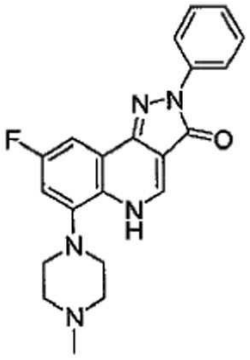


**38**

[0517]

[0518] 6- -8- -2- -2,5- -[4,3-c] -3- (**38**): , **4** **37** . m/z 295.3 ($MH^+$).

[0519] 42

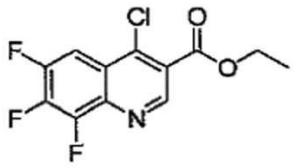


**39**

[0520]

[0521] 8- -6-(4- -1- )-2- -2,5- - [4,3-c] -3- (**39**): , **5** **38** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

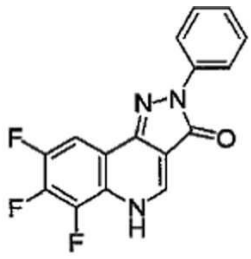
[0522] 43



42

[0523]

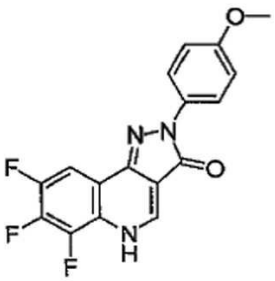
[0524] 4- -6,7,8- - -3- (**42**): , 2 **3** 4- -6,7,8- - -3- . $^1$H-NMR ($CDCl_3$) δ (ppm): 1.44 (3H, t, J = 7.14 Hz), 4.55 (2H, q, J = 7.14 Hz), 8.04 (1H, m), 9.22 (1H, s). m/z 290.7 ($MH^+$).



**43a**

[0525]

[0526] 6,7,8- -2- -2,5- - -[4,3-c] -3- (**43a**): , **4a** **42** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

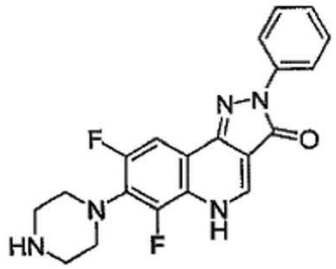


**43b**

[0527]

[0528] 6,7,8- -2-(4- )-2,5- - -[4,3-c] -3- (**43b**): , **4a** **42** 4- . m/z 346.2 ($MH^+$).

[0529] 44

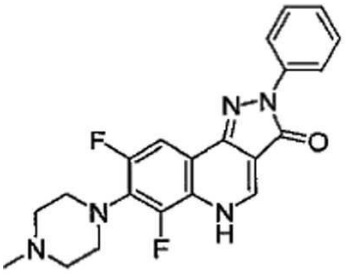


**44a**

[0530]

[0531] 6,8- -2- -7- -1- -2,5- - [4,3-c] -3- (**44a**): , **19b** **43a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0532] 45

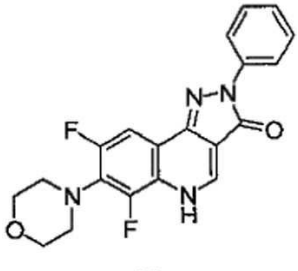


**44b**

[0533]

[0534] 6,8- -7-(4- - -1- )-2- -2,5- - [4,3-c] -3- (**44b**): , **19b** **43a** 1- . $^1$H-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 ($MH^+$).

[0535] 46

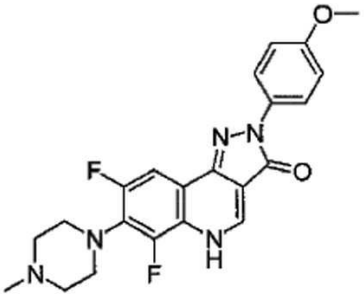


**44c**

[0536]

[0537] 6,8- -7-( -4- )-2- -2,5- - [4,3-c] -3- (**44c**): , **19b** **43a** . $^1$H-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 ($MH^+$).

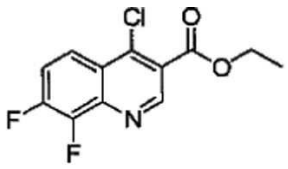
[0538] 47



44d

[0539]

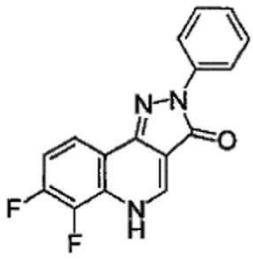
[0540] 6,8- -2-(4- )-7-(4- -1- )-2,5- - [4,3-c] -3- (**44d**): , **19b** **43b** 1- . $^1$H-NMR (DMSO-d6) δ (ppm): 2.28 (3H, s), 2.75 (2H, brm), 2.82 (2H, brm), 3.09 (4H, brm), 3.75 (3H, s), 6.99 (2H, d, J = 9.0 Hz), 7.45 (1H, m), 8.06 (2H, d, J = 9.0 Hz), 8.33 (1H, s). m/z 426.2 ($MH^+$).



46

[0541]

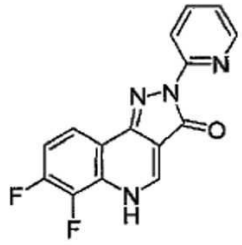
[0542] 4- -7,8- - -3- (**46**): , **2** **3** -7,8- -4- - -3- . $^1$H-NMR ($CDCl_3$) δ (ppm): 1.46 (3H, t, J = 7.14 Hz), 4.52 (2H, q, J = 7.14 Hz), 7.60 (1H, m), 8.24 (1H, m), 9.25 (1H, s). m/z 272.7 ($MH^+$).



47a

[0543]

[0544] 6,7- -2- -2,5- - -[4,3-c] -3- (**47a**): , **4a** **46** . $^1$H-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 ($MH^+$).

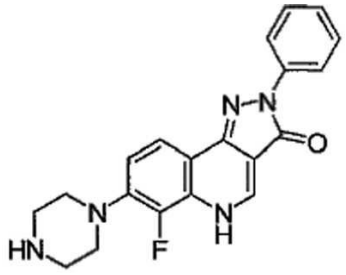


47b

[0545]

[0546] 6,7- -2-(2- )-2,5- - -[4,3-c] -3- (**47b**): , **4a** **46** -2- . $^1$H-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 ($MH^+$).

[0547] 48

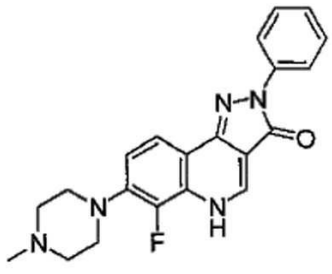


48a

[0548]

[0549] 6- -2- -7- -1- -2,5- - [4,3-c] -3- (**48a**): , **19b** **47a** . $^1$H-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 ($MH^+$).

[0550] 49

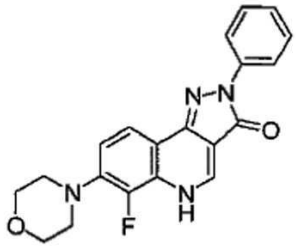


48b

[0551]

[0552] 6- -7-(4- - -1- )-2- -2,5- - [4,3-c] -3- (**48b**): , **19b** **47a** 1- . $^1$H-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 ($MH^+$).

[0553] 50

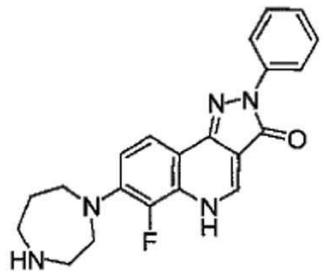


48c

[0554]

[0555] 6- -7-( -4- )-2- -2,5- - [4,3-c] -3- (**48c**): , **19b** **47a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0556] 51

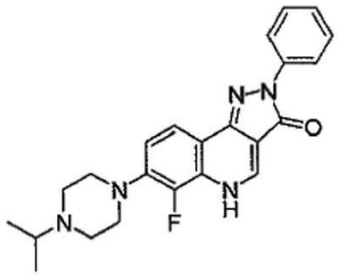


48d

[0557]

[0558] 6- -7-( [1,4]- -1- )-2- -2,5- - [4,3-c] -3- (**48d**): , **19b** **47a** [1,4]- . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

[0559] 52



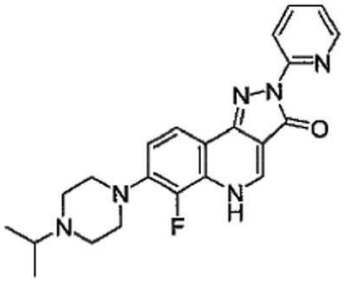
48e

[0560]

[0561] 6- -7-(4- - -1- )-2- -2,5- - [4,3-c] -3- (**48e**): , 19b **47a** 1- - . $^1$H-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 ($MH^+$).

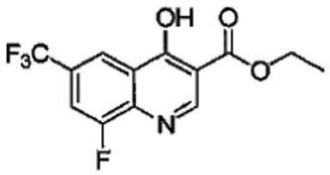
[0562] 53



48f

[0563]

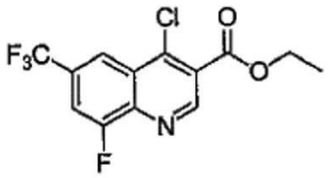
[0564] 6- -7-(4- - -1- )-2-(2'- )-2,5- - [4,3-c] -3- (**48f**): , **19b** **47b** . $^1$H-NMR (DMSO-d6) δ (ppm): 3.18 (4H, brm), 3.80 (4H, brm), 7.19 (1H, dd, J= 7.2, 4.9 Hz), 7.25 (1H, t, J = 8.5 Hz), 7.84 (1H, dd, J = 8.5, 2.0 Hz), 7.88 (1H, dd, J = 8.6, 2.07 Hz), 8.18 (1H, d, J = 8.4 Hz), 8.43 (1H, s), 8.47 (1H,m). m/z 365.3 ($MH^+$).



49

[0565]

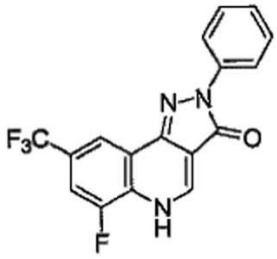
[0566] 8- -4- -6- - -3- (**49**): , **1** 4- 2- -4- - . $^1$H-NMR (DMSO-d6) δ (ppm): 1.25 (3H, t, J = 7.14 Hz), 4.11 (2H, q, J = 7.14 Hz), 8.00 (2H, m), 8.70 (1H, s). m/z 304.2 ($MH^+$).



50

[0567]

[0568] 4- -8- -6- - -3- (**50**): , **2** **3** **49** . $^1$H-NMR ($CDCl_3$) 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 ($MH^+$).

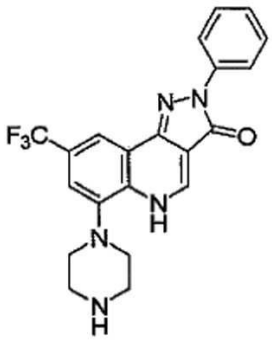


**51**

[0569]

[0570] 6- -2- -8- -2,5- - -[4,3-c] -3- (**51**): , **4a** **50** . $^1$H-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 ($MH^+$).

[0571] 54

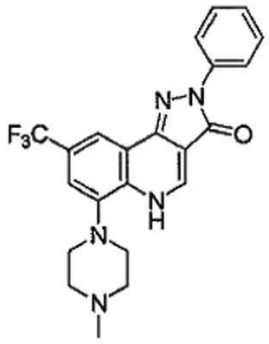


**52a**

[0572]

[0573] 2- -6- -1- -8- -2,5- - [4,3-c] -3- (**52a**): , **19b** **51** . $^1$H-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 ($MH^+$).

[0574] 55



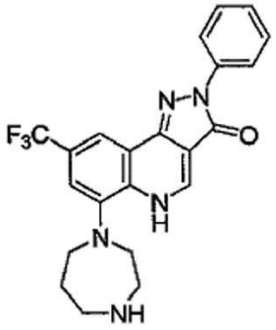
**52b**

[0575]

[0576] 2- -6-(4- -1- )-8- -2,5- - [4,3-c] -3- (**52**b): , **19b** **51** 4- . $^1$H-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 ($MH^+$).

[0577] 56

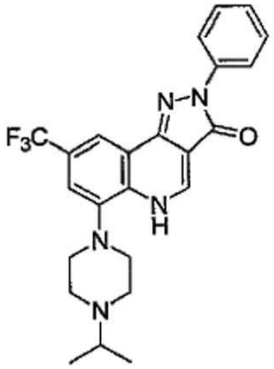


52c

[0578]

[0579] 2- -6-( [1,4]- -1- )-8- -2,5- - [4,3-c] -3- (**52c**): , **19b** **51** [1,4]- . $^1$H-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 ($MH^+$).

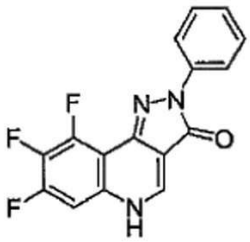
[0580] 57



52d

[0581]

[0582] 2- -6-(4- - -1- )-8- -2,5- - [4,3-c] -3- (**52d**): , **19b** **51** 1- - . $^1$H-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 ($MH^+$).

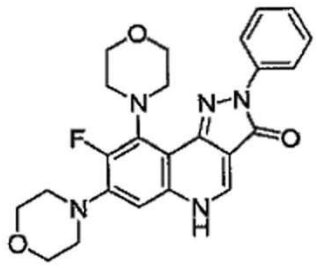


54

[0583]

[0584] 7,8,9- -2- -2,5- - -[4,3-c] -3- (**54**): , 3,4,5- 4 **4a** . $^1$H-NMR (DMSO-d6) 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 ($MH^+$).

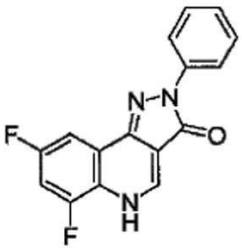
[0585] 58



55

[0586]

[0587] 7,9- ( -4- )-8- -2- -2,5- - [4,3-c] -3- (**55**): , **19b** **53** . $^1$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 ($MH^+$).

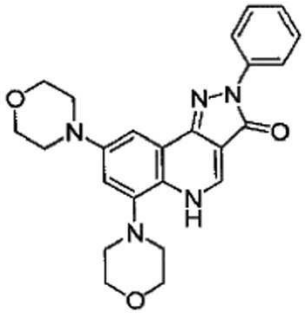


57

[0588]

[0589] 6,8- -2- -2,5- - -[4,3-c] -3- (**57**): , 2,4- 4 **4a** . $^1$H-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 ($MH^+$).

[0590] 59

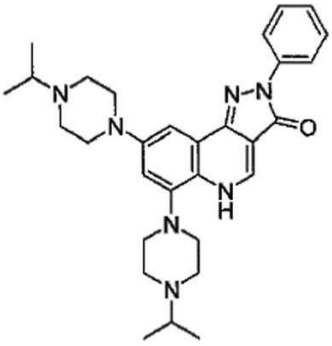


58a

[0591]

[0592] 6,8- ( -4- )-2- -2,5- - [4,3-c] -3- (**58a**): , **19b** **53** . $^1$H-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 ($MH^+$).

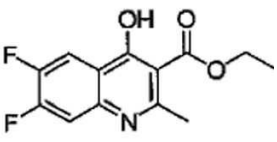
[0593] 60



58b

[0594]

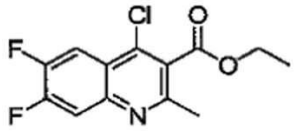
[0595] 6,8- (4- - -1- )-2- -2,5- - [4,3-c] -3- (**58b**): , **19b** **53** 1- - . $^1$H-NMR (DMSO-d6) δ (ppm): 0.99 (6H, d, J = 6.8 Hz), 1.01 (6H, d, J = 7.4 Hz), 2.72 (4H, brm), 2.83 (6H, br,m), 2.92 (4H, brm), 3.22 (4H, brm), 7.19 (3H, m), 7.41 (2H, m), 8.24 (3H, m). m/z 514.4 ($MH^+$).



60

[0596]

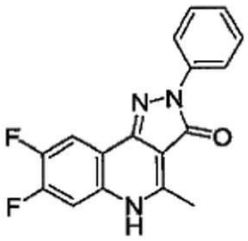
[0597] 6,7- -4- -2- - -3- (**60**): N,N- - , N,N- (1.1 ) (1.1 ) . 10 120 . , 6,7-4- -2- - -3- (2g) , , . $^1$H NMR (DMSO-d6) δ (ppm): 1.21 (3H, t, J = 7.14 Hz), 2.30 (3H, s), 4.10 (2H, q, J = 7.14 Hz), 7.43 (1H, dd, J = 10.71, 7.69 Hz), 7.82 (1H, dd, J = 10.69, 8.24 Hz. m/z 268.7 ($MH^+$).



61

[0598]

[0599] 4- -6,7- -2- - -3- (61): 4- **60** 30 ( ) . , , , . $^1$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 ($MH^+$).

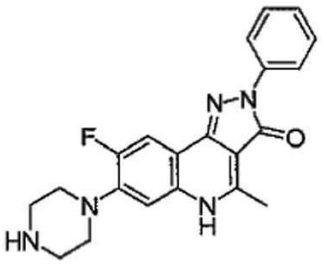


62

[0600]

[0601] 7,8- -4- -2- -2,5- - [4,3-c] -3- (62): , **4a** **61** . $^1$H NMR (DMSO-d6) 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 ($MH^+$).

[0602] 61

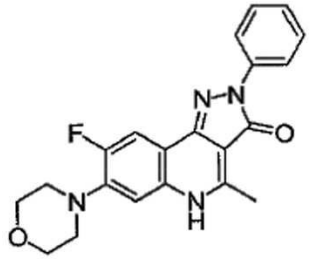


63a

[0603]

[0604] 8- -4- -2- -7- -1- -2,5- - [4,3-c] -3- (**63a**): , **19b** **62** . $^1$H-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 ($MH^+$).

[0605] 62



63b

[0606]

[0607] 8- -4- -7- -4- -2- -2,5- - [4,3-c] -3- (**63b**): , **19b** 62 . $^{1}$H-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 ($MH^+$).

[0608]

[0609] $GABA_A$ . $IC_{50}$ 3- (sub) nM 10 μM .

[0610]

[0611] 175 ± 25g (whole brain)( ) pH 7.4 Na-K $GABA_A$ . 5 mg 1 nM ($^{3}$H)- (flunitrazepam) 25 60 . 30 μM GABA . 10 μM (diazepam) . , ($^{3}$H)- . 2 (Damm, H. W., *et al* (1978) *Res. Comm. Chem. Pathol. Pharmacol.* 22: 597-560, ; Speth, R.C., *et al.* (1979) *Life Sci.* 24: 351-357, ).

[0612]

[0613] ,

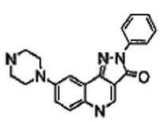
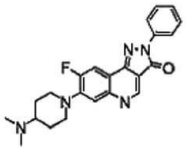
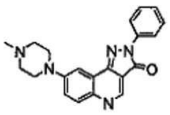
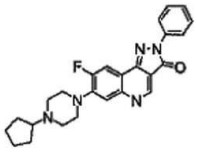
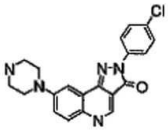
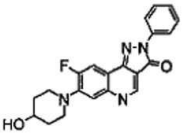
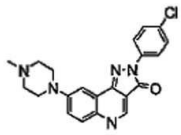
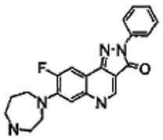
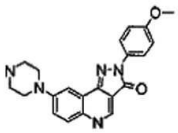
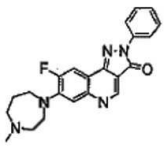
[0614] A 1 mM $IC_{50}$ ,

[0615] B 1 mM $IC_{50}$ ,

[0616] C 1 nM $IC_{50}$ .

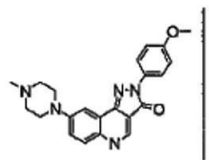
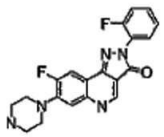
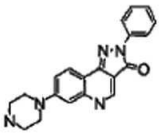
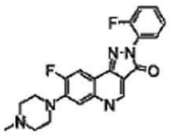
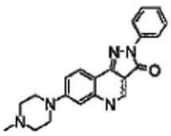
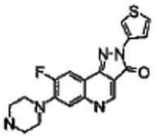
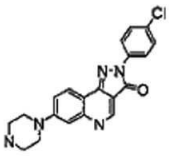
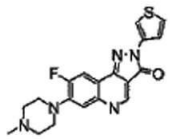
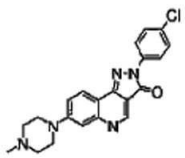
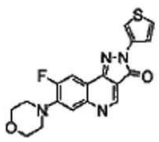
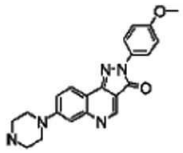
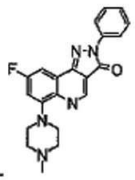
[0617] 1 . . 1 , . 1 . , . .

[0618] [ 1]

| No. | 구조 | BZ 결합 분석 ($IC_{50}$) | EP 결과 | No. | 구조 | BZ 결합 분석 ($IC_{50}$) | EP 결과 |
|---|---|---|---|---|---|---|---|
| 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 | |

[0619]

[0620]

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

[0621]

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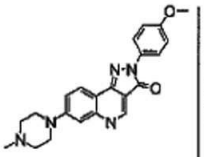
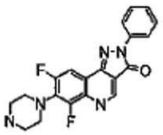
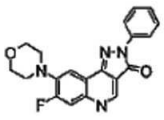
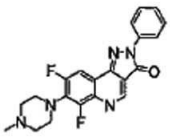
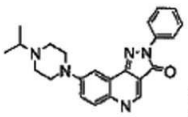
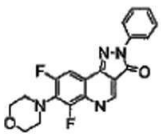
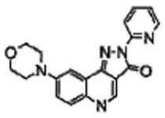
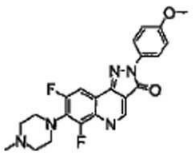
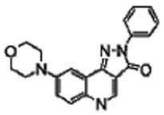
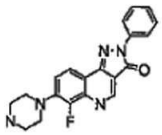
| | | | | | | | |
| 14f |  | A | Neg | 44a |  | B | Neg |
| 19a |  | C | Pos | 44b |  | B | Pos |
| 19b |  | B | Pos | 44c |  | B | Pos |
| 19c |  | B | Neg | 44d |  | B | Pos |
| 19d |  | B | Neg | 48a |  | A | |

[0622]

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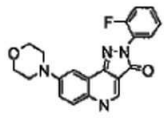
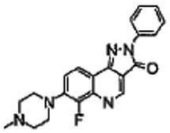
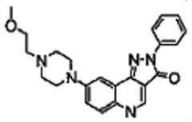
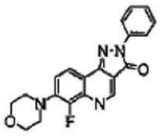
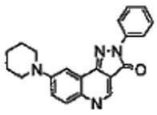
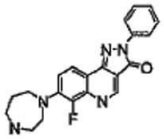
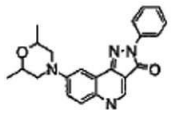
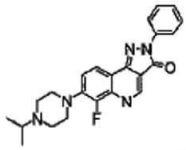
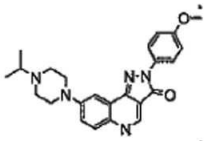
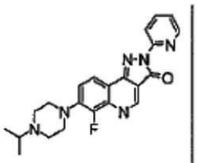
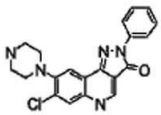
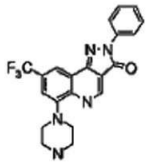
| 19e |  | B | Neg | 48b |  | A | |
| 19f |  | B | Pos | 48c |  | B | |
| 19g |  | B | Pos | 48d |  | B | |
| 19h |  | B | | 48e |  | B | |
| 19i |  | B | Pos | 48f |  | B | |
| 19j |  | B | Neg | 52a |  | B | |

[0623]

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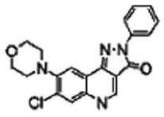
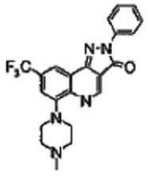
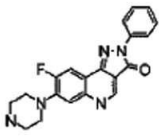
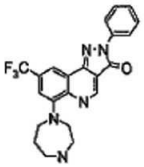
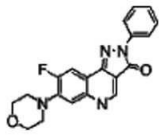
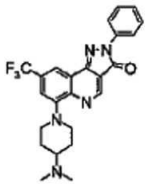
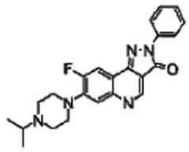
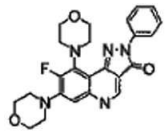
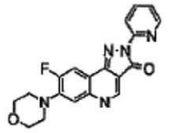
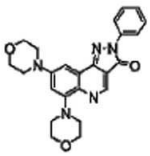
| 19k |  | B | Pos | 52b |  | B | |
| 28a |  | B | Pos | 52c |  | B | |
| 28b |  | B | Pos | 52d |  | B | |
| 28c |  | B | Pos | 55 |  | B | |
| 28d |  | B | Neg | 58a |  | B | Neg |

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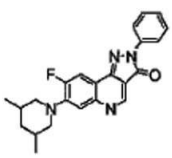
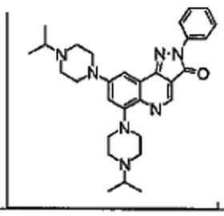
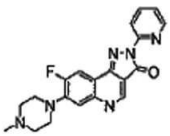
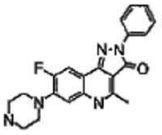
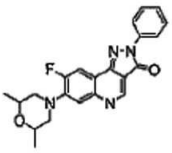
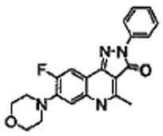
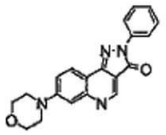
|---|---|---|---|---|---|---|---|
| 28e |  | B | Pos | 58b |  | B | Neg |
| 28f |  | B | Pos | 63a |  | A | |
| 28g |  | B | Pos | 63b |  | A | |
| 28h |  | B | Pos | | | | |

[0624]

[0625] $GABA_A$ .

[0626] _____

[0627] RNA

[0628] $GABA_A$ cDNA (insert)

mRNA . α2, α3 γ3 cDNA pBluescript, SK
. α1 α5 cDNA prC β2 cDNA
pcDNA1 . g 2s cDNA (construct) pGH19
. DH5α cDNA maxiprep
. cDNA cDNA
[XbaI(α1, β2), NotI(α3, γ2s), SacII(α2) ApaI(α5)] .
, cDNA K , / / ,
. - (1.5% ) cDNA .
-20 . T7 RNA *in vitro* . ,
mRNA -80 . Message Machine Kit(Ambion, Austin, TX) *in vitro*
, .

[0629] (Xenopus oocyte) $GABA_A$ :

[0630] $GABA_A$ : 0.15% (Tricaine) 45 ,
(follicular oocyte) .
(NaCl 96 mM, $MgCl_2$ 1 mM, KCl 2mM, Hepes 50 mM, 2.5 mM, 100

μg/mL, - 50 U/mL, pH 7.4) . 0.2% (type II, Sigma Chemical Co., St Louis, MO) 1.5-2 , Dumont 5 6 18-20 Barth (NaCl 84 mM, $NaHCO_3$ 2.4 mM, $MgSO_4$ 0.82 mM, KCl 1 mM, $Ca(NO_3)_2$ 0.33 mM, $CaCl_2$ 0.41 mM, Tris/HCl 7.5 mM, 2.5 mM, 50 μg/mL, - 100 units/mL, pH 7.4) 1-5 - (post-injection) . 0.3-0.5 ng RNA 1:1:2 50 nL RNA (Drummond, Broomall, PA) . 18-20 Barth 1-5 .

[0631] :

[0632] Warner - (Warner Instruments, Inc., Foster City, CA) , $GABA_A$ (Park-Chung, M.A., *et al.* (1999) *Brain Res.* 830: 72-87, ). (puller)(Sutter Instrument Co., CA) . 3M 1-3 MΩ . ND-96 . -70 mV (holding potential) . 10 Hz 100 Hz . - . 30 mL , 50 mL/sec . 20-25 , 150 . (custom-developed) . (22-24 ) . (Hill) .

[0633] $I_{GABA}=E_{max}/(1+(EC_{50}/c)nH)$

[0634] $E_{max}$ , $EC_{50}$ 50% , $n_H$ (Hill) , c . GABA - (fit) , GABA $EC_{20}$ , - . . GABA $EC_{20}$ 2-4 . :

[0635] % =(I'/I-1)×100

[0636] , I GABA $EC_{20}$ , I' (Lippa A, *et al.* (2005) *Proc. Natl. Acad. Sci USA* 102(20): 7380-7385, ).

[0637] 10 μM , .

[0638] _____

[0639] , ( / , ) . .

[0640]

[0641] (object recognition) , ( reinforcement)( ) . . , " " , . , . ,

. ,
(Bourtchouladze, R., e*t al.* (2003) *Proc. Natl Acad. Sci. USA* 100: 10518-10522, ).
(neuroimaging) (prefrontal cortex, PFC)
(Deibert, E., *et al.* (1999) *Neurology* 52: 1413-1417, ).
,
(Mitchell, J. B. Laiacona, J. (1998) *Behav. Brain Res.* 97: 107-113,
). (Teng, E.
*et al.* (2000) *J. Neuroscience* 20: 3853-3863, ; Mumby, D.G. (2001) *Behavioural Brain Research* 127: 159-181, ). ,
- .

[0642] ( (explicit) (implicit) ) .
" (memory acquisition curve)" , , , , ,
, ,
. NOR
, (i) (asymtotic)( )
( ) (ii)
. (
(" ") ).
(statistical power) .
:

[0643] , .
( , : L=48 cm; W=38 cm H=20 cm (Plexiglas) ;
: L=70 cm; W=60 cm H=35 cm ). ,
15 (Pittenger, C, *et al.* (2002) *Neuron* 34: 447-462, ; Bourtchouladze, R., *et al.* (2003) *Proc. Natl Acad. Sci. USA* 100: 10518-10522, ). 24 .
( ) ,
. , ( - )
. 15 . 24 10
' .
' , ( , ) .
, , 90% ,
.

[0644] . ,
(blind) : ;
; ; ( ). - (memory score)-
(Ennaceur, A. Aggleton, J.P. (1997) *Behav. Brain Res.* 88: 181-193,
; Bourtchouladze, R., *et. al.* (2003) *Proc. Natl. Acad. Sci. USA* 100: 10518-10522, ). (Statview 5.0.1; SAS Institute, Inc)
Student's unpaired *t* test . ±
(SEM) .

[0645] NOR , 1 ( ) ,
( (radial arm maze), (match) ) (attentional process; priming ) . 24 (memory consolidation)
STM . LTM (reference memory)
.

[0646] . ,

.