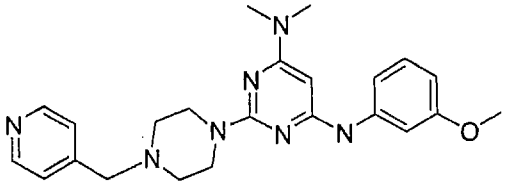
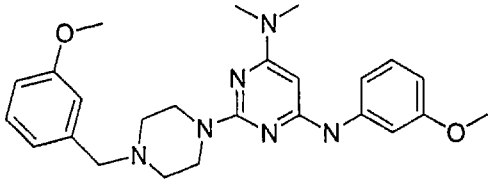
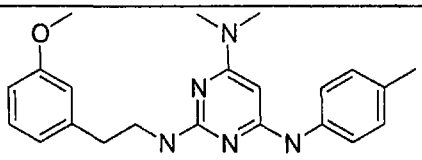
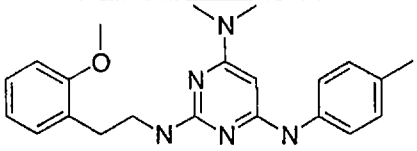
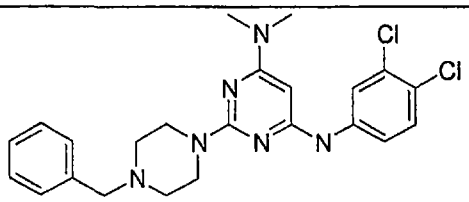
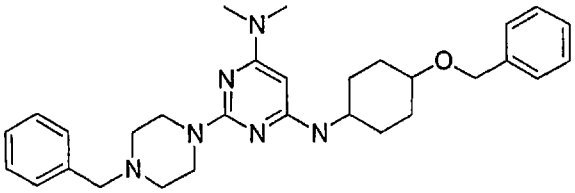
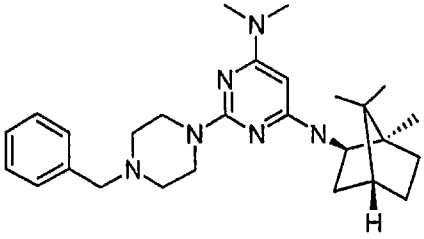
Table 3a.

147		640
148		276
149		138*
150		180
151		11
152		172
153		55

* The binding assay normally used for the indolone compounds was used to test this compound.

Table 3a.

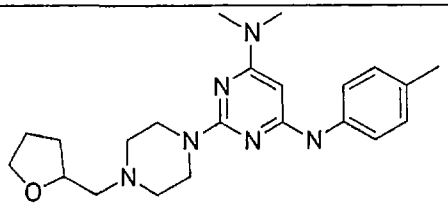
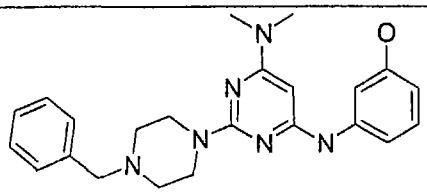
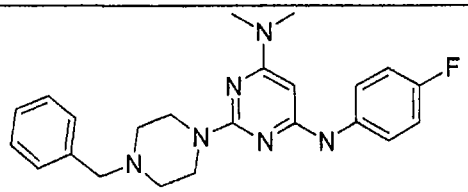
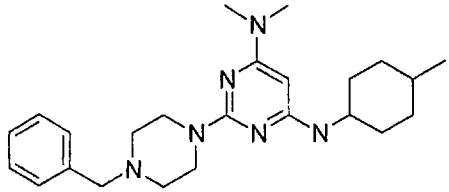
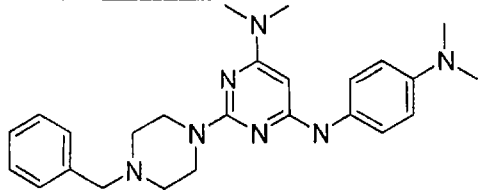
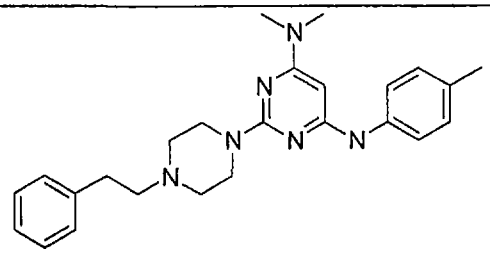
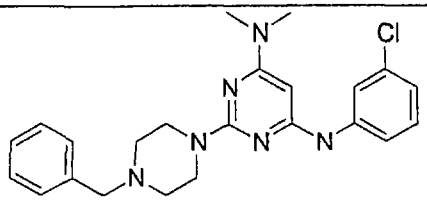
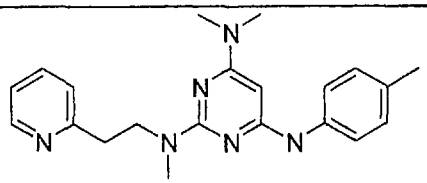
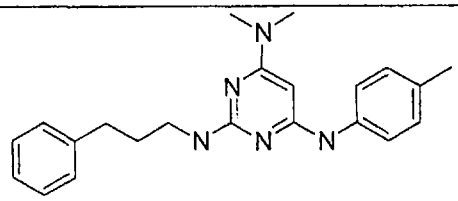
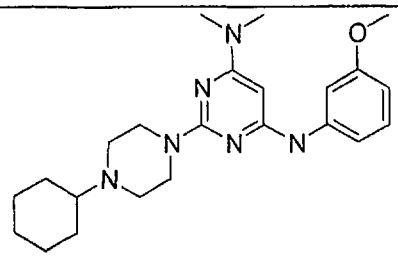
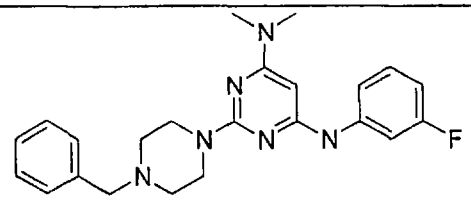
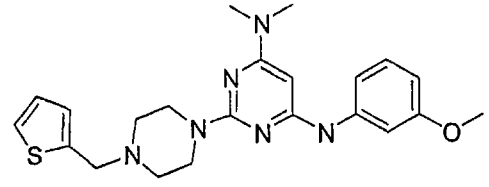
154		441
155		316
156		61
157		273
158		941
159		180

Table 3a.

160		26
161		114
162		42
163		500
164		60
165		139*

* The binding assay normally used for the indolone compounds was used to test this compound.

Table 3a.

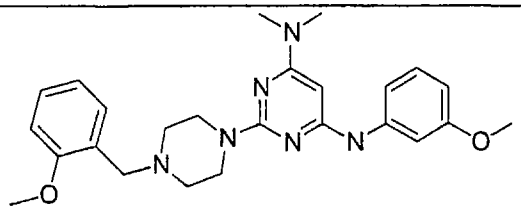
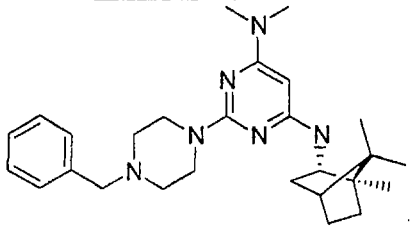
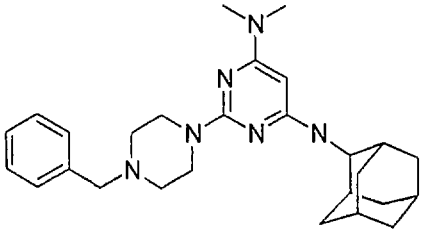
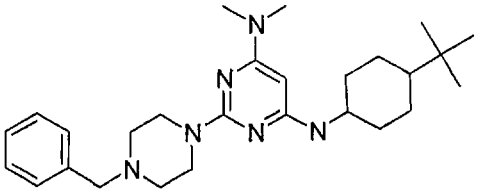
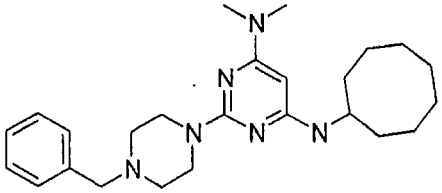
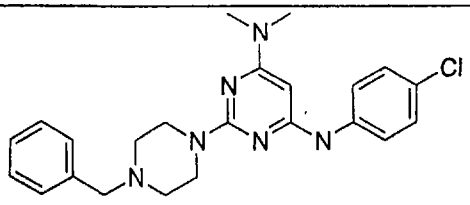
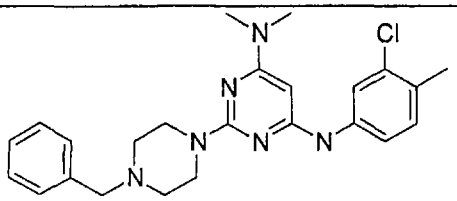
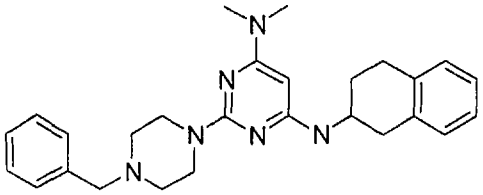
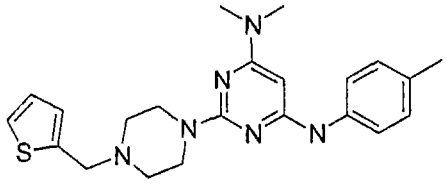
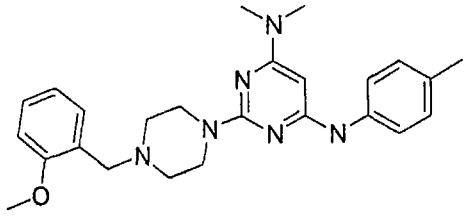
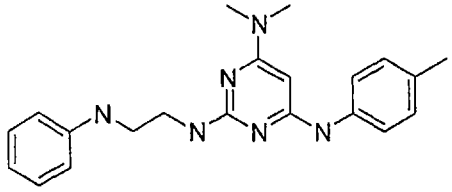
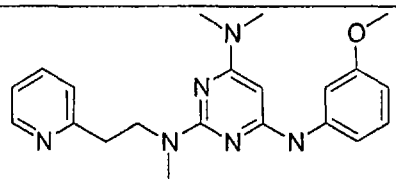
166		263
167		50
168		50
169		77
170		91
171		25

Table 3a.

172		20
173		117
174		325*
175		56
176		608
177		142

* The binding assay normally used for the indolone compounds was used to test this compound.

Table 3a.

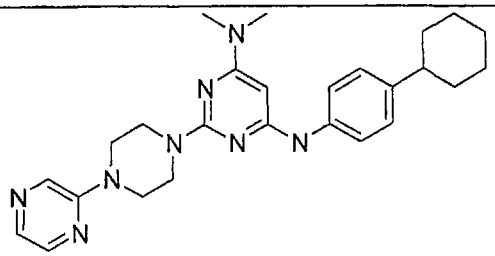
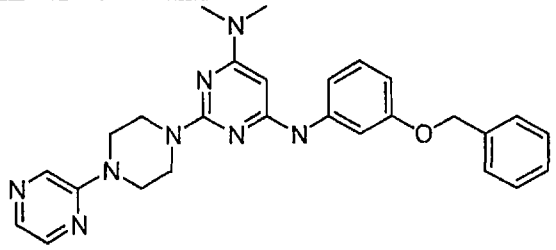
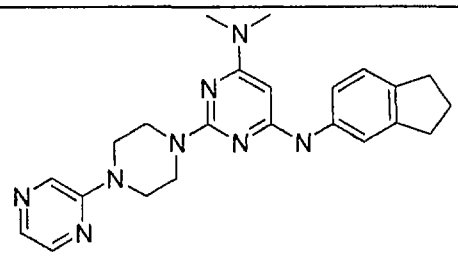
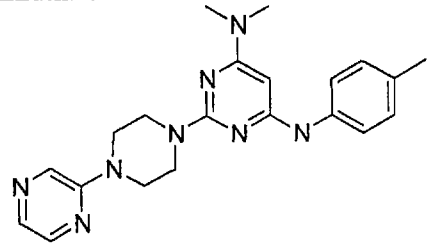
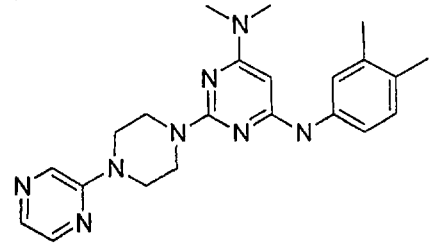
178		26
179		15
180		151
181		750
183		66

Table 3a.

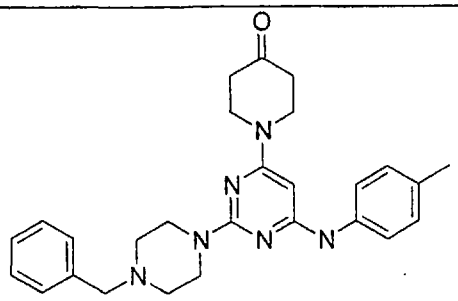
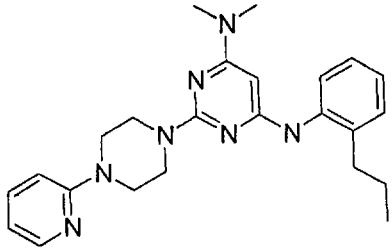
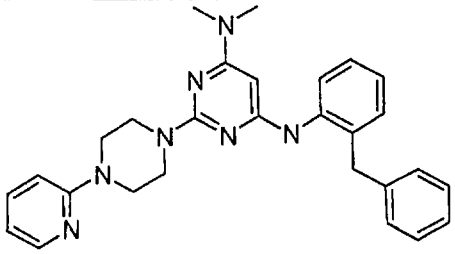
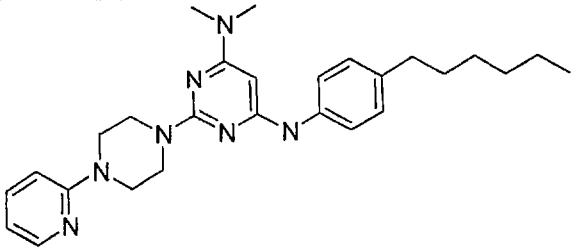
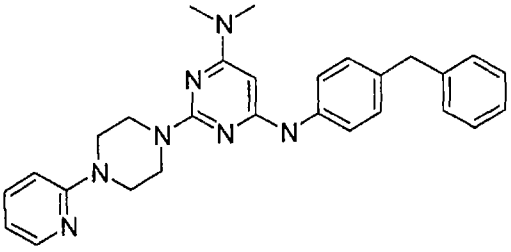
184		163
185		365
186		69
187		19
188		27

Table 3a.

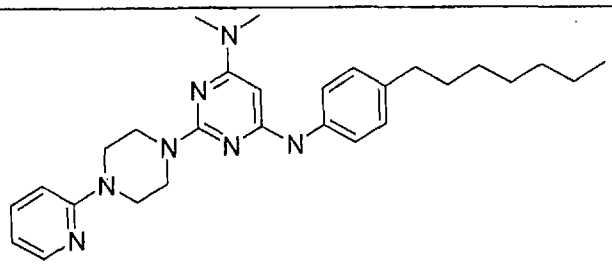
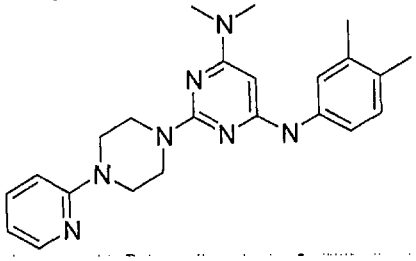
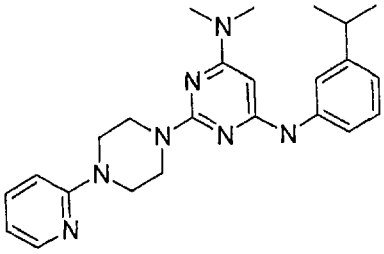
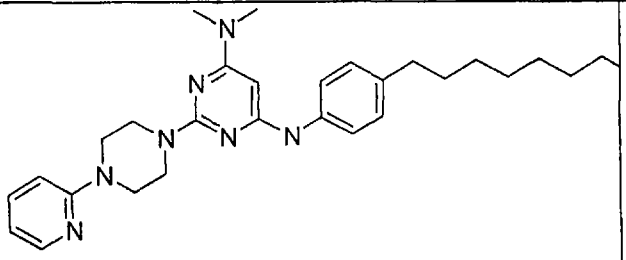
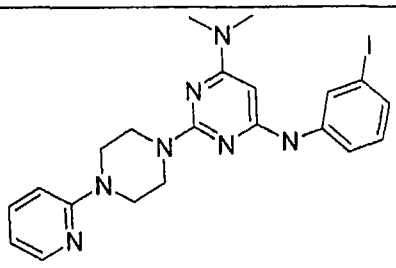
189		26
190		153
191		75
192		18
193		244

Table 3a.

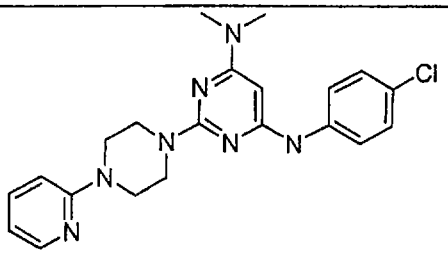
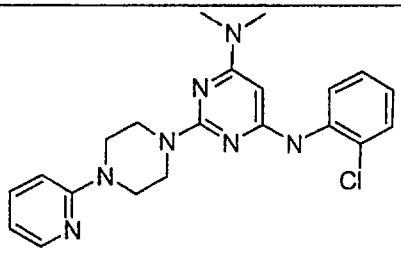
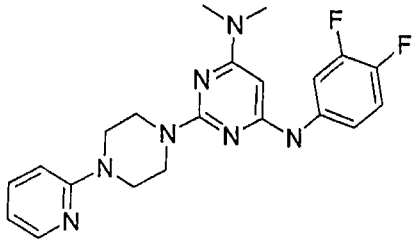
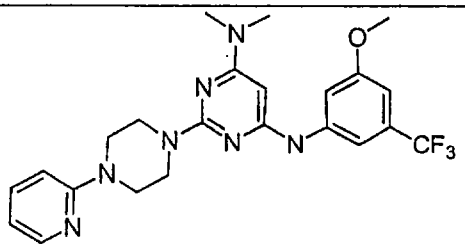
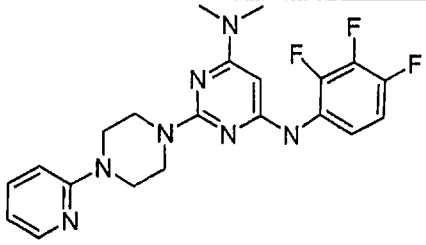
194		248
195		388
196		443
197		666
198		560

Table 3a.

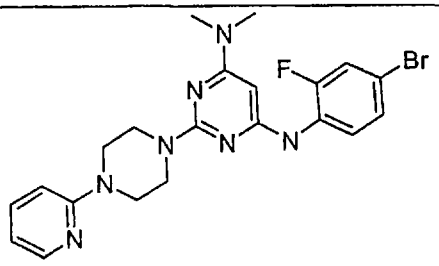
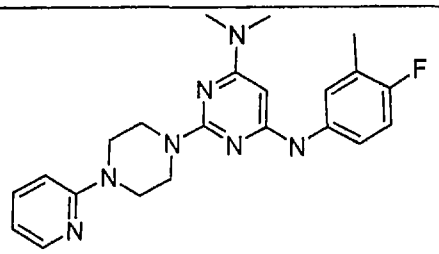
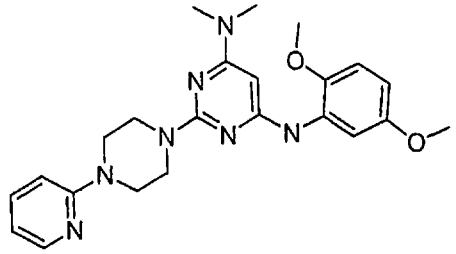
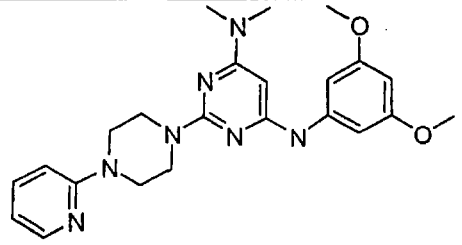
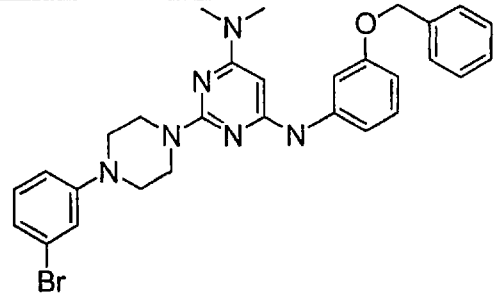
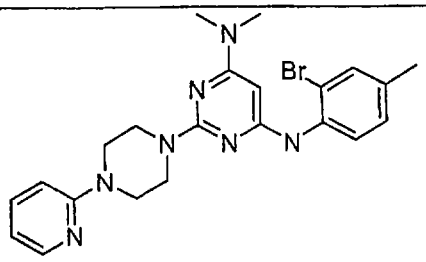
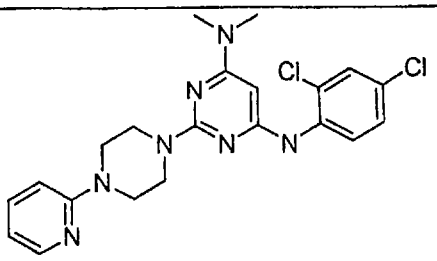
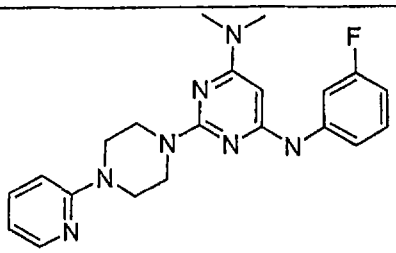
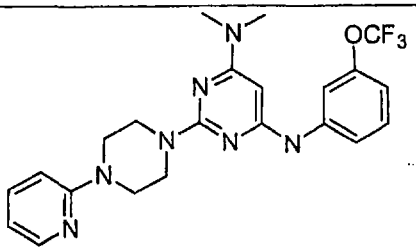
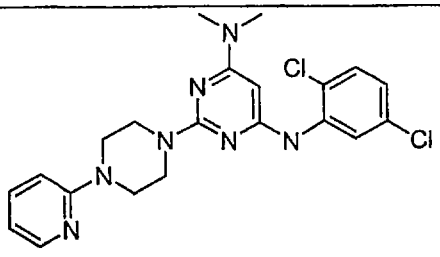
199		199
200		311
201		566
202		740
203		52

Table 3a.

204		269
205		193
206		454
207		58
208		120

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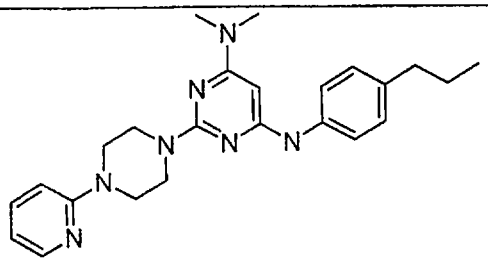
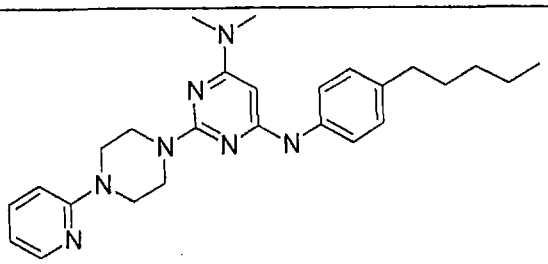
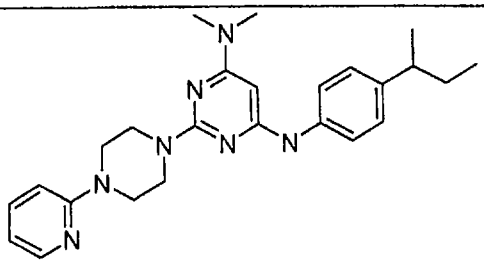
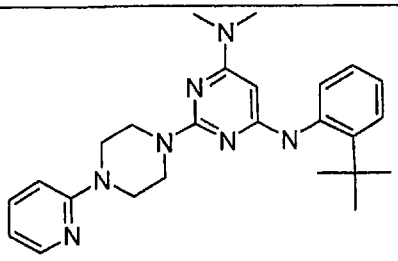
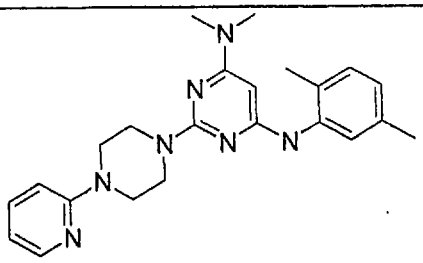
209		205
210		58
211		58
212		231
213		165

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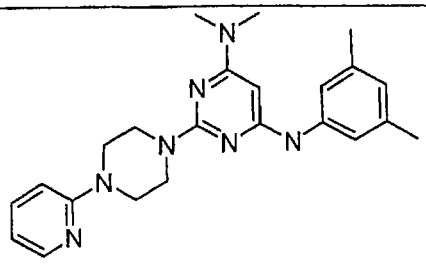
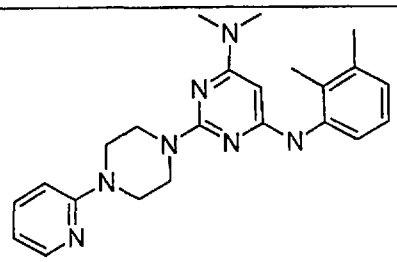
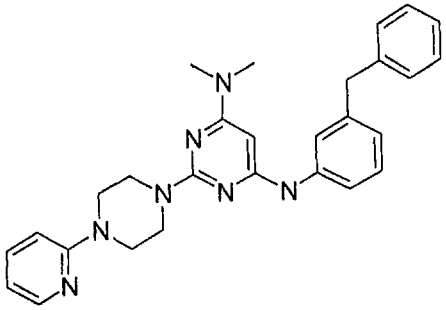
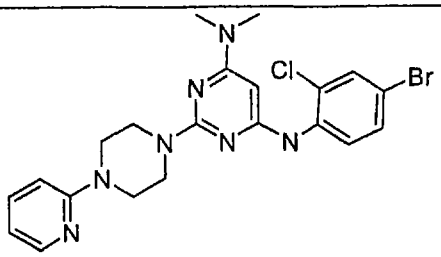
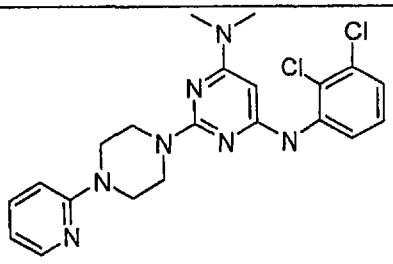
214		676
215		450
216		50
217		190
218		616

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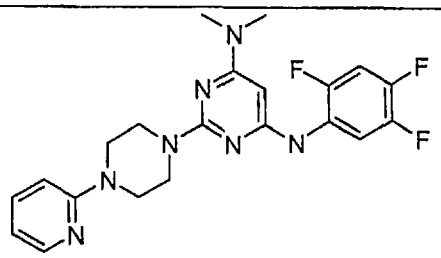
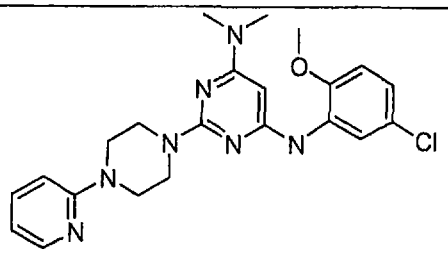
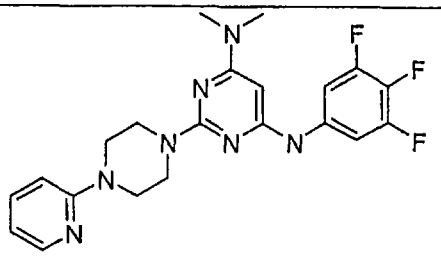
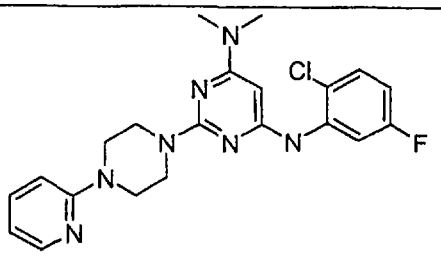
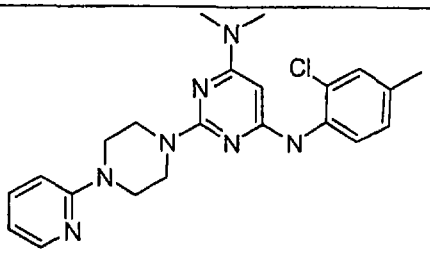
219		558
220		708
221		213
222		847
223		559

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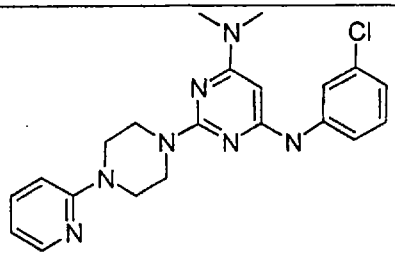
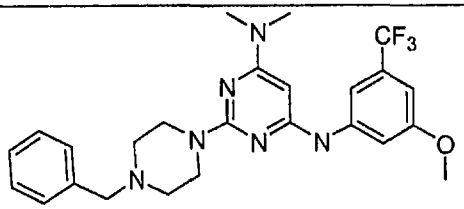
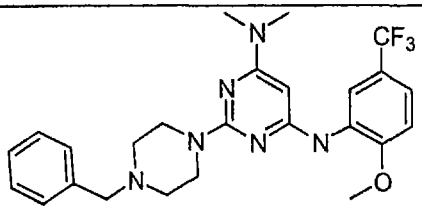
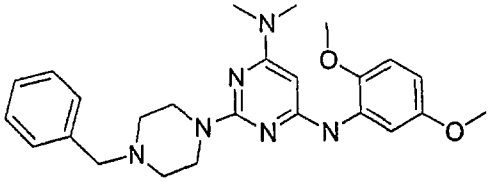
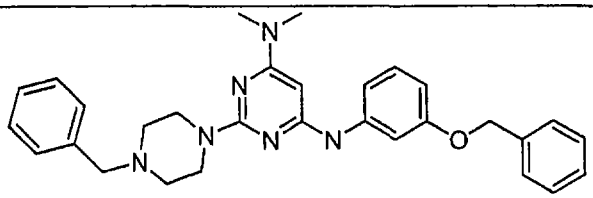
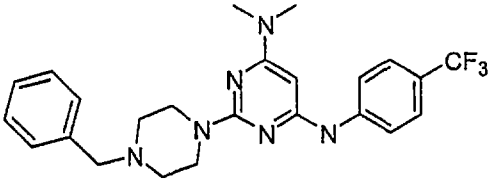
224		218
225		66
226		72
227		600
228		32
229		37

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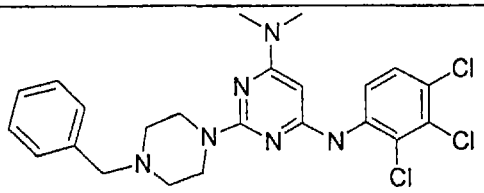
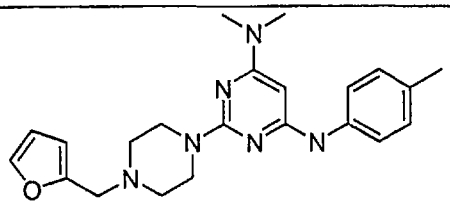
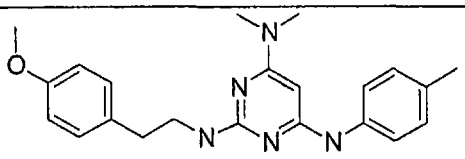
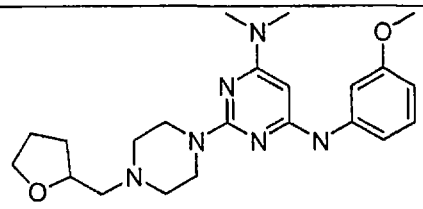
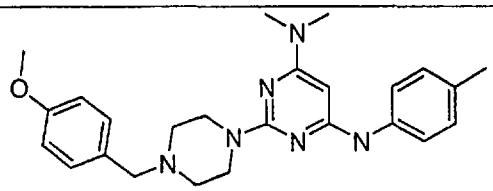
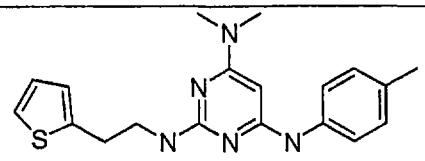
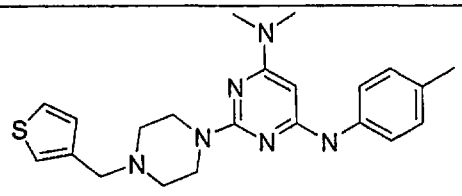
230		52
231		136
232		155*
233		869
235		114*
237		404*
238		331*

* The binding assay normally used for the indolone compounds was used to test this compound.

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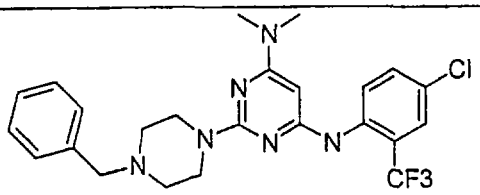
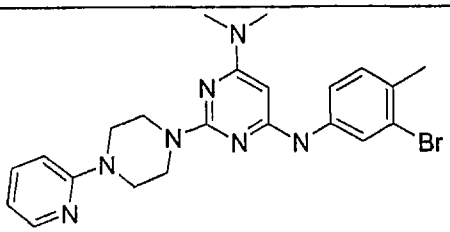
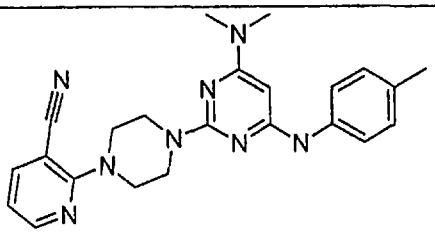
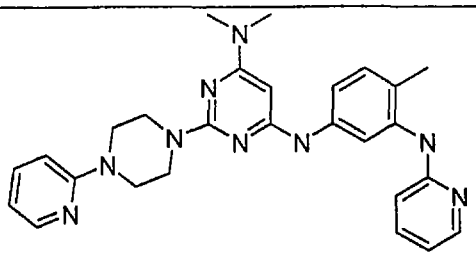
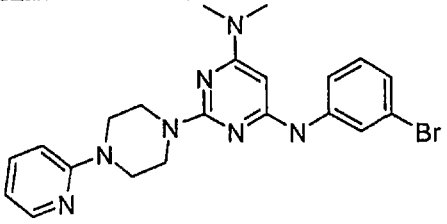
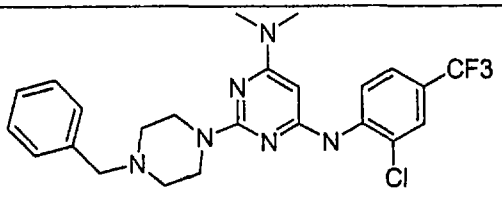
39		59
240		77
241		261
242		166
243		46
244		55

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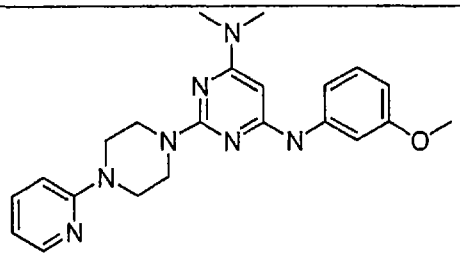
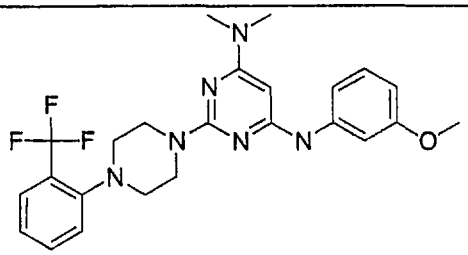
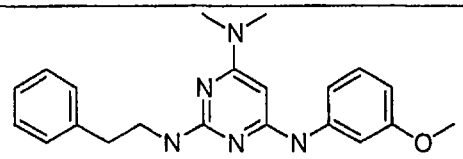
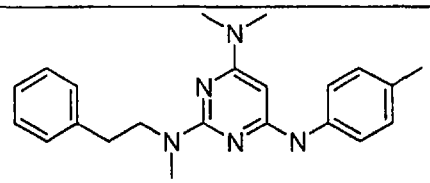
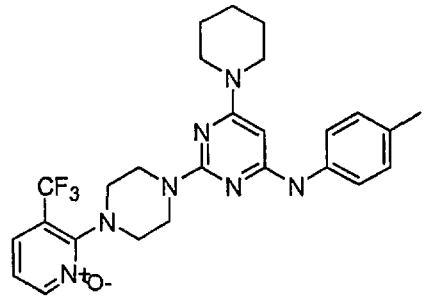
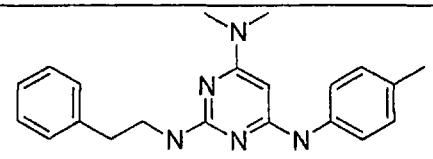
245		537
246		270
247		195
248		33
249		386
250		119

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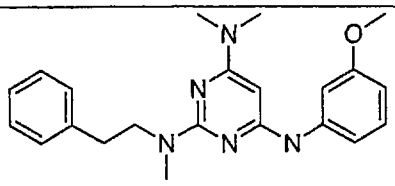
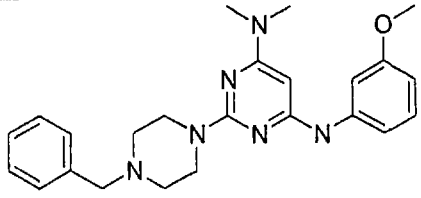
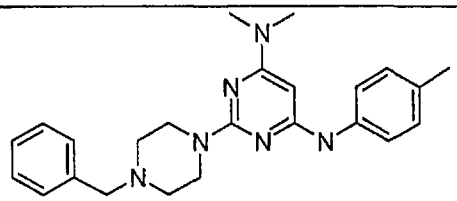
251		54
252		88
253		49

B. General Procedure for Preparing Indolones

General Procedure for Synthesis of Iminoisatins. The appropriately substituted isatin (10 mg - 10 g) was placed in a flask and the appropriate aniline (1.0 - 1.1 equivalents) was added and the mixture was stirred to homogeneity. The mixture was then heated to 110 °C for 2-7 hours and then cooled. Solids were crystallized from hot methanol and filtered, giving the desired products (usually as an inseparable interconverting mixture of E/Z isomers).

Procedure A:

1-(3-THIENYL)-1*H*-INDOLE-2,3-DIONE: Triethylamine (56.9 mL, 0.408 mol), was added to a mixture of 1*H*-indole-2,3-dione (15.0 g, 0.102 mol), copper (II) acetate (46.0 g, 0.255 mol), and 3-thienylboronic acid (19.6 g, 0.153 mol) in CH_2Cl_2 (500 mL). The reaction mixture was stirred overnight, filtered through Celite, rinsed with EtOAc/hexane (1:1, 300 mL), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica using Hexane/EtOAc (1:1), giving the desired product (1.1 g, 50 %).

Procedure B:

(3*E*)-3-[(4-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A solution of 1-(3-Thienyl)-1*H*-indole-

2,3-dione (20 mg, 0.087 mmol) in 1% HOAc/MeOH (8 mL) was added to a solution of *p*-toluidine (19 mg, 0.18 mmol) in 1% HOAc/MeOH (8 mL). The reaction mixture was stirred for 12 h at room temperature, heated at 50 °C for 1 h, and concentrated *in vacuo*. The residue was purified by preparative TLC on silica using EtOAc/hexanes (3:7, 0.1 % TEA) giving the desired product (14 mg, 50%).

Procedure C:

(3Z)-1-PHENYL-3-{[4-(3-THIENYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A mixture of (3Z)-3-[(4-bromophenyl)imino]-1-phenyl-1,3-dihydro-2*H*-indol-2-one (50.0 mg, 0.133 mmol), thiophene-3-boronic acid (26.0 mg, 0.199 mmol), tetrakis(triphenylphosphine)palladium(0) (31.0 mg, 0.0268 mmol in THF (5 mL), and aqueous Na_2CO_3 (2M, 100 µL) was heated at 67 °C for 24 h. The crude product was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2 (3 x 1 ml), and concentrated. The crude product was purified by preparative TLC using 10 % methanol in $CHCl_3$, giving the desired product (18 mg, 35%).

Procedure D:

(3Z)-5-BROMO-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A mixture of 5-bromo-1*H*-indole-2,3-dione (1.0 g, 0.442 mmol) and 3-trifluoromethylaniline (0.993 g, 6.2 mmol)in a solution of 1% acetic acid in methanol was stirred at 50 °C for 12 h. The crude product was concentrated *in vacuo*, giving the desired crude product (640 mg, 40%).

Procedure E:

(3Z)-5-BROMO-1-PHENYL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A mixture of (3*z*)-5-bromo-3-{[3-(trifluoromethyl)phenyl]imino}-1,3-dihydro-2*h*-indol-2-one (100 mg, 0.272 mmol), copper (II) acetate (54 mg, 0.33 mmol), triethylamine (82.8 mg, 0.817 mmol) , and benzene boronic acid (40 mg, 0.325 mmol) in 5 mL of CH_2Cl_2 was stirred at room temperature for 12 h. The crude mixture was concentrated *in vacuo* and purified by preparative TLC using EtOAc:hexane (3:7, 1% triethylamine), giving the desired product (22 mg, 20%).

Procedure F:

(3Z)-1,5-DIPHENYL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A mixture of (3z)-5-bromo-1-phenyl-3-{[3-(trifluoromethyl)phenyl]imino}-1,3-dihydro-2*H*-indol-2-one (22 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium(0) (12.0 mg, 0.01 mmol), benzene boronic acid (10 mg, 0.08 mmol) in THF (5 mL), and aqueous Na_2CO_3 (2M, 100 µL) was heated at 67 °C for 24 h. The crude product was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2 (3 x 1 ml), concentrated, and purified by preparative TLC using 10 % methanol in $CHCl_3$, giving the desired product (4 mg, 18%).

Procedure G:

ETHYL 5-[(2,3-DIOXO-2,3-DIHYDRO-1*H*-INDOL-1-YL)METHYL]-2-FUROATE: A mixture of ethyl 5-(chloromethyl)-2-furoate (148 mg, 1.01 mmol) in dioxane (15 ml) was added to a mixture of NaH (48 mg, 1.20 mmol) in dioxane (10 mL) under argon at 0 °C. The mixture was stirred for 1 h at room temperature, refluxed under argon for 16 h, cooled to room temperature, and then concentrated *in vacuo*. The residue was purified by preparative TLC using EtOAc/hexane (3:7), giving the desired product (56 mg, 19 %).

Procedure H:

ETHYL 5-[((3Z)-2-OXO-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-2,3-DIHYDRO-1*H*-INDOL-1-YL)METHYL]-2-FUROATE: A mixture of ethyl 5-[(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)methyl]-2-furoate (60 mg, 0.200 mmol) and 3-trifluromethylaniline (32 mg, 0.200 mmol) was heated at 140 °C for 2 h. The residue was dissolved in $CHCl_3$ (1 mL) and purified by preparative TLC using EtOAc/hexane (6:4), giving the desired product (20 mg, 23 %).

Procedure I:

6-METHOXY-1-PHENYL-1*H*-INDOLE-2,3-DIONE: A solution of *N*-(3-methoxyphenyl)-*N*-phenylamine (1.14 g, 5.72 in ether (3 mL) was added to a solution of oxylyl chloride (728 g, 5.75 mmol)and heated at reflux for 1 h. The resulting mixture was cooled to room temperature, concentrated to dryness, and redissolved in nitrobenzene (35 mL). The solution was added to a solution of $AlCl_3$ in nitrobenzene (0.762 g, 5.72 mmol), and the resulting mixture was heated at 70 °C for 16 h. The crude product was concentrated *in vacuo* and purified by column

chromatography using EtOAc/hexane (1:1), giving the desired product 60, mg, 50 %).

Procedure J:

(3Z)-1-(4-BROMOPHENYL)-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A solution of (3Z)-3-{[3-(trifluoromethyl)phenyl]imino}-1,3-dihydro-2*H*-indol-2-one (100 mg, 0.344 mmol), copper (II) acetate (93 mg, 0.516 mmol), triethylamine (105 mg, 1.03 mmol), and 4-bromobenzene boronic acid (104 mg, 0.516 mmol) in 5 mL of CH_2Cl_2 was stirred at room temperature for 12 h. The crude mixture was concentrated *in vacuo* and purified by preparative TLC using EtOAc:hexane (3:7, 1% triethylamine), giving the desired product (65 mg, 42%).

Procedure K:

A solution of (3Z)-1-(4-bromophenyl)-3-{[3-(trifluoromethyl)phenyl]imino}-1,3-dihydro-2*H*-indol-2-one (30 mg, 0.068), tetrakis(triphenylphosphine)palladium(0) (16.0 mg, 0.014 mmol), benzene boronic acid (13 mg, 0.101 mmol) in THF (5 mL), and aqueous Na_2CO_3 (0.45 M, 300 µL) was heated at 67 °C for 40 h. The crude product was concentrated *in vacuo* and the residue was extracted with

CH_2Cl_2 (3 x 1 ml), concentrated, and purified by preparative TLC using 10 % methanol in $CHCl_3$, giving the desired product (5 mg, 16%).

The compounds of Examples 92 - 107, inclusive, were purchased from Bionet Research Ltd., 3 Highfield Industrial Estate, Camelford, Cornwall PL32 9QZ, UK. These compounds can also be synthesized using the procedure described above.

Example 91: 3-[(2-METHOXYPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 92: 1-PHENYL-3-[[3-(TRIFLUOROMETHYL)PHENYL]IMINO]-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 93: 3-[(3-METHYLPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 94: 3-[(3-CHLOROPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 95: 1-PHENYL-3-[[4-(TRIFLUOROMETHYL)PHENYL]IMINO]-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 96: 3-[(4-METHYLPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 97: 3-[(4-CHLOROPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 98: 3-[(4-BROMOPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 99: 3-[(4-FLUOROPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 100: 3-[(4-PHENOXYPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 101: 3-[(4-ETHOXYPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 102: 3-[(4-METHOXYPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 103: 3-[(3,5-DICHLOROPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 104: 3-[(3,5-DIMETHYLPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE

Example 105: 1-ALLYL-3-[(3,4-DICHLOROPHENYL)IMINO]-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 106: 1-ALLYL-3-[(3,5-DICHLOROPHENYL)IMINO]-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 107: 3-[(4-BROMOPHENYL)IMINO]-1-ISOPROPYL-1,3-DIHYDRO-2H-INDOL-2-ONE

The methods that follow demonstrate procedures useful for synthesizing compounds of this invention (illustrated in

Schemes 6 and 7). Substituted isatins useful for synthesizing compounds of this invention can alternatively be obtained using the procedures described in the following references:

Garden, S. J.; Da Silva, L. E.; Pinto, A.C.; *Synthetic Communications*, 1998, 28, 1679 - 1689.

Coppola, G.M.; *Journal of Heterocyclic Chemistry*, 1987, 24, 1249.

Hess, B.A. Jr; Corbino, S.; *Journal of Heterocyclic Chemistry*, 1971, 8, 161.

Bryant, W. M. III; Huhn, G.F.; Jensen, J.H.; Pierce, M. E.; Stammbach, C.; *Synthetic Communications*, 1993, 23, 1617 - 1625.

Example 108: 1-[(5-CHLORO-2-THIENYL)METHYL]-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A mixture of 1-[(5-chloro-2-thienyl)methyl]-2*H*-indole-2,3-dione (25 mg, 0.09 mmol) (prepared as described below) and 3-trifluoromethylaniline (11.3 μL, 0.09 mmol) was heated neat at 140 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 3:7 ethyl acetate in hexane as the eluent, giving the desired product (23 mg 0.05 mmol, 61 %). ^{1}H NMR (400 MHz): δ (major isomer) 7.57 (t, *J* = 7.7, 1H), 7.53 (t, *J* = 7.8, 1H), 7.33 (t, *J* = 7.8, 1H), 7.28 (s, 1H), 7.19 (d, *J* = 7.6, 2H), 6.94 - 6.72 (m, 4H), 6.56 (d, *J* = 7.7, 1H), 5.02 (s, 2H); ESI-MS *m/z* found 421 (MH^+).

1-[(5-CHLORO-2-THIENYL)METHYL]-2*H*-INDOLE-2,3-DIONE: A solution of isatin (125 mg, 0.85 mmol) in anhydrous dioxane (10 mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 24 mg,

0.62 mmol) in anhydrous dioxane (10 mL) at 0 °C under argon. The mixture was allowed to stir for 5 minutes and then 2-chloro-5-(chloromethyl)thiophene (0.12 mL, 1.02 mmol) in dioxane (10 mL) was added dropwise to the resulting mixture. The reaction mixture was heated at reflux under argon for 16 h and concentrated *in vacuo*. The crude material was purified preparative TLC using 1:24 methanol in chloroform as the eluent, giving the desired product as a yellow solid (53 mg, 0.19 mmol, 22 %). ^{1}H NMR (400 MHz): δ 7.62 (d, *J* = 7.4, 1H), 7.56 (t, *J* = 7.8, 1H), 7.14 (t, *J* = 7.7, 1H), 6.94 (d, *J* = 8.0, 1H), 6.90 (d, *J* = 3.2, 1H), 6.78 (d, *J* = 3.7, 1H), 4.90 (s, 2H).

Example 109: 1-(3-THIENYL)-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: A mixture of 1-(3-thienyl)-2*H*-indole-2,3-dione (25 mg, 0.11 mmol) (prepared as described below) and 3-trifluoromethylaniline (14 uL, 0.11 mmol) was heated neat at 140 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 3:7 ethyl acetate and hexane as the eluent, giving the desired product as a yellow solid (7.3 mg, 0.02 mmol, 22 %). ^{1}H NMR (400 MHz) δ 7.62 - 7.19 (m, 9H), 6.94 (d, *J* = 8.0, 1H), 6.76 (t, *J* = 7.6, 1H); ESI-MS *m/z* found 373 (MH^+).

1-(3-THIENYL)-2*H*-INDOLE-2,3-DIONE: Copper(II) acetate monohydrate (4.25 g, 23.4 mmol) was heated at reflux in acetic anhydride (30 mL) for 2 h. The mixture was filtered and washed with anhydrous ether (500 mL). The solid was dried in *vacuo* at 55 °C for 16 h. Dichloromethane (1 mL) was added to a mixture of

copper(II) acetate (62 mg, 0.34 mmol), isatin (50 mg, 0.34 mmol), and thiophene-3-boronic acid (87 mg, 0.68 mmol), followed by triethylamine (0.10 mL, 0.68 mmol) under argon. The resulting solution was stirred for 16 h at room temperature. The reaction mixture was then recharged with 0.10 mmol copper(II) acetate, 0.10 mmol of 3-thiophene boronic acid, and 1 drop of triethylamine, and the mixture was heated at 50 °C for 6 h. The crude material was purified by preparative TLC using 3:97 methanol in chloroform as the eluent, giving the desired product as a yellow solid (25 mg, 0.11 mmol, 33 %). ^{1}H NMR (400 MHz): δ 7.70 (d, *J* = 7.5, 1H), 7.58 (t, *J* = 7.8, 1H), 7.50 (d, *J* = 5.1, 1H), 7.48 (s, 1H), 7.24 (d, *J* = 5.1, 1H), 7.18 (t, *J* = 7.51, 1H), 7.05 (d, *J* = 8.0, 1H).

Example 110: 2-METHYL-5-[(2-OXO-1-PHENYL-1,2-DIHYDRO-3*H*-INDOL-3-YLIDENE)AMINO]-2*H*-ISOINDOLE-1,3(2*H*)-DIONE: A mixture of 1-phenylisatin (50 mg, 0.22 mmol) and 4-amino-N-methylpthalimide (40 mg, 0.22 mmol) was heated neat at 215 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 3:7 ethyl acetate and hexane as the eluent, giving the desired product as a yellow solid (8 mg, 0.02 mmol, 10 %). ^{1}H NMR (400 MHz): δ 7.88 (d, *J* = 7.8, 1H), 7.83 - 7.80 (m, 1H), 7.51 (t, *J* = 7.5, 1H), 7.47 - 7.18 (m, 6H), 7.02 (t, *J* = 8.0, 1H), 6.91 - 6.79 (m, 2H), 6.58 (d, *J* = 7.5, 1H), 3.22 (s, 3H); ESI-MS *m/z* found 382 (MH^+).

Example 111: 1-[(5-CHLORO-1-BENZOTHIEN-3-YL)METHYL]-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-

2-ONE: A mixture of 1-[(5-chloro-1-benzothien-3-yl)methyl]-2*H*-indole-2,3-dione (50 mg, 0.15 mmol) (prepared as described below) and 3-trifluoromethylaniline (0.020 mL, 0.15 mmol) was heated neat at 140 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 1:3 ethyl acetate and hexane as the eluent giving the desired product as a yellow solid (13 mg, 0.030 mmol, 18%). ^{1}H NMR (400 MHz): δ 7.98 (d, *J* = 2.0, 1H), 7.80 (d, *J* = 8.6, 1H), 7.58 (t, *J* = 7.7, 1H), 7.52 (d, *J* = 8.1, 1H), 7.43 (s, 1H), 7.38 (dd, *J* = 8.6, 1.9, 1H), 7.31 (overlapping singlet and dt, *J* = 1.2, 7.8, 2H), 7.24 (d, *J* = 7.8, 1H), 6.87 (d, *J* = 7.9, 1H), 6.77 (t, *J* = 7.7, 1H), 6.59 (d, *J* = 7.7, 1H), 5.20 (s, 2H). ESI-MS *m/z* found 471 (MH^+ with ^{35}Cl), 473 (MH^+ with ^{37}Cl).

1-[(5-CHLORO-1-BENZOTHIEN-3-YL)METHYL]-2*H*-INDOLE-2,3-dione: A solution of isatin (125mg, 0.85 mmol) in anhydrous dioxane (10 mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 25 mg, 0.62 mmol) in anhydrous dioxane (10 mL) at 0 °C under argon. The mixture was allowed to stir for 5 minutes and then a solution of 3-(bromomethyl)-5-chlorobenzo[b]thiophene (267 mg, 1.02 mmol) in dioxane (10 mL) was added dropwise to the reaction mixture. The reaction mixture was heated at reflux under argon for 16 h and concentrated in *vacuo*. The crude material was purified by preparative TLC using 1:24 methanol in chloroform as the eluent, giving the desired product as a yellow solid (125 mg, 0.38 mmol, 45%). ^{1}H NMR (400 MHz): δ 7.89 (s, 1H), 7.79 (d, *J* = 8.5, 1H), 7.65 (d, *J* = 7.5, 1H), 7.54 (t, *J* = 8.0, 1H), 7.42 (s, 1H), 7.38 (d, *J* =

8.5, 1H), 7.14 (t, *J* = 7.5, 1H), 6.88 (d, *J* = 7.8, 1H), 5.13 (s, 2H).

Example 112: 3-(1*H*-INDOL-5-YLIMINO)-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: 1-phenylisatin (51.8 mg, 0.23 mmol) and 5-aminoindole (31 mg, 0.23 mmol) were mixed and heated at 140 °C for 2 h. The resulting crude product was purified by preparative TLC using ethyl acetate/hexane (6:4) as the eluent, giving the desired product as a yellow solid (10.8 mg, 14%). ^{1}H NMR (400 MHz): δ 8.28 (s, 1H), 7.57 (t, *J* = 7.7, 2H), 7.49 - 7.40 (m, 6H), 7.29 - 7.23 (m, 1H), 7.03 (dd, *J* = 8.5, 1.7, 1H), 6.98 (d, *J* = 7.6, 1H), 6.83 (d, *J* = 8.0, 1H), 6.74, *J* = 7.6, 1H), 6.59 (s, 1H); ESI-MS *m/z* found 338 (MH^+).

Example 113: 3-[(6-CHLORO-3-PYRIDINYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: 1-phenylisatin (23.0 mg, 0.10 mmol) and 5-amino-2-chloropyridine (12.8 mg, 0.10 mmol) were mixed and heated at 140 °C for 7 h. The resulting crude product was purified by preparative TLC using hexane/ethyl acetate (8:2) as the eluent, giving the desired product as a yellow solid (19.7 mg, 59%). ^{1}H NMR (400 MHz) δ 8.15 (d, *J* = 8, 1H), 7.6 - 7.2 (m, 9H), 6.85 - 6.75 (m, 2H); ESI-MS *m/z* found 334 (MH^+).

Example 114: 3-[(2-METHYL-1,3-BENZOTHIAZOL-5-YL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: 5-amino-2-methylbenzothiazole (52.2 mg, 0.31 mmmol) was mixed with 1-phenylisatin (69.7 mg, 0.31 mmol) and heated at 140 °C for 3 h. The resulting crude product was purified by preparative TLC using ethyl acetate/hexane (6:4) as the

eluent to give the desired product as a yellow solid (36.9 mg, 32.3 %). ^{1}H NMR Data: δ 7.9-6.7 (m, 12H), 2.9 (s, 3H). ESI-MS *m/z* found 370 (MH^+).

Example 254: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-(2-PYRIDINYLMETHYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures H and K (for substitution of 2-picolyl chloride). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 - 8.46 (m, 1H), 7.87 - 7.78 (m, 1H), 7.64 (d, 1H, *J* = 7.1), 7.53 - 7.31 (m, 5H), 7.28 (d, 1H, *J* = 4.1), 7.12 (d, 1H, *J* = 8.1), 6.58-6.53 (m, 1H), 5.51 (s, 2H); ESI-MS *m/z* 381 (MH^+).

Example 255: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-[(3,5-DIMETHYL-4-ISOXAZOLYL)METHYL]-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B (microwave heating). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,63 (d, 1H, *J* = 9.1), 7.46 (dt, 1H, *J* = 8.1, 2.0), 7.28 (d, 1H, *J* = 2.1), 7.02 (d, 1H, *J*= 2.0), 6.88 (dt, 1H, *J* 8.0, 2.1), 6.74 - 6.72 (m, 1H), 6.72 - 6.70 (m, 1H), 5.53 (s, 2H), 2.50 (s, 3H), 2.24 (s, 3H); ESI-MS *m/z* 399 (MH^+).

Example 256: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-[3-(TRIFLUOROMETHYL)PHENYL]-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 - 7.87 (m, 1H), 7.83 - 7.79 (m, 1H), 7.67 (d, 1H, *J*

= 8), 7.46 - 7.40 (m, 1H), 7.33 (d, 1H, *J* = 2), 7.08 - 7.05 (m, 1H), 6.96 - 6.80 (m, 5H); ESI-MS *m/z* 435 (MH^+).

Example 257: (3Z)-1-(3,5-DICHLOROPHENYL)-3-[(3,4-DICHLOROPHENYL)IMINO]-1,3-DIHYDRO-2*H*-INDOL-2-ONE:

Prepared by Procedures A and B. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 8.1), 7.79 (d, 1H, *J* = 6.0), 7.72 - 7.68 (m, 1H), 7.59 - 7.45 (m, 1H), 7.46 (d, 1H, *J* = 8.1), 7.32 (dt, 1H, *J* = 8.0, 2.1), 7.23 (d, 1H, *J* = 2.5), 6.97 (dd, 1H, *J* = 8.0, 2.1), 6.92 - 6.87 (m, 1H), 6.85 - 6.81 (m, 1H); ESI-MS *m/z* 435 (MH^+).

Example 258: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-6-METHOXY-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures K, L, and B. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.54 (m, 1H), 7.53 - 7.38 (m, 3H), 7.29 (d, 1H, *J* = 2.0), 7.17 (d, 1H, *J* = 8.1), 7.12 (d, 1H, *J* = 8.0), 6.84 (d, 1H, *J* = 2.5), 6.78 (d, 1H, *J* = 8), 6.6 (dd, 2H, *J* = 8.0, 2.0), 6.55 (dd, 2H, *J* = 8.1, 2.5); ESI-MS *m/z* (398 MH^+).

Example 259: (3Z)-3-[(4-CHLORO-3-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.62 (m, 2H), 7.49 (s, 1H), 7.47 (s, 1H), 7.41 (dt, 1H,

J = 7.1, 1.6), 7.3 (dd, 1H, *J* = 5.0, 1.6), 7.05 - 6.97 (m, 1H, 6.93 - 6.86 (m, 1H), 6.77 (m, 1H), 6.56 (m, 1H), 2.53 (s, 3H); ESI-MS *m/z* 353 (MH^+).

Example 260: (3Z)-3-(2-NAPHTHYLIMINO)-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, *J* = 9.1), 8.06 - 7.99 (m, 1H), 7.89 - 7.80 (m, 1H), 7.78 - 7.71 (m, 1H), 7.71 - 7.47 (m, 4H), 7.41 - 7.35 (m, 1H), 7.33 (d, 1H, *J* = 5.2), 7.28 (d, 1H, *J* = 6.8.1), 7.00 (d, 1H, *J* = 8.0), 6.76 (t, 1H, *J* = 7.8), 6.67 (d, 1H, *J* = 7.9); ESI-MS *m/z* 355 (MH^+).

Example 261: (3Z)-3-[(4-CHLOROPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.56 (m, 2H), 7.54 - 7.48 (m, 1H), 7.41 (dt, 1H, *J* = 8, 2), 7.32 - 7.28 (m, 1H), 7.11 - 6.99 (m, 3H), 6.89 (dt, 1H, *J* = 8), 6.77 - 6.73 (m. 1H), 6.66 - 6.33 (m, 1H); ESI-MS *m/z* 339 (MH^+).

Example 262: (3Z)-3-[(4-IODOPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.74

(m, 2H), 7.53 - 7.48 (m, 2H), 7.35 (dt, 1H, *J* = 8.0, 1.2), 7.29 - 7.24 (m, 1H), 6.98 (d, 1H, *J* = 8.0), 6.89 - 6.75 (m, 4H); ESI-MS *m/z* 431 (MH^+).

Example 263: (3Z)-3-[(4-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.44 (m, 2H), 7.35 - 7.22 (m, 4H), 6.99 - 6.93 (m, 3H), 6.87 - 6.78 (m, 2H), 2.42 (s, 3H); ESI-MS *m/z* 319 (MH^+).

Example 264: (3Z)-3-[(3,5-DIFLUOROPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.16 (m, 4H), 6.99 (dt, 1H, *J* = 8.2, 0.8), 6.89 (dt, 1H, *J* = 7.7, 1.1), 6.76 (d, 1H, *J* = 7.5), 6.71 (tt, 1H, *J* = 9.3, 2.3), 6.64 - 6.57 (m, 2H); ESI-MS *m/z* 341 (MH^+).

Example 265: (3Z)-3-([1,1'-BIPHENYL]-4-YLIMINO)-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz,

$CDCl_3$) δ 7.73 - 7.12 (m, 13H), 6.99 (d, 1H, *J* = 8.0), 6.89 (d, 1H, *J* = 8.0), 6.82 (dt, 1H, *J* = 7.6, 1.0); ESI-MS *m/z* 381 (MH+).

Example 266: ETHYL 3-{[(3*Z*)-2-OXO-1-(3-THIENYL)-1,2-DIHYDRO-3*H*-INDOL-3-YLIDENE]AMINO}BENZOATE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J* = 7.4), 7.75 - 7.17 (m, 6H), 6.98 (d, 1H, *J* = 8.0), 6.87 - 6.78 (m, 2H), 6.63 (d, 1H, *J* = 7.8), 4.45 - 4.32 (m, 2H), 1.43 - 1.33 (m, 3H); ESI-MS *m/z* 377 (MH+).

Example 267: (3Z)-3-[(6-CHLORO-3-PYRIDINYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 - 6.81 (m, 10H); ESI-MS *m/z* 340.13 (MH^+).

Example 268: 3Z)-3-[(4-PHENOXYPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 - 6.70 (m, 16H); ESI-MS *m/z* 397 (MH^+).

Example 269: (3Z)-3-[(4-BROMOPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 6.55 (m, 11H); ESI-MS *m/z* 383 (MH^+).

Example 270: (3Z)-3-[(3-CHLOROPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 6.50 (m, 11H); ESI-MS *m/z* 339 (MH^+).

Example 271: (3Z)-3-[(3-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: : Prepared by Procedures A and B (1% HOAc in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 - 6.78 (m, 11H), 2.39 (s, 3H); ESI-MS *m/z* 319 (MH^+).

Example 272: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: : Prepared by Procedures A and B (1% HOAc in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 6.80 (m, 10H); ESI-MS *m/z* 373 (MH^+).

Example 273: (3Z)-1-(2-PYRIDINYLMETHYL)-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: : Prepared by Procedure B. ESI-MS *m/z* 382 (MH^+).

Example 274: (3Z)-3-[(3,5-DICHLOROPHENYL)IMINO]-1-(2-PYRIDINYLMETHYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 382 (MH^+).

Example 275: (3Z)-1-[(3,5-DIMETHYL-4-ISOXAZOLYL)METHYL]-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 400 (MH^+).

Example 276: (3Z)-3-[(3,4-DIFLUOROPHENYL)IMINO]-1-(3-PYRIDINYLMETHYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 350 (MH^+).

Example 277: (3Z)-1-(3-PYRIDINYLMETHYL)-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 382 ((MH$^+$).

Example 278: (3Z)-3-[(3,4-DIFLUOROPHENYL)IMINO]-1-(2-PYRIDINYLMETHYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 350 (MH$^+$).

Example 279: (3Z)-3-[(3,5-DICHLOROPHENYL)IMINO]-1-(3-PYRIDINYLMETHYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 384 (MH$^+$).

Example 280: (3Z)-3-[(3,5-DICHLOROPHENYL)IMINO]-1-[(3,5-DIMETHYL-4-ISOXAZOLYL)METHYL]-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 402 (MH$^+$).

Example 281: (3Z)-3-[(9-ETHYL-9*H*-CARBAZOL-3-YL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: : Prepared by Procedure H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 - 6.66 (m, 16H), 4.47 - 4.35 (m, 2H), 1.55 - 1.44 (m, 3H); ESI-MS *m/z* 416 (MH$^+$).

Example 282: (3Z)-1-PHENYL-3-(5-QUINOLINYLIMINO)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: : Prepared by Procedure H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 - 9.32 (m, 1H), 8.55 - 8.50 (m, 1H), 8.01 - 6.62 (m, 12H), 6.43 - 6.35 (m, 1H); ESI-MS *m/z* 350 (MH^+).

Example 283: (3Z)-3-[(4-IODOPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 425 (MH^+).

Example 285: (3Z)-3-[(3,4-DIFLUOROPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 335 (MH^+).

Example 286: (3Z)-3-[(2-CHLORO-4-METHYLPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 347 (MH^+ with ^{35}Cl), 349 (MH^+ with ^{37}Cl).

Example 287: (3Z)-3-[(2,4-DIMETHOXYPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure

B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 359 (MH^+).

Example 288: 3-{[(3Z)-2-OXO-1-PHENYL-1,2-DIHYDRO-3*H*-INDOL-3-YLIDENE]AMINO}BENZONITRILE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 324 (MH^+).

Example 289: (3Z)-3-{[2-METHYL-5-(TRIFLUOROMETHYL)PHENYL]IMINO}-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 381 (MH^+).

Example 290: (3Z)-3-[(4-CHLORO-3-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 353 (MH^+).

Example 291: (3Z)-3-(6-QUINOLINYLIMINO)-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 356 (MH^+).

Example 292: (3Z)-3-[(4-CHLOROPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 339 (MH^+).

Example 295: (3Z)-3-[(3-ISOPROPYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 347 (MH^+).

Example 296: (3Z)-3-[(4-CYCLOHEXYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 387 (MH^+).

Example 297: (4-{[(3Z)-2-OXO-1-PHENYL-1,2-DIHYDRO-3*H*-INDOL-3-YLIDENE]AMINO}PHENYL)ACETONITRILE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 339 (MH^+).

Example 298: (3Z)-3-[(2,2-DIFLUORO-1,3-BENZODIOXOL-5-YL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH_2, 3 Å molecular sieves). ESI-MS *m/z* 379(MH^+).

Example 299: (3Z)-3-(1,3-BENZOTHIAZOL-6-YLIMINO)-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure H. ESI-MS *m/z* 356 (MH^+).

Example 300: (3Z)-1-TETRAHYDRO-2*H*-PYRAN-4-YL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures G and H. ESI-MS *m/z* 375 (MH^+).

Example 301: (3Z)-3-(1*H*-INDAZOL-6-YLIMINO)-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure H. ESI-MS *m/z* 339 (MH^+).

Example 302: (3Z)-3-[(3-CHLOROPHENYL)IMINO]-6-METHOXY-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures I and H. ESI-MS *m/z* 363 (MH^+).

Example 303: (3Z)-6-METHOXY-1-PHENYL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures I and H. ESI-MS *m/z* 397 (MH^+).

Example 304: (3Z)-1-PHENYL-3-{[4-(3-THIENYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE:
Prepared by Procedures H and C. ESI-MS *m/z* 381 (MH^+).

Example 305: (3Z)-1-PHENYL-3-{[3'-(TRIFLUOROMETHYL)[1,1'-BIPHENYL]-4-YL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE:

Prepared by Procedures H and C. ESI-MS *m/z* 443 (MH^+).

Example 306: (3Z)-1-PHENYL-3-{[4-(3-PYRIDINYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE:

Prepared by Procedures H and C. ESI-MS *m/z* 376 (MH^+).

Example 307: (3Z)-3-[(3-BROMOPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedure B. ESI-MS *m/z* 378 (MH^+).

Example 308: (3Z)-1,5-DIPHENYL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures D, E, and F. ESI-MS *m/z* 443 (MH^+).

Example 309: (3Z)-1-[1,1'-BIPHENYL]-4-YL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-

ONE: Prepared by Procedures H (6 eq of aniline), J, and K. ESI-MS *m/z* 443 (MH^+).

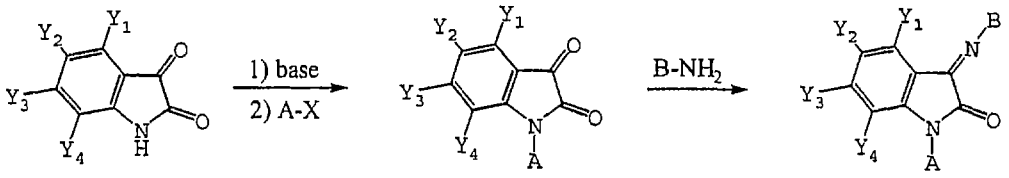
Example 310: (3Z)-1-(4-HYDROXYPHENYL)-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures H (6 eq of aniline) and E. ESI-MS *m/z* 383 (MH^+).

Example 311: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-(3-PYRIDINYLMETHYL)-1,3-DIHYDRO-2*H*-INDOL-2-ONE: Prepared by Procedures H (75 °C, 2 h), K (3-picolyl chloride), and B. ESI-MS *m/z* 383 (MH

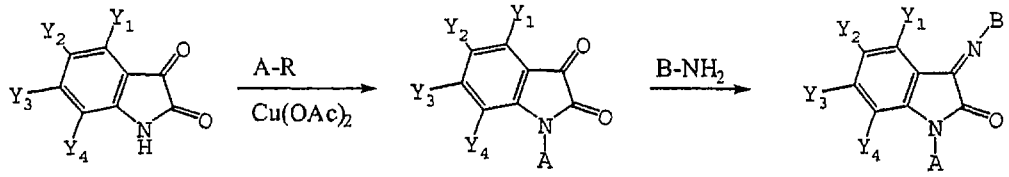
Examples 91-114 and 254-311 as described above are merely illustrative of the methods used to synthesize indolone derivatives. Further derivatives may be obtained utilizing methods shown in Schemes 6a, 7a and 8-10. The substituents in Schemes 6a, 7a and 8-10 are described in the Detailed Description.

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form indolone derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

Scheme 6[a]

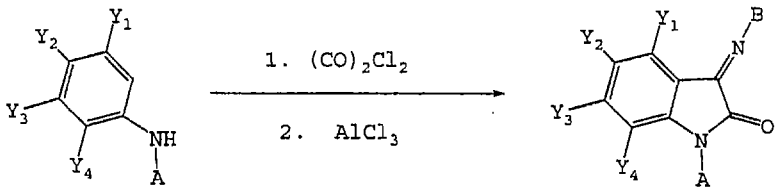


Scheme 7[a]



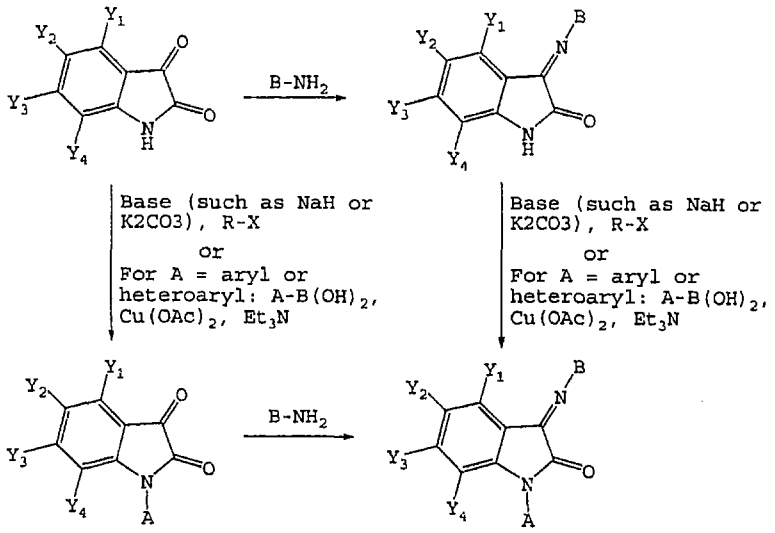
[a]Y_1, Y_2, Y_3, Y_4, A, and B are defined as described in the specification. X is a leaving group such as Cl, Br, I, or OTs. R is boric acid or a dialkylborate group.

Scheme 8[a]. Synthesis of Isatins



[a]Y_1, Y_2, Y_3, Y_4, A, and B are defined as described in the specification. X is a leaving group such as Cl, Br, I, or OTs. R is boric acid or a dialkylborate group.

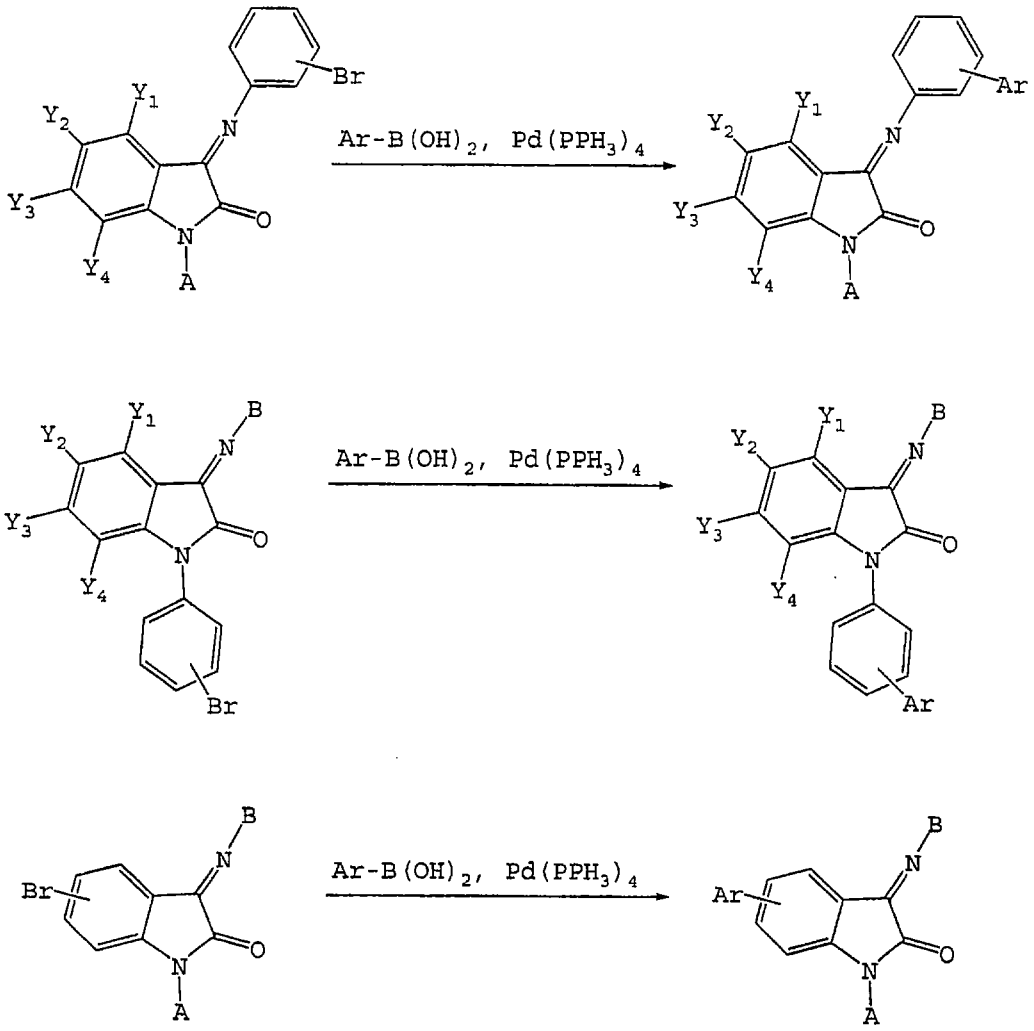
Scheme 9[a]. Synthesis of Substituted Iminoindolones



X is a leaving group such as a halogen or tosylate.

[a]Y_1, Y_2, Y_3, Y_4, A, and B are defined as described in the specification. X is a leaving group such as Cl, Br, I, or OTs. R is boric acid or a dialkylborate group.

Scheme 10[a]. Synthesis of Aryl or Heteroaryl-Substituted Iminoindolones



[a]Y_1, Y_2, Y_3, Y_4, A, and B are defined as described in the specification. X is a leaving group such as Cl, Br, I, or OTs. R is boric acid or a dialkylborate group.

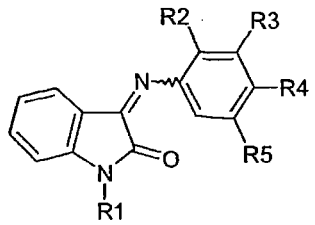
Radioligand Binding of Indolones at Cloned Galanin Receptors

The binding properties of the indolones of the present invention were evaluated at the cloned human galanin receptors, GAL1, GAL2, and GAL3, using protocols described herein.

Radioligand Binding Assay Results

The indolones described in Examples 91-114 and 254-311 were assayed using cloned human galanin receptors. The compounds were found to be selective for the GAL3 receptor. The binding affinities of the compounds of Examples 91-114 and 254-311 are illustrated in Tables 4 and 4a.

Table 4. Binding Affinities of Indolones at Galanin Receptors.



	substitution					Ki (nM)		
Example	R1	R2	R3	R4	R5	GalR1	GalR2	GalR3
91	Ph	OMe	H	H	H	>10000	>10000	527
92	Ph	H	CF_3	H	H	>10000	>10000	38
93	Ph	H	Me	H	H	>10000	>10000	171
94	Ph	H	Cl	H	H	>10000	>10000	49
95	Ph	H	H	CF_3	H	>10000	>10000	29
96	Ph	H	H	Me	H	>10000	>10000	111
97	Ph	H	H	Cl	H	>10000	>10000	51
98	Ph	H	H	Br	H	>10000	>10000	38
99	Ph	H	H	F	H	>10000	>10000	229
100	Ph	H	H	OPh	H	>10000	>10000	90
101	Ph	H	H	OEt	H	>10000	>10000	305
102	Ph	H	H	OMe	H	>10000	>10000	429
103	Ph	H	Cl	H	Cl	>10000	>10000	68
104	Ph	H	Me	H	Me	>10000	>10000	143
105	allyl	H	Cl	Cl	H	>10000	>10000	97
106	allyl	H	Cl	H	Cl	>10000	>10000	62
107	isopropyl	H	H	Br	H	>10000	>10000	126

Key: Ph= Phenyl OMe= Methoxy OEt= Ethoxy
Me= Methyl OPh= Phenoxy

Table 4a.

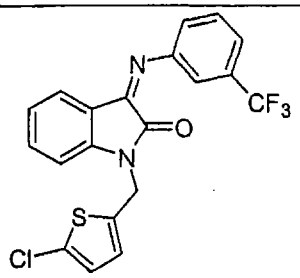
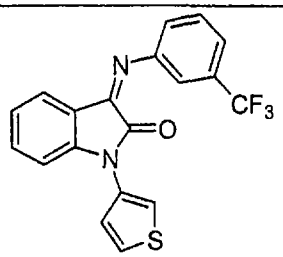
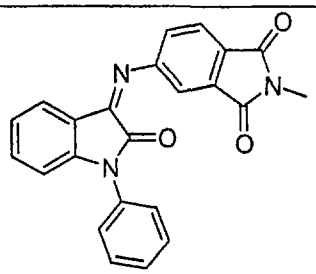
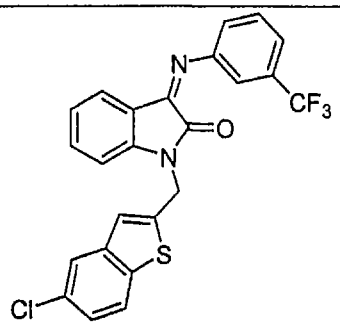
Example	Structure	Ki (nM) Gal3
108		84
109		103
110		138
111		1178

Table 4a.

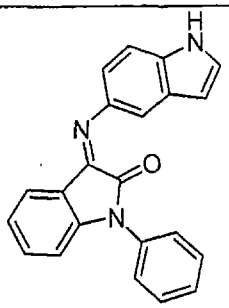
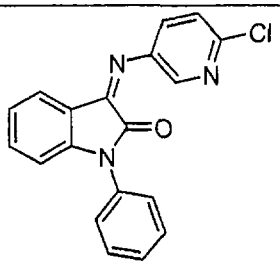
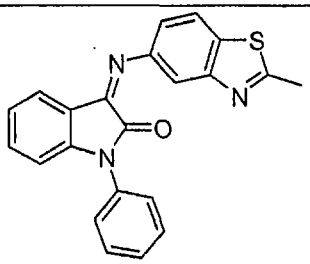
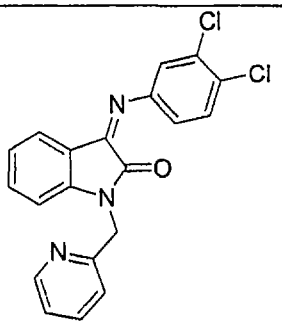
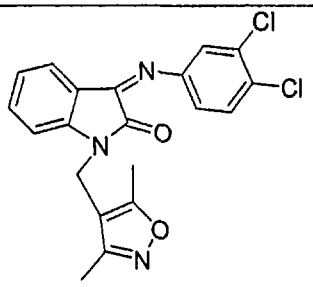
112		2324
113		136
114		569
254		64
255		49

Table 4a.

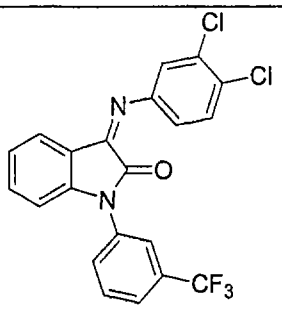
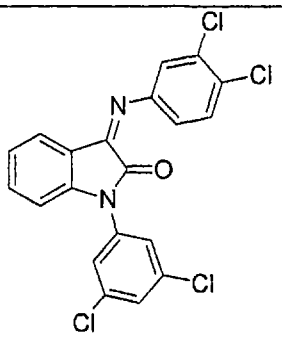
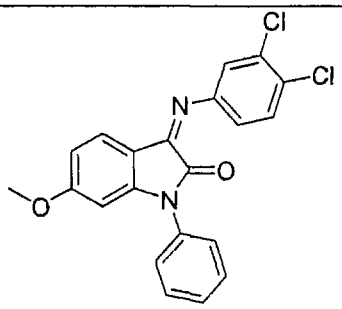
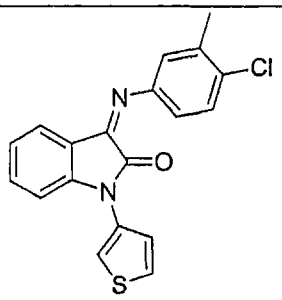
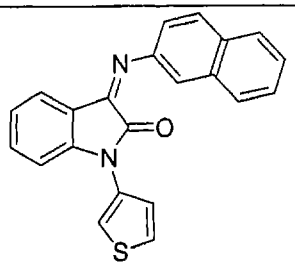
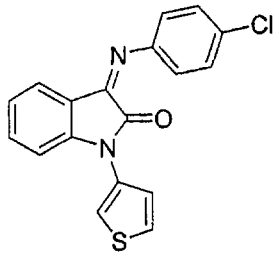
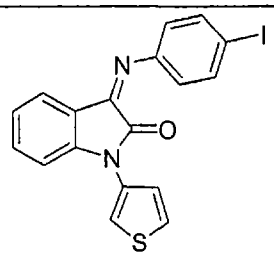
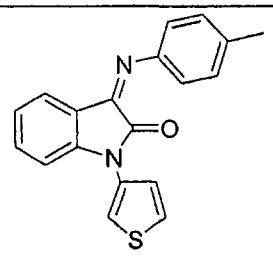
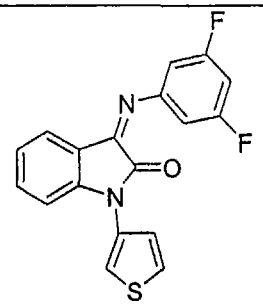
256		18
257		33
258		67
259		55

Table 4a.

260		60
261		34
262		46
263		136
264		27

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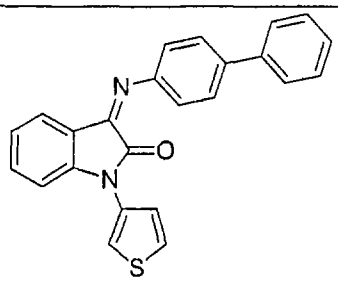
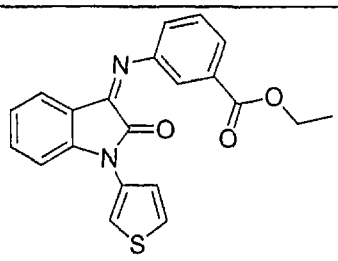
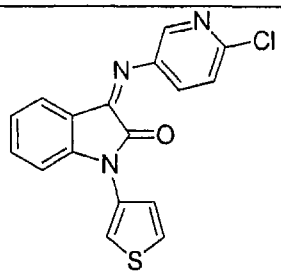
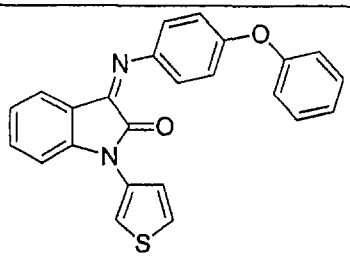
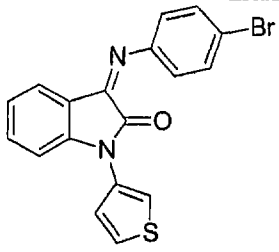
265		80
266		236
267		234
268		57
269		46

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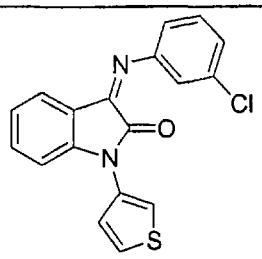
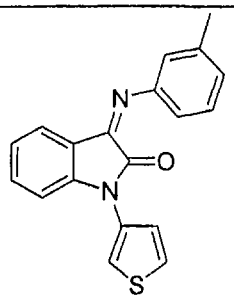
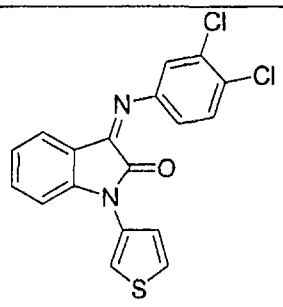
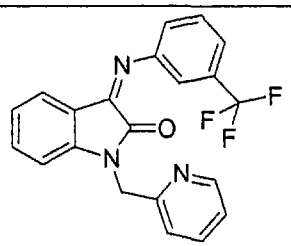
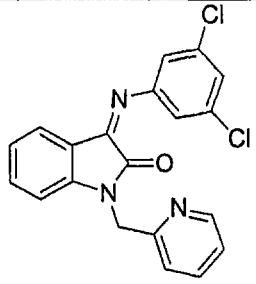
270		42
271		114
272		26
273		202
274		174

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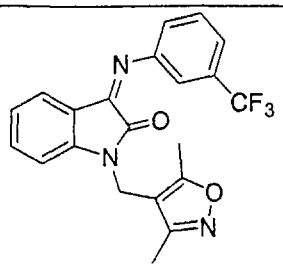
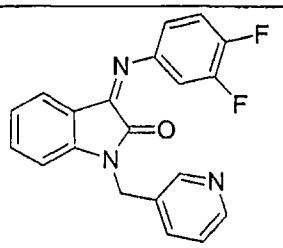
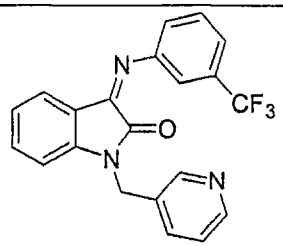
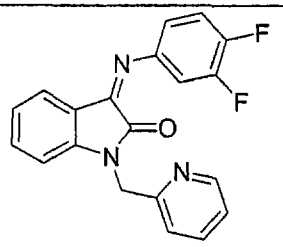
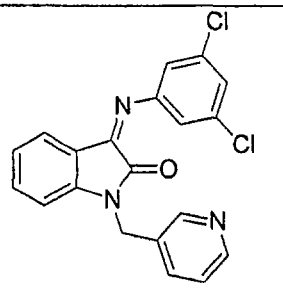
275		595
276		192
277		198
278		340
279		81

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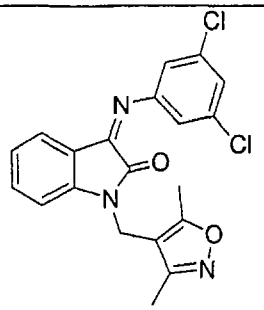
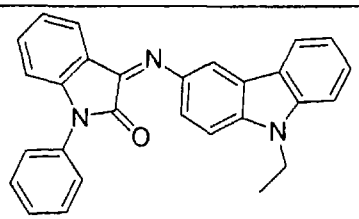
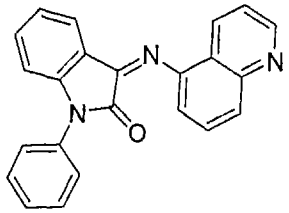
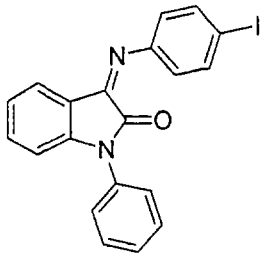
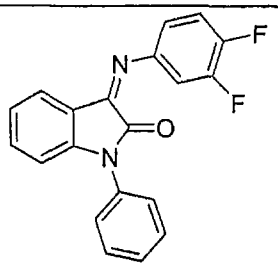
280		521
281		150
282		333
283		33
285		26

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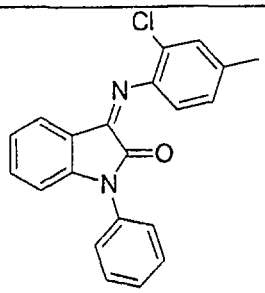
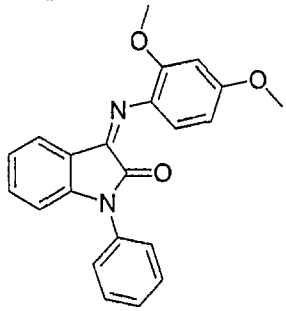
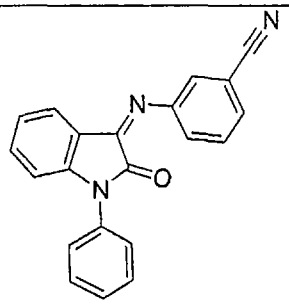
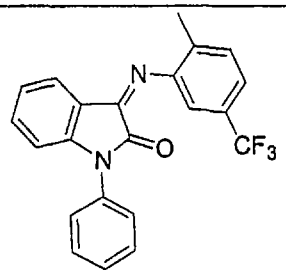
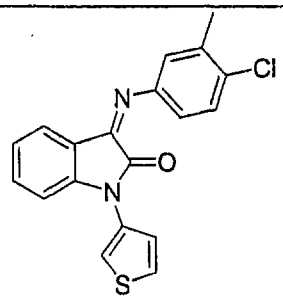
286		38
287		260
288		39
289		59
290		55

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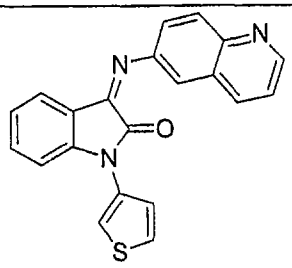
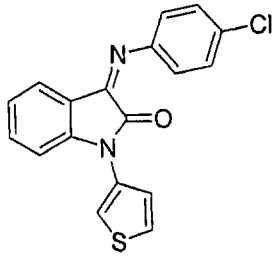
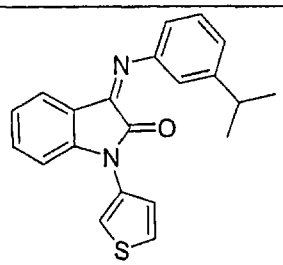
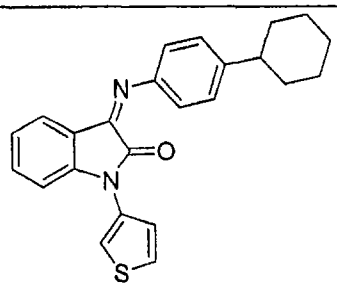
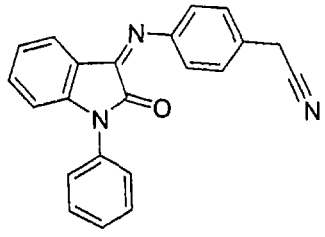
291		271
292		34
295		242
296		82
297		226

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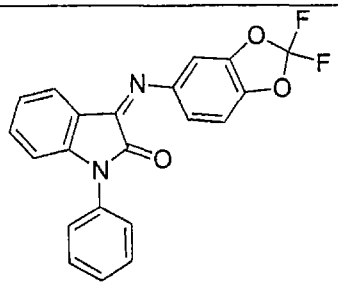
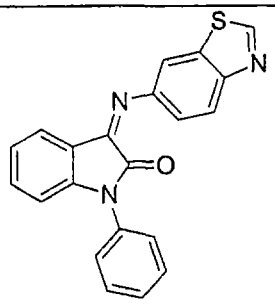
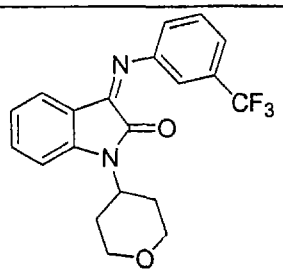
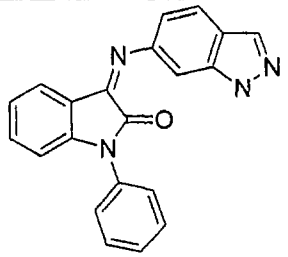
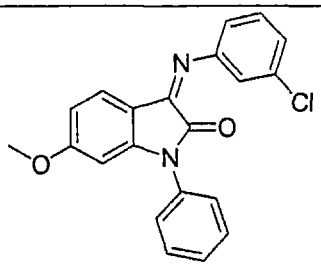
298		22
299		377
300		742
301		875
302		150

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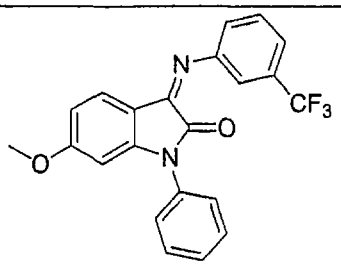
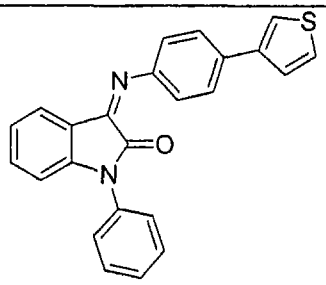
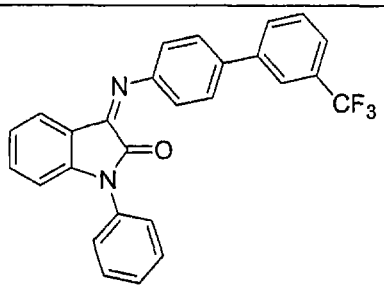
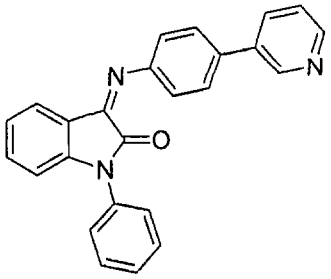
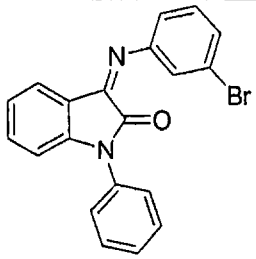
303		214
304		728
305		638
306		160
307		41

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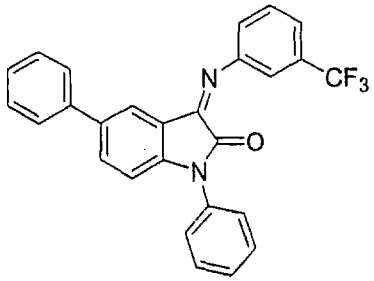
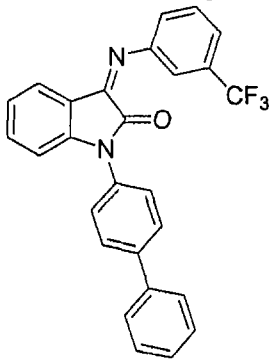
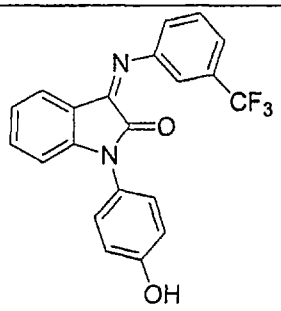
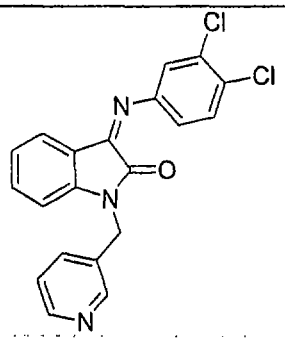
308		98
309		224
310		126
311		32

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

I. In-Vivo Models

A. Materials and Methods

1. Forced Swim Test (FST)

The procedure used in this study was similar to that previously described (Porsolt, et al., 1978), except the water depth (30 cm in this procedure). The greater depth in this test prevented the rats from supporting themselves by touching the bottom of the cylinder with their feet. Swim sessions were conducted by placing rats in individual plexiglass cylinders (46 cm tall x 20 cm in diameter) containing 23-25°C water 30 cm deep (Porsolt, et al. used a depth of only 15 cm; also, see Detke, et al., 1995). Two swim tests were conducted always between 1200 and 1800 hours: an initial 15-min pretest followed 24 h later by a 5-minute test. Drug treatments were administered 60 minutes before the 5-minute test period. All other test sessions were conducted between 1300 to 1700 hours. Following all swim sessions, rats were removed from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes and returned to their home cages. All test sessions were videotaped using a Panasonic color video camera and recorder for scoring later.

Animals

Male Sprague-Dawley rats (Taconic Farms, NY) were used in all experiments. Rats were housed in pairs and maintained on a 12:12-h light-dark cycle. Rats were handled for 5 minutes each day for 5 days prior to behavioral testing.

Behavioral Scoring

The rat's behavior was rated at 5 second intervals during the 5 minute test as one of the following:

1. Immobility- rat remained floating in the water without struggling and was only making those movements necessary to keep its head above water;

2. Climbing - rat was making active movements with its forepaws in and out of the water, usually directed against the walls;

3. Swimming - rat was making active swimming motions, more than necessary to merely maintain its head above water, e.g. moving around in the cylinder; and

4. Diving - entire body of the rat was submerged.

All of the behavior scoring was done by a single rater, who was blind to the treatment condition. The rater was also present in the room throughout the entire test period.

Drug Administration

Animals were randomly assigned to receive a single i.p.

administration of Example 92 (1, 3, 10 or 30 mg/kg, dissolved in 100% DMSO), fluoxetine (10 mg/kg, dissolved in distilled water) or vehicle (equal mixture of DMSO and distilled water) 30 minutes before the start of the 5 minute test period. All injections were given using 1 cc tuberculin syringe with 26 3/8 gauge needles (Becton-Dickinson, VWR Scientific, Bridgeport, NJ). The volume of injection was 1 ml/kg.

In another set of experiments, animals were randomly assigned to receive a single p.o. administration of one of the following treatments: Example 151 (1, 3 or 10 mg/kg), fluoxetine (5 or 10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period. The drugs were dissolved in 100% N,N-dimethylacetamide. All administrations were given using 1 cc tuberculin syringes, to which a 3 inch, curved, stainless steel gavage needle was attached. The volume of administration was 1 ml/kg.

In other sets of experiments, animals were randomly assigned to receive a single p.o. administration of one of the following treatments: Example 103 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 272 (3 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 24 hours before the start of the 5 minute test period; or Example 98 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 34 (0.3, 1, 3 and 10

mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of a 100% solution of dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 49 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 22 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period. The compounds were dissolved in 100% N,N-dimethylacetamide. All administrations were given using 1 cc tuberculin syringes, to which a 3 inch, curved, stainless steel gavage needle was attached. The volume of administration was 1 ml/kg.

The effect of 5 or 10 mg/kg of fluoxetine was utilized in the FST as a positive control.

Data Analysis

The forced swim test data (immobility, swimming, climbing, diving) were subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Student-Newman-Keuls test. The data were analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, MD, 1997). All data are presented as means ± S.E.M.

2. Social Interaction Test (SIT)

Rats were allowed to acclimate to the animal care facility for 5 days and were housed singly for 5 days prior to testing. Animals were handled for 5 minutes per day. The design and procedure for the Social Interaction

Test was carried out as previously described by Kennett, et al. (1997). On the test day, weight matched pairs of rats (± 5%), unfamiliar to each other, were given identical treatments and returned to their home cages. Animals were randomly divided into 5 treatment groups, with 5 pairs per group, and were given one of the following i.p. treatments: Example 92 (10, 30 or 100 mg/kg), vehicle (1 ml/kg) or chlordiazepoxide (5 mg/kg). Dosing was 1 hour prior to testing. Rats were subsequently placed in a white perspex test box or arena (54 x 37 x 26 cm), whose floor was divided up into 24 equal squares, for 15 minutes. An air conditioner was used to generate background noise and to keep the room at approximately 74°F. All sessions were videotaped using a JVC camcorder (model GR-SZ1, Elmwood Park, NJ) with either TDK (HG ultimate brand) or Sony 30 minute videocassettes. All sessions were conducted between 1:00 - 4:30 P.M. Active social interaction, defined as grooming, sniffing, biting, boxing, wrestling, following and crawling over or under, was scored using a stopwatch (Sportsline model no. 226, 1/100 sec. discriminability). The number of episodes of rearing (animal completely raises up its body on its hind limbs), grooming (licking, biting, scratching of body), and face washing (i.e. hands are moved repeatedly over face), and number of squares crossed were scored. Passive social interaction (animals are lying beside or on top of each other) was not scored. All behaviors were assessed later by an observer who was blind as to the treatment of each pair. At the end of each test, the box was thoroughly wiped with moistened paper towels.

Animals

Male albino Sprague-Dawley rats (Taconic Farms, NY) were housed in pairs under a 12 hr light dark cycle (lights on at 0700 hrs.) with free access to food and water.

Drug Administration

Example 92 was dissolved in 100% DMSO (Sigma Chemical Co., St. Louis, MO). Chlordiazepoxide (purchased from Sigma Chemical Co., St. Louis, MO) was dissolved in double distilled water. The vehicle consisted of 50% DMSO (v/v). All drug solutions were made up 10 minutes prior to injection and the solutions were discarded.

Example 34 was dissolved in 5% lactic acid, v/v. The vehicle consisted of 100% dimethylacetamide (DMA) and this was used to make up all drug solutions. All drug solutions were made up fresh each day and any unused solutions were discarded at the end of the test day. The volume of drug solution administered was 1 ml/kg.

Data Analysis

The social interaction data (time interacting, rearing and squares crossed) were subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Student-Newman-Keuls test. The data were subjected to a test of normality (Shapiro-Wilk test). The data were analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, MD, 1997). All data are presented as means ± S.E.M.

B. Results

1. Forced Swim Test

A. The Effect Of Vehicle, Fluoxetine and Example 92 On Immobility, Climbing and Swimming In The Forced Swim Test

Immobility

Statistical analysis indicated that there was a significant drug effect [$F(4,45) = 12.1$, $p < 0.0001$] on immobility. Subsequent post hoc analysis revealed that a single injection of 10 mg/kg i.p. of fluoxetine significantly decreased immobility to 21.0 ± 0.9 (Student-Newman-Keuls value was 36.5, $p < 0.01$) compared to vehicle-treated controls (Table 5 and Figure 1). In addition, a single injection of either 3 or 10 mg/kg i.p. of Example 92 significantly decreased immobility (24 ± 1.1 & 24 ± 0.8 counts at each dose, respectively) compared to vehicle-treated controls 30 ± 1.2 (Student-Newman-Keuls values of 16.8 and 15.7, respectively) (Table 5 and Figure 1). No significant effects on immobility were observed with Example 92 at 30 mg/kg i.p. (Table 5 and Figure 1).

Climbing

The statistical analysis of the climbing counts indicated that there was a significant drug effect [$F(4,45) = 4.4$, $p = 0.004$]. Post hoc analysis indicated that a single injection of 10 mg/kg of fluoxetine did not significantly alter climbing counts compared to vehicle-treated animals (Table 5 and Figure 2). In contrast, a single injection of 10 mg/kg of Example 92 produced a significant increase (16.8 ± 0.6) in climbing counts (Student-Newman-Keuls value = 11.6, $p < 0.01$) compared to vehicle-treated

animals (12 ± 0.8). Example 92 dosed at 1, 3 & 30 mg/kg did not significantly alter climbing.

Swimming

The statistical analysis of the swimming data indicated that there was a significant drug effect [$F(4,45) = 6.6$, $p < 0.0001$] (Table 5 and Figure 3). The post hoc test showed that a single injection of 10 mg/kg i.p. of fluoxetine produced a significant increase (25 ± 1.2) in swimming counts over the vehicle treated animals, 18 ± 1 (Student-Newman-Keuls value of 19.9, $p < 0.01$). In contrast, a single injection of 1, 3 or 10 mg/kg i.p. of Example 92 did not significantly alter swimming counts 20 ± 1.1, 21 ± 0.9,& 18 ± 0.9, respectively (Table 5 and Figure 3). (However, at 30 mg/kg i.p. Example 92 significantly increased swim behavior in the rat, comparable to fluoxetine at 10 mg/kg i.p. (27 ± 2.5 vs. 25 ± 1.2, Table 5 and Figure 3).

Diving

This behavior was rarely observed following a single injection of vehicle (0.1 ± 0.1, one animal dove once), fluoxetine (0.1 ± 0.1, one animal out of 10 dove once), 1 mg/kg of Example 92 (0.6 ± 0.2; 5 animals had counts of 2, 1, 1, 1, and 1), 3 mg/kg of Example 92 (0.6 ± 0.3; 3 animals had counts of 3, 2 and 1) or 10 mg/kg of Example 92 (0.5 ± 0.5; note: only one animal at this dose showed diving behavior and the score was 5). At 30 mg/kg i.p. of Example 92 diving behavior was only observed in two animals (mean = 0.2 ± 0.2). Thus there was no significant drug effect on diving [$F(4,45) = 0.77$, $p = 0.55$].

Table 5. The effect of a single injection of vehicle, fluoxetine and Example 92 on immobility, climbing and swimming in the rat Forced Swim Test.

Treatment	Dose (mg/kg)	Immobility	Climbing	Swimming
Vehicle	---------	30 ± 1.2	12.0 ± 0.8	18 ± 1
Fluoxetine	10	21 ± 0.9[a]	14.3 ± 0.9	25 ± 1.2[b]
Example 92	1	28 ± 1.0	11.7 ± 1.1	20 ± 1.1
Example 92	3	24 ± 1.1[a]	14.6 ± 1.5	21 ± 0.9
Example 92	10	24 ± 0.8[a]	16.8 ± 0.6[c]	18 ± 0.9
Example 92	30	25 ± 3.5	8.6 ± 1.7	27 ± 2.5[d]

Each value represents the mean number of counts per 5 seconds ± S.E.M in a 5 minute observation period.

[a] Significantly less than Vehicle on immobility scores, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[b] Significantly greater than Vehicle and 1,3 & 10 of Example 92, on swim scores, $p < 0.01$, ANOVA and Student-Newman-Keuls.

[c] Significantly greater than vehicle and 1, 3 & 30 mg/kg dose of Example 92 on climbing scores, $p < 0.01$, ANOVA and Student-Newman-Keuls

[d] Significantly greater than Vehicle, 1, 3 and 10 mg/kg i.p. of Example 92 on swim scores, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

The results of the Forced Swim Test indicate that using a modified version of the Lucki forced swim test, a single injection of 10 mg/kg i.p. of fluoxetine produced a significant decrease in immobility and an increase in swimming in male Sprague-Dawley rats. This is consistent with findings from previous studies using the Lucki version (Detke, et al., 1995; Kirby and Lucki, 1997; Lucki, 1997; Page, et al., 1999; Reneric and Lucki, 1998). In addition, the results obtained using fluoxetine are consistent with those using other SSRIs (Detke, et al., 1995). Thus, a modified version of the Lucki forced swim test can consistently detect the antidepressant action of SSRIs such as fluoxetine.

Interestingly, at doses of 3 and 10 mg/kg i.p., Example 92, significantly decreased immobility compared to vehicle-treated animals. The magnitude of the decrease was not significantly different than that of fluoxetine. Thus, based on past interpretations of the Forced Swim Test, our results suggest that Example 92 has antidepressant-like properties.

A single injection of either 1, 3 or 10 mg/kg i.p. of Example 92 did not significantly alter swimming behavior. This is in contrast to the results obtained with fluoxetine, which increased swimming at 10 mg/kg i.p. Previously, it has been reported that compounds which selectively block serotonin uptake significantly increase swimming but not climbing whereas selective NE uptake blockers significantly increase climbing but not swimming behavior (Reneric and Lucki, 1998). Thus, the present

findings suggest that Example 92 exhibits a profile similar to NE and selective serotonin reuptake inhibitors (SSRIs) depending on the dose tested.

Finally, as previously reported by Lucki, diving behavior was rarely observed in vehicle or fluoxetine-treated animals (1 dive in one rat for each group). Example 92 at all doses tested did not produce a significant effect on diving behavior. It is possible that antidepressant drugs do not induce diving behavior.

In conclusion, compared to vehicle-treated animals, Example 92, at doses of 3 and 10 mg/kg, produced a significant decrease in immobility and a significant increase in climbing at the 10 mg/kg dose. At 30mg/kg i.p. Example 92 produced a significant increase in swimming behavior comparable with that observed with the antidepressant fluoxetine, thus supporting the antidepressant-like profile of Example 92.

B. The effect of Example 151, fluoxetine, and vehicle on swimming, climbing, immobility, and diving in the forced swim test.

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(5,46) = 3.5$, $p = 0.0095$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Fisher's LSD value of 2.9) compared to vehicle-treated animals (Table 5a). In contrast, a single p.o. administration of 5 mg/kg of fluoxetine did

not significantly alter immobility compared to vehicle-treated animals.

A single p.o. administration of 1 mg/kg of Example 151 did not significantly alter immobility compared to vehicle-treated animals (Table 5a). In contrast, a single p.o. administration of either 3 or 10 mg/kg of Example 151 significantly decreased immobility compared to animals treated with vehicle (Fisher's LSD values of 2.8 and 2.6, respectively) or 5 mg/kg p.o. of fluoxetine (Fisher's LSD values of 2.6 and 2.4, respectively). There was no significant difference in the reduction in immobility between 10 mg/kg of fluoxetine and 3 and 10 mg/kg of Example 151.

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(5,46) = 5.5$, $p = 0.0005$). *Post hoc* analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to vehicle-treated animals (Student-Newman-Keuls value of 16.8 (Table 5a). In contrast, a single p.o. administration of 5 mg/kg of fluoxetine did not significantly alter swimming compared to vehicle-treated animals.

A single p.o. administration of either 1, 3 or 10 mg/kg of Example 151 significantly increased swimming (Student-Newman-Keuls values of 6.9, 14.8 and 13.4, respectively) compared to vehicle-treated animals. There was no significant difference in the magnitude of the increase

in swimming between the doses of Example 151. The 3 and 10 mg/kg doses of Example 151 produced a significantly greater increase in swimming compared to animals treated with 5 mg/kg p.o. of fluoxetine. There was no significant difference in the increase in swimming between animals treated with 10 mg/kg of fluoxetine and those treated with Example 151.

Climbing behavior

Statistical analysis revealed that climbing was not significantly altered by a single p.o administration of 1, 3 or 10 mg/kg of Example 151 or 5 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(5,46) = 0.81$, $p = 0.55$)(Table 5a).

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 1, 3 or 10 mg/kg of Example 151 or 5 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(5,46) = 0.36$, $p = 0.87$)(Table 5a).

TABLE 5a. The effect of a single p.o. administration of vehicle, 1, 3 and 10 mg/kg of Example 151 and 5 and 10 mg/kg of fluoxetine on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	46 ± 1.8	2.7 ± 0.7	11.4 ± 1.2	0.4 ± 0.4
1 mg/kg EX151	41 ± 2.0	2.3 ± 0.6	16.8 ± 1.4[d]	0.2 ± 0.2
3 mg/kg EX151	38 ± 2.0[a]	2.4 ± 0.5	19.5 ± 1.5[e]	0.3 ± 0.2
10 mg/kg EX151	39 ± 1.8[b]	2.2 ± 0.5	18.9 ± 1.5[e]	0.3 ± 0.2
5 mg/kg Fluox	45 ± 1.3[c]	1.2 ± 0.4	13.9 ± 1.0	0.0 ± 0.0
10 mg/kg Fluox	38 ± 2.3[a]	2.0 ± 0.6	19.8 ± 1.8[e]	0.6 ± 0.6

Each value represents the mean ± S.E.M. A total of 8-9 animals were examined for each treatment group. Fluox = Fluoxetine, EX151 = Example 151. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly less than Vehicle ($p < 0.01$), ANOVA and Fisher's protected t test.

[b]Significantly less than Vehicle ($p < 0.05$), ANOVA and Fisher's protected t test.

[c]Significantly greater than 3 and 10 mg/kg of Example 151 and 10 mg/kg of fluoxetine, ANOVA and ANOVA and Fisher's protected t test.

[d]Significantly greater than Vehicle ($p < 0.05$) and 5 mg/kg of fluoxetine($p < 0.05$), ANOVA and Student-Newman-Keuls test.

[e]Significantly greater than Vehicle ($p < 0.01$) and 5 mg/kg of fluoxetine($p < 0.05$), ANOVA and Student-Newman-Keuls test.

The results of this study indicate that a single p.o. administration of Example 151, at doses of 1,3 and 10 mg/kg, produces a significant increase in swimming behavior. There was no significant difference in the magnitude of the increase in swimming between the doses of Example 151, although the 1 mg/kg dose produced a lower increase. In contrast, only the 3 and 10 mg/kg doses of Example 151 significantly decreased immobility compared to vehicle-treated animals. Thus, it appears that a single p.o. administration of either 3 or 10 mg/kg, compared to 1 mg/kg of Example 151, produce a more robust antidepressant profile in the FST in male Sprague-Dawley rats. Our results also indicate that Example 151 produced changes in swimming and immobility that were not significantly different from that of 10 mg/kg p.o. of fluoxetine. This suggests that Example 151 produces behavioral effects similar to that of 10 mg/kg of fluoxetine in the FST.

A single p.o. administration of 5 mg/kg of fluoxetine did not significantly alter swimming, climbing, diving or immobility compared to vehicle treated animals. This finding, together with the data indicating that 10 mg/kg of fluoxetine produces a significant effect on swimming

and immobility in the FST, suggest that the threshold dose of fluoxetine is greater than 5, but less than 10 mg/kg. This is consistent with *ex vivo* data indicating that a p.o. dose of 7 mg/kg of fluoxetine is required to inhibit 5-HT uptake in the CNS by 50% (Leonard, 1996).

In conclusion, the results of this study indicate that a single p.o. administration of Example 151 (particularly the 3 and 10 mg/kg doses) produces behavioral effects in the FST in rats that resemble those of antidepressants.

C. The Effect of a Single P.O. Administration of Example 103, Fluoxetine and Vehicle on Swimming, Immobility, Climbing and Diving in the Forced Swim Test

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(4,40) = 6.3$, $p = 0.0005$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 8.3) compared to vehicle-treated animals (Table 5b). The decrease in immobility produced by fluoxetine was significantly greater than that of either 3 or 10 mg/kg p.o. of Example 103 (Student-Newman-Keuls values of 9.1 and 6.1, respectively).

A single p.o. administration of either 3 or 10 mg/kg of Example 103 did not significantly alter immobility compared to vehicle-treated animals. However, the 30 mg/kg dose of Example 103 produced a significant decrease in immobility (Student-Newman-Keuls values of 13.9)

compared to vehicle-treated animals. In addition, the decrease in immobility produced by 30 mg/kg of Example 103 was significantly greater than that of 3 and 10 mg/kg of Example 103 (Student-Newman-Keuls values of 14.4 and 10.6, respectively). There was no significant difference between fluoxetine and 30 mg/kg of Example 103 in the reduction of immobility.

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(4,40) = 9.2$, $p < 0.0001$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to animals treated with vehicle, 3 or 10 mg/kg p.o. of Example 103 (Student-Newman-Keuls values of 14.9, 15.3 and 11.6, respectively) (Table 5b).

A single p.o. administration of either 3 or 10 mg/kg of Example 103 did not significantly alter swimming behavior compared to vehicle-treated animals. A single p.o. administration of 30 mg/kg of Example 103 produced a significantly greater increase in swimming behavior compared to animals treated with either vehicle, 3 or 10 mg/kg of Example 103 (Student-Newman-Keuls values of 18, 18.6 and 14.5 respectively).

Climbing behavior

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 103 or 10 mg/kg of

fluoxetine compared to vehicle-treated animals (ANOVA, $F(4,40) = 1.2$, $p = 0.31$)(Table 5b).

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 103 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(4,40) = 1.1$, $p = 0.36$)(Table 5b).

TABLE 5b. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 103 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	44 ± 1.7	2.9 ± 0.7	13.1 ± 1.2	0.4 ± 0.2
3 mg/kg EX103	44 ± 2.7	2.8 ± 0.6	13.2 ± 1.9	0.5 ± 0.4
10 mg/kg EX103	42 ± 2.2	3.5 ± 0.6	14.3 ± 1.6	0.4 ± 0.2
30mg/kg EX103	32 ± 1.8[a]	4.8 ± 0.7	22.7 ± 1.1[c]	1.1 ± 0.5
10 mg/kg Fluox	34 ± 2.3[b]	3.8 ± 0.8	21.8 ± 1.4[c]	0.1 ± 0.1

Each value represents the mean ± S.E.M. A total of 8-10 animals were examined for each treatment group. Fluox = Fluoxetine, EX103 = Example 103. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly less than Vehicle, 3 and 10 mg/kg of Example 103, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[b]Signficantly less than Vehicle, 3 and 10 mg/kg of Example 103, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[c]Signficantly greater than Vehicle, 3 and 10 mg/kg of Example 103, P < 0.01, ANOVA and Student-Newman-Keuls test.

The results of this study indicated that as previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility in male rats in the FST compared to vehicle-treated animals. The magnitude of these changes are similar to those reported of our past studies with 10 mg/kg p.o. of fluoxetine. In contrast, neither climbing nor diving behavior was significantly altered by a single p.o. administration of 10 mg/kg of fluoxetine.

A single p.o. administration of either 3 or 10 mg/kg of Example 103 did not significantly alter swimming, climbing, immobility or diving in male rats in the FST, indicating that at these doses using the p.o. route, Example 103 does not exhibit antidepressant action in the FST. In contrast, a single p.o. administration of 30 mg/kg of Example 103 produced a significant increase in swimming and a significant decrease in immobility compared to animals treated with vehicle or 10 mg/kg of Example 103. However, the 30 mg/kg p.o. dose of Example 103 did not significantly alter diving or climbing counts compared to vehicle-treated animals. The increase in swimming counts produced by 30 mg/kg p.o. of Example 103 was comparable to that for 10 mg/kg of fluoxetine.

In conclusion, a single p.o. administration of 30 mg/kg of Example 103 (one hour before the last swim test)

increases swimming and decreases immobility counts in the FST, suggesting that Example 103 has antidepressant properties.

D. Effect of a single p.o. administration of Example 272, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(2,27) = 5.2$, $p = 0.0126$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine and 3 mg/kg of Example 272 significantly decreased immobility (Student-Newman-Keuls values of 5.4 and 9.8, respectively) compared to vehicle-treated animals (Table 5c). There was no significant difference between fluoxetine and 3 mg/kg of Example 272 in the reduction of immobility (Student-Newman-Keuls value of 0.53).

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(2,27) = 9.9$, $p < 0.0007$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine and Example 272 produced a significant increase in swimming behavior compared to animals treated with vehicle (Student-Newman-Keuls values of 11.9 and 17.5, respectively) (Table 5c). There was no significant difference in the increase in swimming between 10 mg/kg of fluoxetine and 3 mg/kg of Example 272 (Student-Newman-Keuls value of 0.42).

Climbing behavior

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of either 3 mg/kg of Example 272 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(2,27) = 1.8$, $p = 0.19$) (Table 5c).

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3 mg/kg of Example 272 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(2,27) = 0.65$, $p = 0.53$) (Table 5c).

TABLE 5c. The effect of a single p.o. administration of vehicle, fluoxetine and Example 272 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	43 ± 3.3	2.4 ± 0.4	13.4 ± 2.2	0.2 ± 0.1
3 mg/kg EX272	33 ± 1.8[a]	3.9 ± 0.6	22.9 ± 1.3[b]	0.6 ± 0.4
10 mg/kg FLUOX	35 ± 1.7[a]	3.3 ± 0.6	21.4 ± 1.0[b]	0.2 ± 0.1

Each value represents the mean ± S.E.M. A total of 9-10 animals were examined for each treatment group. Abbreviations: FLUOX = Fluoxetine, EX272 = Example 272. Animals received 1 p.o. administration of the appropriate treatment 24 hours before the test day.

[a]Significantly less than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[b]Significantly less than Vehicle, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

The finding of this study indicate that a single p.o. administration of 3 mg/kg of the compound Example 272 produced a significant increase in swimming and a significant decrease in immobility 24 hours after administration compared to vehicle-treated animals. However, the administration of Example 272 did not significantly alter climbing or diving compared to

vehicle-treated animals. These results are similar to those of a single p.o. administration of 10 mg/kg of fluoxetine. Our finding suggest that a single p.o. administration of 3 mg/kg of Example 272 has the profile of an antidepressant in male Sprague-Dawley rats in the Lucki version of the FST.

E. Effect of a single p.o. administration of Example 98, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test.

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(4,43) = 7.5$, $p = 0.0001$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 23.8) compared to vehicle-treated animals (Table 5d).

A single p.o. administration of 3, 10 or 30 mg/kg of Example 98 significantly decreased immobility compared to vehicle-treated animals (Student-Newman-Keuls values of 19.3, 9.7 and 13.7, respectively). There was no significant difference between fluoxetine and 3, 10 or 30 mg/kg of Example 98 in the magnitude of the reduction of immobility. There were no significant differences between the doses of Example 98 regarding the magnitude of the decrease in immobility.

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(4,43) = 11$, $p <$

0.0001). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to vehicle-treated animals (Student-Newman-Keuls value of 35.1) (Table 5d).

A single p.o. administration of 3, 10 or 30 mg/kg of Example 98 significantly increased swimming compared to vehicle-treated animals (Student-Newman-Keuls values of 24.4, 14.7 and 25.1, respectively) (Table 5d). There was no significant difference between fluoxetine and 3, 10 or 30 mg/kg of Example 98 in the magnitude of the increase in swimming. There were no significant differences between the doses of Example 98 regarding the magnitude of the increase in immobility.

Climbing behavior

There was a significant treatment effect on climbing behavior (ANOVA, $F(4,43) = 2.8$, $p = 0.04$) (Table 5d). Post hoc tests indicated that this was the result of the 3 mg/kg dose of Example 98 producing a significantly greater increase in climbing compared to 30 mg/kg of Example 98 (Table 5d; Student-Newman-Keuls value of 8.6). There was no significant difference in the number of climbing counts between animals treated with vehicle and Example 98.

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 98 or 10 mg/kg of fluoxetine

compared to vehicle-treated animals (ANOVA, $F(4,43) = 1.29$, $p = 0.29$) (Table 5d).

TABLE 5d. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 98 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	48 ± 1.2	2.5 ± 0.5	8.8 ± 0.9	0.4 ± 0.3
3 mg/kg EX98	35 ± 2.6[a]	4.3 ± 0.9[b]	20.4 ± 1.9[c]	0.1 ± 0.1
10 mg/kg EX98	39 ± 1.1[a]	2.4 ± 0.3	17.6 ± 1.0[c]	0.8 ± 0.4
30 mg/kg EX98	38 ± 2.3[a]	2.0 ± 0.3	20.3 ± 2.1[c]	0.2 ± 0.2
10 mg/kg Fluox	34 ± 3.0[a]	3.4 ± 0.8	22.8 ± 2.2[c]	0.1 ± 0.1

Each value represents the mean ± S.E.M. A total of 10 animals were examined for each treatment group, except for the fluoxetine and 3 mg/kg groups, where a total of 9 animals were examined. Vehicle = 100% DMA.

Fluox = Fluoxetine, EX98 = Example 98. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly less than Vehicle, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[b]Significantly greater than 30 mg/kg of Example 98, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[c]Significantly greater than Vehicle, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

The results of this study clearly indicate that in male Sprague-Dawley rats, a single p.o. administration of 3, 10 or 30 mg/kg of Example 98 produces a significant increase in swimming and a significant decrease in immobility compared to vehicle-treated animals in the FST. In addition, the Example 98 induced alterations were similar in magnitude to that of a single p.o. administration of 10 mg/kg p.o. of fluoxetine. However, neither fluoxetine nor Example 98 produced a significant alteration in climbing or diving compared to vehicle-treated animals.

In conclusion, these results indicate that a single p.o. administration of Example 98 produces a profile in the modified Lucki version of the FST resembling that of the clinically established antidepressant fluoxetine.

F. Effect of a single p.o. administration of Example 34, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test.

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(5,44) = 18.1$, $p < 0.0001$). Post hoc analyses revealed that a single p.o.

administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 39.6) compared to vehicle-treated animals (Table 5e). Fluoxetine also produced a significantly greater decrease in immobility compared to the 0.3 and 10 mg/kg doses of Example 34 (Student-Newman-Keuls values of 15.3 and 29.8, respectively). There was no significant difference in the magnitude of the decrease in immobility between fluoxetine and the 1 and 3 mg/doses of Example 34.

A single p.o. administration of 0.3, 1 and 3 mg/kg of Example 34 significantly decreased immobility compared to vehicle-treated animals (Student-Newman-Keuls values of 7.03, 41.6 and 42.0, respectively)(Table 5e). However, a single p.o. administration of 10 mg/kg of Example 34 did not significantly decrease in immobility compared to vehicle-treated animals. The magnitude of the decrease in immobility produced by 1 and 3 mg/kg doses of Example 34 was significantly greater than that for the 0.3 (Student-Newman-Keuls values of 14.5 and 15.3) and 10 mg/kg (Student-Newman-Keuls of 30.6 and 31.3, respectively) doses of Example 34 (Student-Newman-Keuls of 21.3 and 10.8, respectively).

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(5,44) = 33.0$, $p < 0.0001$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming compared to animals treated with vehicle, 0.3 or 10 mg/kg of Example 34 (Student-Newman-Keuls values of 73.7, 30.0 and 53.9,

respectively) (Table 5e). There was no significant difference in swimming behavior between fluoxetine and the 1 and 3 mg/kg p.o. of Example 34.

A single p.o. administration of either 0.3, 1 or 3 mg/kg of Example 34 produced a significant increase in swimming behavior compared to vehicle-treated animals (Student-Newman-Keuls values of 12.1, 72.1 and 80.3, respectively) (Table 5e). In addition, the magnitude of the increase in swimming was greater for the 1 and 3 mg/kg doses (Student-Newman-Keuls values of 50.4 and 57.9, respectively) compared to 0.3 mg/kg of Example 34.

Climbing behavior

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(5,44) = 3.2.$, $p = 0.014$)(Table 5e). Post hoc analyses revealed that a single p.o. administration of 1 mg/kg of Example 34 produced a significant increase in climbing compared to vehicle-treated animals (Student-Newman-Keuls value of 9.2) (Table 5e)

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 0.3, 1, 3 or 10 mg/kg of Example 34 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(5,44) = 0.75$, $p = 0.59$)(Table 5e).

TABLE 5e. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and Example 34 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	52 ± 1.3	2.1 ± 0.6	6.0 ± 0.6	0.8 ± 0.7
0.3 mg/kg EX34	45 ± 1.5[a]	3.3 ± 0.7	11.6 ± 0.9[d]	0.2 ± 0.1
1 mg/kg EX34	35 ± 1.9[b]	5.0 ± 0.8[c]	19.6 ± 1.3[d,e]	0.3 ± 0.2
3 mg/kg EX34	35 ± 2.0[b]	4.3 ± 0.8	20.8 ± 1.3[d,e]	0.3 ± 0.3
10 mg/kg EX34	49 ± 1.4	2.0 ± 0.4	8.2 ± 1.2	0.4 ± 0.3
10 mg/kg Fluox	34 ± 3.3[b]	4.5 ± 1.2	21.3 ± 1.8[d,e]	1.0 ± 0.8

Each value represents the mean ± S.E.M. A total of 9 animals were examined for each treatment group, except for the 3 mg/kg Example 34 and fluoxetine groups, were a total of 8 and 6 animals were examined, respectively. Fluox = Fluoxetine, EX34 = Example 34. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly less than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[b]Significantly less than Vehicle, 0.3 and 10 mg/kg of Example 34, ANOVA and Student-Newman-Keuls test.

[c]Significantly greater than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[d]Significantly greater than Vehicle ($p < 0.01$) and 10 mg/kg Example 34 (all $p < 0.01$ except for 0.3 mg/kg of Example 34, $p < 0.05$), ANOVA and Student-Newman-Keuls test.

[e]Significantly greater 0.3 mg/kg of Example 34, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

The results of this study indicate that a single p.o. administration (one hour before the final swim test) of either 0.3, 1 or 3 mg/kg of Example 34 produced a significant increase in swimming and a significant decrease in immobility compared to vehicle-treated animals. However, a single p.o. administration of 10 mg/kg of Example 34 did not significantly alter swimming or climbing compared to vehicle-treated animals. Currently, the explanation for the lack of effect of 10 mg/kg p.o. of Example 34 is unknown. The 1 mg/kg dose of Example 34 produced a significant increase in climbing compared to vehicle-treated animals. The magnitude of the alterations in swimming and immobility produced by 1 and 3 mg/kg p.o. of Example 34 was significantly greater than that for the 0.3 and 10 mg/kg doses of Example 34. Finally, none of the doses of Example 34 significantly

altered diving behavior compared to vehicle-treated controls.

As previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility compared to vehicle-treated controls. The effect of fluoxetine on swimming and immobility was similar to that for the 1 and 3 mg/kg doses of Example 34 but was significantly greater than that of 0.3 and 10 mg/kg of Example 34. A single p.o. administration of 10 mg/kg of fluoxetine did not significantly alter climbing or diving behavior compared to vehicle-treated controls.

In conclusion, these results indicate that a single p.o. administration of 0.3, 1 or 3 mg/kg Example 34 produces an effect in the FST that resembles that of antidepressants in male Sprague-Dawley rats.

G. Effect of a single p.o. administration of Example 49, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test.

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(4,41) = 6.5$, $p = 0.0004$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 15.6) compared to vehicle-treated animals (Table 5f).

A single p.o. administration of either 3 or 10 mg/kg of Example 49 did not significantly alter immobility compared to vehicle-treated animals. However, the 30 mg/kg dose of Example 49 produced a significant decrease in immobility (Student-Newman-Keuls values of 8.0) compared to vehicle-treated animals. In addition, the decrease in immobility produced by either fluoxetine or 30 mg/kg of Example 49 was significantly greater than that of the 10 mg/kg dose of Example 49. There was no significant difference between fluoxetine and 30 mg/kg of Example 49 in the reduction of immobility.

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(4,41) = 16.2$, $p < 0.0001$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to animals treated with vehicle, 3, 10 or 30 mg/kg p.o. of Example 49 (Student-Newman-Keuls values of 42.7, 20.9, 47.5 and 8.4, respectively) (Table 5f).

A single p.o. administration of either 3 or 10 mg/kg of Example 49 did not significantly alter swimming behavior compared to vehicle-treated animals. A single p.o. administration of 30 mg/kg of Example 49 produced a significantly greater increase in swimming behavior compared to animals treated with vehicle, 3 or 10 mg/kg of Example 49 (Student-Newman-Keuls values of 14 and 16.9, respectively).

Climbing behavior

There was a significant treatment effect on climbing behavior (ANOVA, $F(4,42) = 5.9$, $p = 0.007$). Post hoc tests indicated that this was the results of the vehicle, 3, 10 and 30 mg/kg doses of Example 49 producing a significantly greater increase in climbing counts compared to fluoxetine-treated animals (Table 5f; Student-Newman-Keuls values of 7.9, 18.1, 14.05 and 12.9, respectively). There was no significant difference in the number of climbing counts between animals treated with vehicle and Example 49.

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 49 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(4,41) = 1.06$, $p = 0.38$)(Table 5f).

TABLE 5f. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 49 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	47 ± 1.2	1.8 ± 0.3	10.6 ± 1.1	0.2 ± 0.2
3 mg/kg EX 49	43 ± 1.9	3.0 ± 0.7	13.1 ± 1.4	1.0 ± 0.7
10 mg/kg EX49	48 ± 1.7	2.4 ± 0.7	10.0 ± 1.0	0.0 ± 0.0
30 mg/kg EX49	41 ± 2.0[a]	2.3 ± 0.4	16.7 ± 1.3[d]	0.4 ± 0.4
10 mg/kg Fluox	38 ± 1.3[b]	0.0 ± 0.0[c]	21.6 ± 1.1[e]	0.8 ± 0.5

Each value represents the mean ± S.E.M. A total of 10 animals were examined for each treatment group, except for the fluoxetine and 3 mg/kg groups, where a total of 9 and 7 animals were examined, respectively.

Fluox = Fluoxetine, EX49 = Example 49. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly less than Vehicle and 10 mg/kg of Example 49, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[b]Signficantly less than Vehicle and 10 mg/kg of Example 49, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[c]Signficantly less than all other treatment groups, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[d]Signficantly greater than vehicle and 10 mg/kg of Example 49, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[e]Signficantly greater than all other treatment groups, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

The results of this study indicated that as previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility in male rats in the FST compared to vehicle-treated animals. The magnitude of these changes are similar to those reported of our past studies with 10 mg/kg p.o. of fluoxetine. In contrast, climbing behavior was significantly decreased by a single p.o. administration of 10 mg/kg of fluoxetine compared to all other treatment groups. However, this could be related to the fact that fluoxetine has a much greater effect on swimming than climbing and it is likely that fluoxetine is not producing climbing as opposed to actually decreasing climbing. Finally, fluoxetine, as previously reported, does not significantly alter diving compared to vehicle-treated behavior.

A single p.o. administration of either 3 or 10 mg/kg of Example 49 did not significantly alter swimming, climbing, immobility or diving in male rats in the FST, indicating that at these doses using the p.o. route, Example 49 does not exhibit antidepressant action in the FST. In contrast, a single p.o. administration of 30

mg/kg of Example 49 produced a significant increase in swimming and a significant decrease in immobility compared to animals treated with vehicle, or 3 and 10 mg/kg of Example 49. However, the 30 mg/kg p.o. dose of Example 49 did not significantly alter diving or climbing counts compared to vehicle-treated animals. The increase in swimming counts produced by 30 mg/kg p.o. of Example 49 was comparable to that of 10 mg/kg of fluoxetine, although Example 49 was less effective than fluoxetine in reducing immobility.

In conclusion, a single p.o. administration of 30 mg/kg of Example 49 (one hour before the last swim test) increases swimming and decreases immobility counts in the FST, suggesting that Example 49 may have antidepressant properties in this model.

H. Effect of a single p.o. administration of Example 22, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA, $F(4,44) = 20.2$, $p < 0.0001$). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 20.1) compared to vehicle-treated animals (Table 5g).

A single p.o. administration of 10 or 30 mg/kg doses of Example 22 produced a significant decrease in immobility compared to vehicle-treated animals (Student-Newman-Keuls

values of 12.2 and 55.0, respectively). In addition, the decrease in immobility produced the either fluoxetine or the 10 and 30 mg/kg doses of Example 22 (Student-Newman-Keuls values of 21.2, 13.0 and 56.8, respectively) was significantly greater than that of the 3 mg/kg dose of Example 22. The decrease in immobility produced by 30 mg/kg i.p. of Example 22 was significantly greater than that of the 10 mg/kg dose (Student-Newman-Keuls value 16.2). In addition, the magnitude of the decrease in immobility produced by 30 mg/kg of Example 22 was significantly greater than that of fluoxetine (Student-Newman-Keuls value of 9.3).

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA, $F(4,44) = 35.00$, $p < 0.0001$). Post hoc analyses revealed that a single i.p. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming compared to animals treated with vehicle, 3 or 10 mg/kg of Example 22 (Student-Newman-Keuls values of 49.6, 51.3 and 5.8, respectively) (Table 5g).

A single p.o. administration of 3 mg/kg did not significant alter swimming behavior compared to vehicle-treated animals (Table 5g). However, a single p.o. administration of 30 mg/kg of Example 22 produced a significantly greater increase in swimming behavior compared to animals treated with vehicle, 3 or 10 mg/kg of Example 22 and fluoxetine (Student-Newman-Keuls values of 85.9, 88.1, 22.7 and 5.84, respectively).

Climbing behavior

There was a significant treatment effect on climbing behavior (ANOVA, $F(4,44) = 4.1$, $p = 0.0066$). Post hoc tests indicated that a single p.o. administration of 30 mg/kg dose of Example 22 produced a significant increase in climbing compared to animals treated with vehicle, 3 or 10 mg/kg of Example 22 and fluoxetine (Student-Newman-Keuls values of 10.5, 11.1, 5.8 and 11.8, respectively).

Diving

Statistical analysis revealed that diving was not significantly altered by a single i.p. administration of 3, 10 or 30 mg/kg of Example 22 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA, $F(4,44) = 0.58$, $p = 0.68$) (Table 5g).

TABLE 5g. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and Example 22 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	50 ± 1.6	2.1 ± 0.7	7.8 ± 1.0	0.3 ± 0.3
3 mg/kg EX22	50 ± 0.9	2.0 ± 0.6	7.6 ± 0.5	0.4 ± 0.4
10 mg/kg EX22	41 ± 1.3[c]	2.9 ± 0.5	15.3 ± 0.8[g]	0.4 ± 0.3
30 mg/kg EX22	31 ± 2.8[b]	5.2 ± 1.0[a]	23.2 ± 2.0[f]	0.0 ± 0.0
10 mg/kg Fluox	39 ± 1.7[d]	1.9 ± 0.5	19.2 ± 1.2[e]	0.0 ± 0.0

Each value represents the mean ± S.E.M. A total of 10 animals were examined for each treatment group, except for the 30 mg/kg dose of Example 22, where a total of 9 animals were examined.

Fluox = Fluoxetine, EX22 = Example 22. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly greater than the vehicle ($p < 0.01$), 3 mg/kg Example 22 ($p < 0.01$), 10 mg/kg Example 22 ($p < 0.05$) and 10 mg/kg of fluoxetine ($p < 0.05$), ANOVA and Student-Newman-Keuls test.

[b]Significantly less than all other treatment groups, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[c]Significantly less than vehicle, 3 and 30 mg/kg of Example 22 ($p < 0.01$) and 10 mg/kg of fluoxetine ($p < 0.05$), ANOVA and Student-Newman-Keuls.

[d]Significantly less than vehicle, 3 and 30 mg/kg of Example 22, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[e]Significantly greater than the vehicle, 3 and 10 mg/kg of Example 22, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[f]Significantly greater than the vehicle, 3 and 10 mg/kg of Example 22, $p < 0.01$ and fluoxetine, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[g]Significantly greater than the vehicle and 3 mg/kg of Example 22, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

The results of this study indicated that as previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility in male Sprague-Dawley rats in the FST compared to vehicle-treated animals. The magnitude of these changes are similar to those reported of our past studies with 10 mg/kg p.o. of fluoxetine. In contrast, neither climbing nor diving

behavior was significantly altered by a single i.p. administration of 10 mg/kg of fluoxetine.

A single p.o. administration of 3 mg/kg of Example 22 did not significantly alter swimming in male rats in the FST. In contrast, a single p.o. administration of 10 or 30 mg/kg of Example 22 produced a significant increase in swimming and a significant decrease in immobility compared to animals treated with vehicle or 3 mg/kg of Example 22. In addition, the magnitude of the increase in swimming behavior produced by 30 mg/kg p.o. of Example 22 was significantly greater than that of 10 mg/kg of Example 22 and 10 mg/kg of fluoxetine. The rank order of the treatments for increasing swimming is: 30 mg/kg Example 22 > fluoxetine > 10 mg/kg Example 22 > 3 mg/kg Example 22

Climbing behavior was significantly greater in animals treated with 30 mg/kg p.o. of Example 22 compared to animals treated p.o. with either vehicle, 3 or 10 mg/kg of Example 22 or 10 mg/kg of fluoxetine. None of the other treatments besides 30 mg/kg of Example 22 significantly altered climbing behavior compared to vehicle-treated animals. The rank order of the treatments for increasing climbing is: 30 mg/kg Example 22 >> 3 Mg/kg Example 22 = 10 mg/kg Example 22 = fluoxetine.

A single p.o. administration of 3 mg/kg of Example 22 did not significantly alter swimming compared to vehicle-treated animals. However, the 10 and 30 mg/kg doses produced a significantly greater decrease in immobility

compared to vehicle-treated animals, with the effect at 30 mg/kg being greater then that of 10 mg/kg. Furthermore, 30 mg/kg p.o. of Example 22 produced a significantly greater decrease in immobility than 10 mg/kg p.o. of fluoxetine. The rank order of the treatments for decreasing immobility is 30 mg/kg Example 22 > 10 mg/kg Example 22 = fluoxetine > 3 mg/kg Example 22.

In conclusion, a single p.o. administration of 10 or 30 mg/kg of Example 22 significantly increases swimming and significantly decreases immobility in vehicle-treated male Sprague-Dawley rats. This suggests that at these doses, Example 22 has antidepressant properties.

I. Effect of a single p.o. administration of Example 95, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test

Statistical analysis indicated that a single p.o. administration of 10 or 30 mg/kg Example 95 significantly increased rat immobility and significantly decreased swim behavior in the rat forced swim test at both doses (Table 5h, $p < 0.01$, ANOVA and Student-Newman-Keuls, respectively).

TABLE 5h. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 95 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	42 ± 1.7	2.3 ± 0.5	14.7 ± 1.0	0.1 ± 0.1
3 mg/kg EX95	40 ± 3.3	2.6 ± 0.8	17.1 ± 2.5	0.0 ± 0.0
10 mg/kg EX95	52 ± 1.2[a]	1.3 ± 0.5	6.9 ± 0.9[b]	0.1 ± 0.1
30mg/kg EX95	54 ± 0.9[a]	1.0 ± 0.3	4.8 ± 0.7[b]	0.0 ± 0.0
10 mg/kg Fluox	38 ± 2.2	1.9 ± 0.6	20.0 ± 1.5[c]	0.1 ± 0.1

Each value represents the mean ± S.E.M. A total of 8 animals were examined for each treatment group, except for the vehicle, where a total of 10 animals were examined. Fluox = Fluoxetine; EX95 = Example 95. Experiments were conducted 1 hr. after the appropriate treatment.

[a]Significantly less than Vehicle, 3 mg/kg of Example 95 and 10 mg/kg of fluoxetine, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[b]Signficantly less than Vehicle, 3 mg/kg of Example 95 and 10 mg/kg of fluoxetine, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[c]Signficantly greater than Vehicle ($p < 0.05$), 10 and 30 mg/kg of Example 95 ($p < 0.01$), ANOVA and Student-Newman-Keuls test.

A single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to vehicle-treated animals. In addition, fluoxetine significantly decreased immobility compared to vehicle-treated animals. A single p.o. administration of 3 mg/kg of Example 95 did not significantly alter swimming, climbing, immobility or diving behavior compared to vehicle-treated animals. In contrast, a single p.o. administration of either 10 or 30 mg/kg of Example 95 produced a significant increase in immobility and a significant decrease in swimming behavior compared to vehicle-treated animals. There was no significant difference in the magnitude of change in swimming and immobility between the 10 and 30 mg/kg doses of Example 95.

These data indicate that at a doses of 10 and 30 mg/kg p.o., Example 95 produced effects opposite of that seen with antidepressants in the rat forced swim test, suggesting that Example 95 does not produce antidepressant-like actions in the forced swim test in male Sprague-Dawley rats.

2. Social Interaction Test

A. The Effect Of Example 92 And Chlordiazepoxide On Behavior In The Rat Social Interaction Test

A single i.p. administration of either 10 or 30 mg/kg of Example 92 significantly increased social interaction (Table 6 and Figure 4), as did the benzodiazepine anxiolytic, chlordiazepoxide (Student-Newman-Keuls value of 31.3) compared to vehicle-treated animals [ANOVA, $F(4,45) = 10.3$, $p < 0.0001$; Student-Newman-Keuls values for the 10 and 30 mg/kg doses were 8.61 and 19.55, respectively]. However, the 100 mg/kg i.p. dose of Example 92 did not significantly alter social interaction time compared to vehicle-treated animals (Table 6 and Figure 4). The degree of social interaction was greater in the chlordiazepoxide-treated animals compared to those that received either the 10 or 30 mg/kg doses of Example 92.

Table 6. The Effect Of A Single Injection Of Vehicle, Chlordiazepoxide And Example 92 On The Social Interaction And Rearing Of Unfamiliar Cage Mates In A Familiar Arena

Drug Social Treatment (i.p.)	Interaction (sec)[a]
Vehicle, 1 ml/kg	96 ± 12
Chlordiazepoxide, 5 mg/kg	188 ± 15[b]
Example 92, 10 mg/kg	144 ± 12[b]
Example 92, 30 mg/kg	169 ± 13[c]
Example 92, 100 mg/kg	117 ± 6[d]

[a] Each value represents the mean seconds of social interaction ± S.E.M.

[b] Significantly greater than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[c] Significantly greater than Vehicle, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[d] Significantly less than 30 mg/kg dose and chlordiazepoxide, $p < 0.01$, ANOVA and Student-Newman-Keuls.

B. The Effect Of Example 92 And Chlordiazepoxide On Rearing Behavior, Locomotor Activity And Grooming In The Rat Social Interaction Test

The administration of 10 and 30 mg/kg, but not 100 mg/kg of Example 92, significantly increased rearing behavior compared to either vehicle or chlordiazepoxide [ANOVA, $F(4,45) = 2.6$, $p = 0.046$; See Table 13]. In addition, the number of rearings at the 10 mg/kg dose of Example 92 was significantly greater than that produced by chlordiazepoxide (Table 13).

The administration of either Example 92 or chlordiazepoxide did not significantly alter the number of grooming bouts compared to vehicle-treated animals [$F(4,45) = .67$, $p = 0.62$].

A single injection of either 10 or 30 mg/kg i.p. of Example 92 or 5 mg/kg i.p. of chlordiazepoxide did not significantly alter the number of squares crossed (Table 13). However, the number of squares crossed following the 100 mg/kg dose of Example 92 was significantly lower than animals treated with either vehicle, 10 mg/kp i.p. of Example 92, 30 mg/kg i.p. of Example 92 or 5 mg/kg i.p. of chlordiazepoxide. [ANOVA, $F(4,43) = 6.94$, $p = 0.0002$].

Table 13. The Effect of a Single Injection of Vehicle, Chlordiazepoxide and Example 92 on the Number of Rearings, Squares Crossed and Grooming Bouts in the Rat Social Interaction Test.

Drug Treatment (i.p.)	Rearings	Squares Crossed	Grooming Bouts
Vehicle, 1 ml/kg	33 ± 4	393 ± 26	5.1 ± 1.1
Chlordiazepoxide, 5 mg/kg	30 ± 2	287 ± 28	7.3 ± 1.3
Example 92, 10 mg/kg	47 ± 8[a]	298 ± 40	6.1 ± 0.5
Example 92, 30 mg/kg	45 ± 5[b]	368 ± 36	6.2 ± 0.7
Example 92, 100 mg/kg	31 ± 4	195 ± 19[c]	6.8 ± 1.3

All values represent the mean ± S.E.M.

[a] Significantly greater than chlordiazepoxide, $p < 0.05$, ANOVA and Student-Newman-Keuls test

[b] Significantly greater than vehicle and chlordiazepoxide, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[c] Significantly less than 10 & 30 mg/kg of Example 92 ($p < 0.01$), vehicle ($p < 0.01$) and chlordiazepoxide ($p < 0.05$), ANOVA and Student-Newman-Keuls test.

At doses of 10 and 30 mg/kg i.p., Example 92 produced a significant increase in social interaction time in male rats compared to vehicle-treated animals. Also, the anxiolytic agent (5 mg/kg i.p. chlordiazepoxide) produced a significant increase in social interaction time compared to vehicle-treated animals. The response produced by the 30 mg/kg dose of Example 92 was comparable to that of the positive control, chlordiazepoxide. The 30 mg/kg dose of Example 92 produced a significant increase in rearing compared to vehicle- and chlordiazepoxide-treated animals. Previously, it has been shown that in the Social Interaction Test, psychostimulants such as amphetamine and caffeine, increase social interaction and locomotor activity, whereas anxiolytics increase social interaction time. (File, 1985; File and Hyde, 1979; Guy and Gardner, 1985). Consistent with an increase in social interaction, Example 92 increased rearing behavior. However, it did not produce an increase in horizontal locomotor activity or grooming bouts. In addition, Example 92 did not elicit stereotypes or produce aggressive behaviors. In fact, locomotor activity as measured by squares crossed was significantly reduced at the 100 mg/kg i.p. dose of Example 92 compared to vehicle-treated animals. This decrease in locomotor activity did not appear to be accompanied by ataxia or sedation. Thus, it is unlikely that Example 92 is producing a non-specific effect on social interaction through motor stimulation. In order to justify this claim, in another study (not reported), the effect of Example 92 was dosed to familiar cage mates in the social interaction test and no significant increase in interaction in this variation of the Social Interaction Test was observed. In this test, the anxiogenic stimulus

of a novel partner is removed and therefore only locomotor activity and normal behavior are observed (Guy and Gardner, 1985). In conclusion, the results of this study indicate that Example 92, at doses of 10 and 30 mg/kg i.p., significantly increases social interaction time without producing an increase in horizontal locomotor activity or grooming bouts. Furthermore, the effect produced by the 30 mg/kg of Example 92 was comparable to that observed for 5 mg/kg of chlordiazepoxide, the active control. No increase in social interaction was observed at the 100 mg/kg dose of Example 92. However, a decrease in the number of squares crossed was observed. In summary, Example 92 has the profile of an anxiolytic drug in the Social Interaction Test.

C. The effect of a single p.o. administration of Example 34, vehicle and chlordiazepoxide on the duration of social interaction in the rat social interaction test.

There was a significant treatment effect on the duration of social interaction (ANOVA, $F(5,40) = 11.8$, $p < 0.001$). Subsequent post hoc analyses indicated that a single p.o. administration of either 0.03, 0.1, 0.3 and 1 mg/kg of Example 34 (Student-Newman-Keuls test values of 8.0, 10.6, 4.3 and 13.2, respectively) significantly increased social interaction, as did chlordiazepoxide (Student-Newman-Keuls value of 57.1), compare to vehicle-treated animals (Table 6a). The duration of social interaction produced by chlordiazepoxide was significantly greater than that of 0.03, 0.1, 0.3 and 1 mg/kg p.o. of Example 34 (Student-Newman-Keuls values of 19.6, 18.6, 26.2 and 17.6, respectively). There was no significant difference

in the duration of social interaction between the various doses of Example 34 (Table 6a).

Table 6a. The effect of a single p.o. administration of vehicle, chlordiazepoxide and Example 34 on social interaction time in unfamiliar cage mates in a familiar arena

Drug Treatment (p.o.)	Social Interaction (sec)
Vehicle, 1 ml/kg	27 ± 1.4[A]
Chlordiazepoxide, 5 mg/kg	122 ± 18[$]
Example 34, 0.03 mg/kg	62 ± 11[*]
Example 34, 0.1 mg/kg	66 ± 7[*]
Example 34, 0.3 mg/kg	53 ± 6[*]
Example 34, 1 mg/kg	69 ± 6[#]

Animals received one p.o administration of the appropriate treatment and all experiments were conducted one hour after the last injection.

[A]Each value represents the mean seconds of social interaction ± S.E.M. A total of 6-8 animals were examined for each treatment group.

*Significantly greater than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[#]Significantly greater than Vehicle, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

[$]Significantly greater than all other treatment groups, $p < 0.01$, ANOVA and Student-Newman-Keuls test.

D. The effect of a single p.o. administration of Example 34, vehicle and chlordiazepoxide on rearing behavior, locomotor activity and grooming in the social interaction test.

Statistical analysis indicated a significant effect of treatment on rearing behavior (ANOVA, $F(5,40) = 3.5$, $p = 0.01$; Table 14). Post hoc analyses revealed that the the number of rears following 0.3 mg/kg of Example 34 was significantly lower than that of 0.1 and 1 mg/kg p.o. of Example 34 (Student-Newman-Keuls values of 8.8 amd 9.4, respectively).

Statistical analysis indicated a significant effect of treatment on number of squares crossed ($F(5,40) = 2.9$, $p = 0.03$). Post hoc analyses indicated that a single p.o. administration of 0.3 mg/kg of Example 34 produced a significantly greater effect on the number of squares crossed compared to vehicle-treated animals (Student-Newman-Keuls values of 10.4).

Statistical analysis indicated a significant effect of treatment on grooming behavior ($F(5,40) = 4.3$, $p = 0.004$). Post hoc analyses indicated that the number of grooming episodes was significantly lower in the 0.03 mg/kg group compared to animals treated with 0.1, 0.3 or 1 mg/kg p.o. of Example 34 (Student-Newman-Keuls values of 11, 8 and 9.7, respectively (Table 14). In additon, the number of grooming episodes was significantly greater in animals treated with 0.1 mg/kg p.o. of Example 34 compared to those treated with vehicle (Table 14).

Table 14. The effect of a single p.o. administration of vehicle, chlordiazepoxide and Example 34 on the number of rearings, grooming episodes and squares crossed in the social interaction test in unfamiliar cage mates in a familiar arena

Drug Treatment (p.o.)	Rearing	Squares Crossed	Grooming bouts
Vehicle, 1 ml/kg	34 ± 3	250 ± 31	4.6 ± 0.7
Chlordiazepoxide, 5 mg/kg	35 ± 2	265 ± 30	5.3 ± 0.7
Example 34, 0.03 mg/kg	27 ± 3*	312 ± 23	4.0 ± 0.4&
Example 34, 0.1 mg/kg	40 ± 5	295 ± 40	7.6 ± 0.5+
Example 34, 0.3 mg/kg	27 ± 2$	363 ± 17	7.2 ± 1.1
Example 34, 1 mg/kg	40 ± 1	343 ± 15@	7.3 ± 0.8

Animals received one p.o administration of the appropriate treatment and all experiments were conducted one hour after the last injection. All values represent the mean ± S.E.M. A total of 6-8 animals were examined for each treatment group.

*Significantly less than 0.1 mg/kg of Example 34, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

$Significantly less than 0.1 and 1mg/kg of Example 34, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[@]Significantly greater than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[&]Significantly less than 0.1, 0.3 and 1 mg/kg of Example 34, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

[+]Significantly greater than Vehicle, $p < 0.05$, ANOVA and Student-Newman-Keuls test.

One of the main findings of this study was that in paired, unfamiliar male Sprague-Dawley rats, a single p.o. administration of either 0.03, 0.1, 0.3 or 1 mg/kg p.o. of Example 34 produced a significant increase (2-2.6 fold) in the duration of social interaction compared to animals treated with vehicle. In addition, there was no significant difference in the magnitude of increase in social interaction between the various doses of Example 34, i.e. there was no dose-response relationship. As previously reported, a single p.o. administration of 5 mg/kg of chlordiazepoxide produced a significant increase in the duration of social interaction compared to vehicle-treated animals.

Rearing behavior was not significantly altered by any of the doses of Example 34 or by chlordiazepoxide compared to vehicle-treated animals, although there were differences between the doses of Example 34. The number of squares crossed was significantly greater following a single p.o. administration of 1 mg/kg of Example 34 compared to vehicle-treated animals, whereas there were no significant differences between the other doses of Example 34 and vehicle. Thus, overall, Example 34 does

not significantly alter locomotor activity, suggesting that it does not produce locomotor activation or stimulation.

Grooming behavior following a single p.o. administration tended to be greater after 0.1, 0.3 and 1 mg/kg of Example 34 compared to animals that had received vehicle, although this was only statistically significant for the 0.1 mg/kg dose. Furthermore, the number of grooming episodes was significantly lower after a single p.o. administration of 0.03 mg/kg of Example 34 compared to 0.1, 0.3 and 1 mg/kg of Example 34.

In conclusion, the above results suggest that a single p.o. administration of 0.03, 0.1, 0.3 or 1 mg/kg of Example 34 produces an anxioltyic action in the social interaction test in male Sprague-Dawley rats.

III Binding Properties of Compounds at Cloned Receptors

A. Materials and Methods

The binding properties of the compounds of the present invention were evaluated at one or more cloned receptors or native, tissue-derived transporters, using protocols described below.

Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin) at 37°C with 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin, 100 µg /ml streptomycin) at 37°C with 5% CO_2. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LM(tk-) cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin, 100 µg/mL streptomycin) at 37°C with 5% CO_2. Stock plates of LM(tk-) cells were trypsinized and split 1:10 every 3-4 days. Chinese Hamster Ovary (CHO) cells were grown on 150 mm plates in HAM's F12 medium with (HAM's F-12 with 10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin, 100 µg/mL streptomycin) at 37°C with 5% CO_2. Stock plates of CHO cells were trypsinized and split 1:8 every 3-4 days.

LM(tk-) cells were stably transfected with the human GAL1 or GAL3 receptor. CHO cells were stably transfected with the human GAL2 receptor.

Stable Transfection

cDNAs for the human and rat GAL1, and human and rat GAL3 receptors were transfected with a G-418 resistant gene into the mouse fibroblast LM(tk-) cell line by a calcium phosphate transfection method (Cullen, 1987). Stably transfected cells were selected with G-418. Human and rat GAL2 receptors were similarly transfected into CHO cells.

Membrane Harvest

Membranes were harvested from stably transfected LM(tk-) cells. Adherent cells were washed twice in ice-cold phosphate buffered saline (138 mM NaCl, 8.1 mM Na2HPO4, 2.5 mM KCl, 1.2 mM KH_2PO4, 0.9 mM CaCl2, 0.5 mM MgCl2, pH 7.4) and lysed by sonication in ice-cold sonication buffer (20 mM Tris-HCl, 5 mM EDTA, pH 7.7). Large particles and debris were cleared by low speed centrifugation (200 x g, 5 min, 4°C). Membranes were collected from the supernatant fraction by centrifugation (32,000 x g, 18 min, 4°C), washed with ice-cold hypotonic buffer, and collected again by centrifugation (32,000 x g, 18 min, 4°C). The final membrane pellet was resuspended by sonication into a small volume of ice-cold binding buffer (~1 ml for every 5 plates: 10 mM NaCl, 20 mM HEPES, 0.22 mM KH_2PO4, 1.26 mM CaCl2, 0.81 mM MgSO4, pH 7.4). Protein concentration was measured by the Bradford method (Bradford, 1976) using Bio-Rad Reagent, with bovine serum albumin as a standard. Membranes were held on ice for up to one hour and used fresh, or flash frozen

and stored in liquid nitrogen. Membranes were prepared similarly from CHO cells.

As described in the Background of the Invention, compounds that block the effects of galanin on the GAL3 receptor subtype can potentially be used for the treatment of depression and anxiety. Biogenic amine transmitter molecules that mediate neuronal signals are currently known in the art and include among others serotonin (5HT), norepinephrine (NE), and dopamine (DA). Recent advances in the molecular studies of the mechanisms for these transmitter molecules, together with the characterization of their pharmacological properties, has enabled the identification of numerous potential targets for therapeutic intervention. Inhibitors of the 5HT, NE and DA transporter systems, and inhibitors of the enzyme, monoamine oxidase, have been widely studied and are known to enhance the action of biogenic amine neurotransmitters. The resultant clinically effective antidepressant drugs are known today as TCAs, SSRIs and MAOIs. (Tatsumi et al., 1997; Iversen, 2000).

In the case of galanin, the evidence presented in this invention suggests that GPCR-targeted molecules that bind to and antagonize the GAL3 receptor may be used for the treatment of depression and/or anxiety disorders. Another approach could involve the administration of an antagonist of the GAL3 receptor, such as those described herein, which also possesses $5HT_4$ receptor antagonist properties (Kennett et al., 1997). A further approach could involve the administration of a GAL3 antagonist, such as those described herein, which also possesses $5HT_{1A}$

receptor binding properties (Razani et al., 1997). However, in any case the GAL3 antagonist(s) should be free of activity at the human GAL1 receptor and the 5HT, NE and DA transporters. Furthermore, the GAL3 antagonist(s) should not inhibit the enzymatic activity of monoamine oxidase A (MAO_A) or monoamine oxidase B (MAO_B) present in the brain (i.e. central MAO). The design of such compounds can be optimized by determining their binding affinity at the recombinant GAL3, GAL1, $5HT_4$, and $5HT_{1A}$ receptors; and the native 5HT, NE and DA transporters. The design of such compounds can be further optimized by determining their interaction with central MAO_A and central MAO_B.

Additionally, the GAL3 antagonist(s) would optimally not bind at the following receptors due to possible side effects: human GAL2; human H_1 histamine; human α_{1A} adrenergic, human α_{1B} adrenergic, human α_{1D} adrenergic, human α_{2A} adrenergic, human α_{2B} adrenergic, and human α_{2C} adrenergic; human dopamine D_1, D_2, D_3, D_4, and D_5; and the human $5HT_{1B}$, human $5HT_{1D}$, human $5HT_{1E}$, human $5HT_{1F}$, human $5HT_{2A}$, rat $5HT_{2C}$, human $5HT_6$, and human $5HT_7$ receptors.

Radioligand Binding Assays and Enzymatic Assays

The methods to obtain the cDNA of the receptors, express said receptors in heterologous systems, and carry out assays to determine binding affinity are described as follows.

Galanin Receptors: Binding assays were performed according to the following published methods: human GAL3 (PCT International Publication No. WO 98/15570), human

GAL1 (PCT International Publication No. WO 95/2260), human GAL2 (PCT International Publication No. WO 97/26853).

Human $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{1F}$, and $5HT_7$ Receptors: The cell lysates of LM(tk-) clonal cell line stably transfected with the genes encoding each of these 5HT receptor-subtypes were prepared as described above. Cell membranes were suspended in 50mM Tris-HCl buffer (pH 7.4 at 37°C) containing 10 mM MgCl2, 0.2 mM EDTA, 10 M pargyline, and 0.1% ascorbate. The affinities of compounds were determined in equilibrium competition binding assays by incubation for 30 minutes at 37 °C in the presence of 5 nM [^{3}H]-serotonin. Nonspecific binding was determined in the presence of 10 μM serotonin. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

Human $5HT_{2A}$ Receptor: The coding sequence of the human $5HT_{2A}$ receptor was obtained from a human brain cortex cDNA library, and cloned into the cloning site of pCEXV-3 eukaryotic expression vector. This construct was transfected into COS-7 cells by the DEAE-dextran method (Cullen, 1987). Cells were harvested after 72 hours and lysed by sonication in 5 mM Tris-HCl, 5 mM EDTA, pH 7.5. The cell lysates were subjected to centrifugation at 1000 rpm for 5 minutes at 4°C, and the supernatant was subjected to centrifugation at 30,000 x g for 20 minutes at 4°C. The pellet was suspended in 50 mM Tris-HCl buffer (pH 7.7 at room temperature) containing 10 mM MgSO4, 0.5 mM EDTA, and 0.1% ascorbate. The affinity of compounds at $5HT_{2A}$ receptors were determined in equilibrium competition

binding assays using [^{3}H]ketanserin (1 nM). Nonspecific binding was defined by the addition of 10 μM mianserin. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

5-HT_{1A} Receptor: The cDNA corresponding to the 5-HT_{1A} receptor open reading frames and variable non-coding 5'- and 3'-regions, was cloned into the eukaryotic expression vector pCEXV-3. These constructs were transfected transiently into COS-7 cells by the DEAE-dextran method (Cullen, 1987), and harvested after 72 hours. Radioligand binding assays were performed as described above for the 5-HT_{2A} receptor, except that ^{3}H-8-OH-DPAT was used as the radioligand and nonspecific binding was determined by the addition of 10 μM mianserin.

Other 5-HT Receptors: Other serotonin receptor binding assays were performed according to published methods: rat $5HT_{2C}$ receptor (Julius et al., 1988); and 5-HT_6 (Monsma, et al., 1993). The binding assays using the 5-HT_4 receptor were performed according to the procedures described in U.S. Patent No. 5,766,879, the disclosure of which is hereby incorporated by reference in its entirety into this application.

Other receptors: Cell membranes expressing human dopamine D_1, D_2, D_4 and rat D_3 receptors were purchased through BioSignal, Inc. (Montreal, Canada). Binding assays using the histamine H_1 receptor; dopamine receptors; and α_{1A}, α_{1B}, and α_2 adrenergic receptors may be carried out according to the procedures described in U.S. Patent No. 5,780,485, the disclosure of which is hereby incorporated by reference in its entirety into this application. Binding assays using the dopamine D_5 receptor may be carried out according to the procedures described in U.S. Patent No. 5,882,855, the disclosure of which is hereby incorporated by reference in its entirety into this application. Binding assays for the human α_{1D} adrenergic receptor may be carried out according to the procedures described in U.S. Patent No. 6,156,518, the disclosure of which is hereby incorporated by reference in its entirety into this application.

The methods to determine binding affinity at native transporters are described in the following publications: 5HT transporter and NE transporter (Owens

et al., 1997), and DA transporter (Javitch et al, 1984).

The methods to determine activity at monoamine oxidase enzymes (for example, central MAO_A and MAO_B) are described by Otsuka and Kobayashi, 1964, and were performed by NovaScreen (Hanover, MD) with the following modifications.

Central Monoamine Oxidase A Enzyme Assay: Rat brain was used as the enzyme source. The enzyme source was pre-incubated with reference compound (RO 41-1049), test compound (Example 92), and subtype selective blocker (100nM deprenyl) for 60 minutes at 37°C in 50 mM KPO_4 containing 50 µM EDTA and 10 µM dithiothreitol (pH 7.2 at 25°C). Substrate ([^{14}C]Serotonin, 45-60 Ci/mmol) was then added and incubated for 30 minutes. The reaction was stopped by the addition of 0.5 ml of 1-2M citric acid. Radioactive product was extracted into xylene/ethyl acetate fluor and compared to control values by scintillation spectrophotometry in order to ascertain any interactions of test compound with central MAO_A.

Central Monoamine Oxidase B Enzyme Assay: Rat brain was used as the enzyme source. The assay was performed as described above for central MAO_A, except the reference compound was RO 166491 and the subtype selective blocker was 100 nM clorgyline. Also, the substrate ([^{14}C]Phenylethylamine, 0.056 Ci/mmol) was added and incubated for 10 minutes.

Materials

Cell culture media and supplements were from Specialty Media (Lavallette, NJ). Cell culture plates (150 mm and 96-well microtiter) were from Corning (Corning, NY). Polypropylene 96-well microtiter plates were from Costar (Cambridge, MA). Bovine serum albumin (ultra-fat free, A-7511) was from Sigma (St. Louis, MO). All radioligands were from New England Nuclear (Boston, MA). Commercially available peptides and peptide analogs were either from Bachem California (Torrance, CA) or Peninsula (Belmont, CA). All other materials were reagent grade.

Data Analysis

Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA). Enzymatic assay data were derived from a standard curve of reference compound data.

The selectivity ratios for compounds of the claimed invention were calculated from the binding data presented in Tables 1-4, Table 7 and Table 9 of the subject application. More specifically, these ratios were calculated by dividing (a) the binding affinity (K_i value) of said compound to a particular receptor or transporter by (b) the binding affinity (K_i value) of said compound to the human GAL3 receptor. The data presented in Table 8 and Table 10, hereinafter, were calculated using the above described method.

For example, the GAL3/GAL1 selectivity ratio of 10-fold recited in claim 110 of the subject application is characteristic of Example 34. This binding ratio was calculated by dividing (a) the K_i value of 912 for the binding of Example 34 to the GAL1 receptor (see Table 1) by (b) the K_i value of 23 for the binding of Example 34 to the human GAL3 receptor, thus obtaining the result of 39. Therefore the GAL3/GAL1 binding ratio for Example 34 was determined to be greater than 10-fold.

B. Results

The compounds described in the claimed invention were assayed using a panel of cloned receptors and native transporters. The preferred compounds were found to be selective GAL3 antagonists. The binding affinities and selectivity ratios of several compounds are illustrated in Tables 7-10.

Table 7: Antagonist binding affinity (Ki) at the human GAL3 receptor vs. serotonin receptors and several transporters.

Example	hGAL3	$h5HT_{1A}$	$h5HT_{1B}$	$h5HT_{1D}$	$h5HT_{1E}$	$h5HT_{1F}$	$h5HT_{2A}$	$r5HT_{2C}$	$h5HT_{4}$	$h5HT_{6}$	$h5HT_{7}$	r5HT Uptk	rNE Uptk	rDA Uptk
	Ki (nM)	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*
11	91	4682	101	102	9174	1780	6708	802	1308	800	1012	1595	*	5430
15	73	5098	487	1272	11038	4192	11270	572	2301	1457	2527	1737	*	24500
17	87	3477	407	1032	33523	10271	7157	562	2606	711	1797	719	18325	27200
22	28	9714	1981	1852	13230	5773	20689	1717	2457	2264	2672	8483	13085	7480
34	23	*	1059	2976	28282	4803	*	2076	20762	38921	4439	37462	*	3900
49	211	29187	8447	16872	23886	8894	*	6687	13230	13	12268	40666	37585	2010
60	86	33666	5461	9198	1180	2124	26118	1781	1180	47536	3235	25274	46108	14500
77	79	5472	365	716	5888	3237	2242	456	1324	503	1547	821	28083	2790
92	38	*	11323	32139	18934	5290	*	ND	72	*	ND	45111	33879	17800
94	49	*	3349	10764	25227	5683	*	4099	4120	3647	8018	12961	4876	2200
95	29	28288	5226	16018	27211	4446	*	3471	3031	21507	11638	*	6101	12000
97	51	*	5057	14235	22692	4157	*	1950	2550	29131	11283	36308	4412	8440
98	38	24576	2419	9118	16240	3359	*	2260	1210	14018	8464	36329	5496	7430

* = >50000
ND = Not determined

Table 8: Antagonist selectivity ratios determined for the human GAL3 receptor vs. serotonin receptors and several transporters.

Example	hGAL3	$h5HT_{1A}$	$h5HT_{1B}$	$h5HT_{1D}$	$h5HT_{1E}$	$h5HT_{1F}$	$h5HT_{2A}$	$r5HT_{2C}$	$h5HT_4$	$h5HT_6$	$h5HT_7$	r5HT Uptk	rNE Uptk	rDA Uptk
11	1	>30	1	1	>100	20	>30	9	14	9	11	18	>100	>30
15	1	>30	7	17	>100	>30	>100	8	>30	20	>30	24	>100	>100
17	1	>30	5	12	>100	>100	>30	6	30	8	21	8	>100	>100
22	1	>100	>30	>30	>100	>100	>100	>30	>30	>30	>30	>100	>100	>100
34	1	>100	>30	>100	>100	>100	>100	>30	>100	>100	>100	>100	>100	>100
49	1	>100	>30	>30	>100	>30	>100	>30	>30	0	>30	>100	>100	10
60	1	>100	>30	>100	14	25	>100	21	14	>100	>30	>100	>100	>100
77	1	>30	5	9	>30	>30	28	6	17	6	20	10	>100	>30
92	1	>100	>100	>100	>100	>100	>100	ND	2	>100	ND	>100	>100	>100
94	1	>100	>30	>100	>100	>100	>100	>30	>30	>30	>100	>100	>30	>130
95	1	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
97	1	>100	>30	>100	>100	>30	>100	>30	>30	>100	>100	>100	>30	>100
98	1	>100	>30	>100	>100	>30	>100	>30	>30	>100	>100	>100	>100	>100

ND = Not determined

Table 9: Antagonist binding affinity (Ki) at the human GAL3 receptor vs. alpha-adrenergic, dopamine, and histamine receptors.

Example	hGAL3	$h\alpha_{1A}$	$h\alpha_{1B}$	$h\alpha_{1D}$	$h\alpha_{2A}$	$h\alpha_{2B}$	$h\alpha_{2C}$	hD_1	hD_2	rD_3	hD_4	hD_5	hH_1
	Ki (nM)	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*	*Ki (nM)*
11	91	926	1436	264	1819	10235	3004	79	782	2139	4828	64	ND
15	73	3392	853	480	14413	24515	8202	344	2184	8809	13151	78	ND
17	87	996	1167	221	3523	38732	10269	516	1808	2477	22227	89	ND
22	28	1278	1582	368	906	5757	2737	128	1501	5664	11621	63	ND
34	23	3756	15004	1240	3679	15488	8832	290	2500	9922	18716	111	ND
49	211	6646	18852	678	4731	25374	9244	3781	5940	13964	45824	328	ND
60	86	13604	40615	4231	10838	*	7200	600	26815	15295	48756	538	39909
77	79	834	452	217	315	7783	634	60	910	2716	504	122	ND
92	38	ND	*	17175	21943	*	*	*	41369	48180	41369	29290	39909
94	49	12715	31135	4027	12718	45378	47863	2145	6249	423	*	727	ND
95	29	13137	32494	3468	30072	*	48552	4394	9716	466	*	2590	ND
97	51	16921	45845	6454	13569	*	*	25115	*	9716	*	10069	ND
98	38	14500	31693	1891	23236	*	*	2524	3788	592	*	1199	ND

* = >50000
ND = Not determined

Table 10: Antagonist selectivity ratios determined for the human GAL3 receptor vs.
alpha-adrenergic, dopamine, and histamine receptors.

Example	hGAL3	$h\alpha_{1A}$	$h\alpha_{1B}$	$h\alpha_{1D}$	$h\alpha_{2A}$	$h\alpha_{2B}$	$h\alpha_{2C}$	hD_1	hD_2	rD_3	hD_4	hD_5	hH_1
11	1	10	16	3	20	>100	>30	0.9	9	24	>30	0.7	ND
15	1	46	12	7	>100	>100	>100	5	30	>100	>30	1	ND
17	1	11	13	3	>30	>100	>100	6	21	28	>100	1	ND
22	1	>30	>30	13	>30	>100	>100	5	>30	>100	>100	2	ND
34	1	>100	>100	>30	>100	>100	>100	13	>100	>100	>100	5	ND
49	1	>30	>30	3	22	>100	>30	18	28	>30	>100	2	ND
60	1	>100	>100	>30	>100	>100	>30	7	>100	>100	>100	6	>100
77	1	11	6	3	4	>30	8	0.8	11	>30	6	2	ND
92	1	ND	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
94	1	>100	>100	>30	>100	>100	>100	>30	>100	9	>100	15	ND
95	1	>100	>100	>100	>100	>100	>100	>100	>100	16	>100	>30	ND
97	1	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	ND
98	1	>100	>100	>30	>100	>100	>100	>30	>100	16	>100	>30	ND

ND = Not determined

The activity of Example 92 was determined for central MAO_A and central MAO_B using the methods described hereinabove. The results, expressed as percent inhibition, are illustrated in Table 11.

Table 11: Percent inhibition of Example 92 in the central monoamine oxidase enzyme assay

TARGET	SPECIES	% INHIBITION
Monoamine Oxidase A (central)	Rat	10
Monoamine Oxidase B (central)	Rat	1

IV. GAL3 Receptor Localization

A. Materials And Methods

Preparation of the anti-GAL3 Antiserum

BioSource International, Hopkinton, MA performed the immunization and maintenance of rabbits. Following a pre-immune bleed, one peptide for each GAL receptor was injected into a pair of New Zealand white rabbits. The peptide sequences was chosen based on sequence specificity and immunogenicity. The rabbit anti-GAL3 antiserum were raised against C-terminal epitopes corresponding to amino acids 357 - 370 (Genbank accession number AF073798). The peptides were conjugated to the carrier KLH (keyhole limpet hemocyanin) by a cross linker and subcutaneously injected into the rabbits. The generation of the anti-GAL3 antiserum required OVA followed by a third series of injections with the GAL3 peptide conjugated to tetanus toxoid (TTOX). All injections were done using the Freund's Adjuvant System. Once immunoreactivity was established (see below) the antiserum was affinity purified by passing it over an agarose based column thiol coupled to its antigenic peptide. The column was washed and the antiserum was eluted using a low pH glycine buffer. The purified material was dialyzed, the optical density is taken at 280 λ and the purified antiserum was frozen.

Characterization of the anti-GAL3 antiserum

Recombinant GAL1, GAL2, and GAL3 receptor transfected cells

To determine the ability of the GAL3 antiserum to recognize only the GAL3 receptor protein in vitro, COS-7 cells were grown on poly-L-lysine-coated plastic chamber slides (Nalge Nunc International, Naperville, IL) and transfected with recombinant rat GAL receptors (Genbank accession numbers U30290, AF010318, AF073798, respectively) or expression vector only (for mock-transfected cells) as previously described by Borowsky et al. (1999). Receptor expression was confirmed by radioligand binding. Briefly, a subset of slides was washed three times in binding buffer (50 mM Tris, pH 7.5, 5 mM $MgCl_2$, 1 mM EDTA, 0.1% bovine serum albumin, and 0.1% bacitracin) and incubated in 500 µl binding buffer containing porcine ^{125}I-galanin (625,000 dpm) plus or minus 10 µM porcine galanin. After incubation at room temperature for 1 hour, the binding buffer was aspirated and slides were rinsed three times in ice cold 50 mM Tris, pH 7.5. Cells were solubilized in 1 ml of 0.1 N NaOH and 0.05% sodium deoxycholate for 30 minutes then transferred to test tubes for gamma counting of ^{125}I. To evaluate antibody activity another subset of slides were washed with phosphate buffered saline (PBS) (Sigma, St. Louis, MO) to remove the medium and fixed with 4% paraformaldehyde (PFA) (Sigma, St. Louis, MO) then permeabilized using 0.2% Triton X-100/PBS and incubated in 3% normal goat serum for 30 minutes to minimize nonspecific binding of the primary antibody. Cells were incubated overnight at 4°C with the anti-GAL3 antiserum (1:1000 dilution). The cells were rinsed three times with PBS, incubated for 30 minutes at 25°C with goat anti-rabbit IgG (1:200 dilution) (Santa Cruz Biotechnology, Santa Cruz, CA), rinsed and processed using the

peroxidase-antiperoxidase (PAP) reaction of Sternberger et al. (1982). Control experiments for antibody specificity were (1) incubation of the cells in primary antiserum that had been preabsorbed with the respective antigenic peptide (20 μg/ml), (2) incubation without the primary antiserum, or (3) incubation with the primary antiserum replaced by normal goat serum.

Western Blotting

Membranes were prepared from COS-7 cells transiently transfected with the rat recombinant receptors GAL1, GAL2, and GAL3 as previously described (Borowsky et al., 1999). Transfected cells were lysed by sonication in ice-cold sonication buffer (20 mM Tris-HCl, pH 7.7, 5 mM EDTA). Cell lysates were subjected to centrifugation at 4°C for 10 minutes at 200 g. The supernatant was then fractionated by centrifugation at 4°C for 18 minutes at 32,000 g. The resulting membrane pellet was suspended into 50 mM Tris, pH 7.5, 5 mM $MgCl_2$, 1 mM EDTA. Protein samples (1-10 μg) were solubilized in 2 X Laemmli buffer (Bio-Rad, Hercules, CA) and fractionated by SDS-PAGE in 10% polyacrylamide gels. Proteins were transferred to polyvinylidine difluoride membranes for immunoblot analysis in ice-cold 25 mM Tris, pH 8, 192 mM glycine, 20% methanol as previously described by Harlow and Lane (1999). Blots were incubated for 1 hour at 25°C in blocking buffer composed of 5% non-fat dried milk in TTBS (0.1% Tween-20, 500 mM NaCl, 20 mM Tris, pH 7.5) then for 16 hours at 25°C with the receptor-specific polyclonal antibody (1:1000 dilution in blocking buffer)(0.25 mg/ml for GAL2 or 1.5 mg/ml for GAL3). Immunoreactive bands were detected with the Phototope-HRP Detection Kit for

Western Blotting (New England BioLab, Beverly, MA) according to the protocol. Briefly, the blots were incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG then developed with a mixture of LumiGLO plus hydrogen peroxide and recorded by chemiluminescence on Kodak Biomax-ML film (Kodak, Rochester, NY).

Immunohistochemistry

Male Sprague-Dawley rats, (200-250 g; Charles Rivers, Rochester, NY) were anesthetized by intraperitoneal injection of ketamine 20 mg/kg (RBI, Natick, MA) and xylazine 0.2 mg/kg (Bayer, Shawnee Mission, KS) then transcardially perfused with 200 ml PBS, pH 7.4 followed by 200 ml 4% PFA in PBS. The brains and spinal cords were removed, blocked, and postfixed in the same fixative for 4 hours at 4°C then cryoprotected in 30% sucrose in PBS at 4°C for 48 hours before freezing on dry ice. Coronal brain sections and transverse spinal cord sections were cut at 30 μm using a freezing microtome. Tissue sections were immediately immersed in PBS and stored at 4°C until use. Sections were processed free-floating according to the protocol outlined in NEN Life Science Products TSA (Tyramide Signal Amplification) Indirect Kit. Briefly, tissue sections were permeabilized in 0.2% Triton X-100 (Sigma, St. Louis, MO)/PBS, incubated in 1% hydrogen peroxide (Sigma, St. Louis, MO)/PBS to remove endogenous peroxidase activity then blocked in TNB Buffer (0.1 M Tris-HCl, pH 7.5, 0.15 M NaCl, and 0.5% Blocking Reagent. Sections were incubated for 24 hours at 4°C in either the anti-GAL2 or anti-GAL3 antiserum (1:100). Following incubation with the primary antiserum, the tissue sections were washed in

TNT Buffer (0.1 M Tris-HCl, pH 7.4, 0.15 M NaCl, 0.05% Tween 20) followed by incubation at 25°C for 30 minutes with horseradish peroxidase (HRP)-conjugated goat anti-rabbit immunoglobulin (1:200) (Sternberger Monoclonals Inc., Lutherville, MD). Tissue sections were rinsed in TNT Buffer and incubated in a solution containing biotinylated tyramide to amplify the signal then rinsed in TNT buffer and incubated with HRP-conjugated to streptavidin at 25°C for 30 minutes. An immunoperoxidase reaction was done by incubating the section in 3,3'-diaminobenzidine (DAB) (0.05%) in 0.1 mM Tris, pH 7.4 and adding hydrogen peroxide to 0.006% immediately before use. The reaction was stopped in water and the sections mounted on microscopic slide with mounting medium (40% ethanol: gelatin) and counterstained with Cresyl violet then coverslipped for light microscopy.

Optimal GAL3 antibody concentrations (1:200) for rat brain sections were determined in preliminary titration experiments. Experimental controls in the tissue sections included (1) incubation in normal rabbit serum or (2) omission of the primary antiserum.

Analysis

COS-7 cells and tissue sections were examined using a Zeiss Axioscope. A total of 6 male rats were examined with the anti-GAL3 antiserum. The identification of GAL3-LI in the transfected cells and brain regions was based on the presence of immunoreactivity appearing as a brownish precipitate in individual cells and their projections or in the neuropil of the tissue by light

microscopy. The descriptions of neuroanatomic boundaries are based on the atlas of Paxinos and Watson (1998).

B. Results

Characterization of the GAL3 antiserum

Recombinant GAL1, GAL2, and GAL3 receptor transfected cells

The ability of the anti-GAL3 antiserum to recognize only the GAL3 receptor protein in vitro was established by performing immunocytochemistry on COS-7 cells transiently transfected with the recombinant receptor proteins for the rat GAL1, GAL2, and GAL3, or mock-transfected with vector only. Specific porcine ^{125}I-galanin binding was detected for all transfectants except mock-transfected cells. An immune response was detected only in the COS-7 cells incubated with the antiserum generated for the particular recombinant receptor. Specifically, no immune reaction was observed with the anti-GAL3 antiserum (1:1000) in GAL1 or GAL2 transfected cells. Furthermore, no visible immune reaction was detected in the mock-transfected cells. Incubation of the cells in primary antiserum that had been preabsorbed with the antigenic peptide (20 μg/ml) or without the primary antiserum or with the primary replaced by normal goat serum did not result in an immune response.

Taken together, these data demonstrate that the anti-GAL3 antiserum recognizes the receptor against which it was generated and does not show cross reactivity with other known GAL receptors.

Western Blots

To determine the specificity of the anti-GAL3 antiserum, COS-7 cells were transiently transfected either with recombinant rat GAL2 or GAL3 receptors or with expression vector only; membranes were then isolated for evaluation by immunoblotting (see Figure 5). The anti-GAL3 antiserum labeled proteins in membranes only from rat GAL3-transfected cells; a predominant band was evident with an apparent molecular weight of approximately 56 kDa (Figure 5), somewhat higher than the amino acid-derived value of 40.4 kDa. (For comparison, apparent molecular weights determined by SDS-PAGE are 56 kDa (Servin et al., 1987) or 54 kDa (Chen et al., 1992) for native GAL receptors purified from rat brain and 54 kDa (Amiranoff et al., 1989) for native GAL receptors purified from Rin m 5F cells. These values are all higher than the amino acid-derived value any known GAL receptor subtype, including the value of 38.9 kDa for rat GAL1 (Parker et al., 1995). The apparently high molecular weight observed for rat GAL3 very likely reflects post-translational processing such as glycosylation; note that rat GAL3 contains multiple N-terminal glycosylation sites (Smith et al., 1998). Relative to the predominant band, additional species of higher molecular weight as well as lower molecular weight were labeled by the corresponding antiserum (Figure 5). These are presumably receptor-related species composed of protein aggregates of C-terminal fragments, as they are absent in mock-transfected cells.

Immunohistochemical distribution of GAL3-LI in the CNS

GAL3-like immunoreactivity (GAL3-LI) was observed in many regions of the brain, specifically, the neocortex, septum, hippocampus, amygdala, and brainstem (see Table 12). Throughout the brain and spinal cord GAL3-LI was found to be associated with neuronal profiles however, there was neuropil staining observed in several brain regions. Several regions of the CNS almost exclusively expressed GAL3-LI, specifically the accumbens nucleus, dorsal raphe, ventral tegmental area (Table 12). There was no observable staining of the fiber tracts.

The specificity of the anti-GAL3 antiserum was determined in tissue sections by (1) omission of the primary antiserum or (2) incubation with normal rabbit serum. No specific staining was observed in either condition. Preabsorption of the GAL3 primary antiserum with the antigenic peptide (10 μg/ml) decreased but did not completely block staining in the tissue sections as in the transfected cells. This was most likely related to the different localization approaches. In the transiently transfected COS-7 cells the expression of GAL3 receptor protein was relatively high therefore, indirect immunocytochemistry with no amplification was used. In contrast, GAL3 receptor protein expression is presumed to be relatively lower in the tissue sections and for that reason the TSA (amplification) technique was employed. It is possible that because of the amplification (1000-fold) in the TSA technique even small amounts of unabsorbed antiserum may result in a signal.

Distribution of GAL3-LI in the rat CNS

Cerebral cortex

GAL3-LI was widespread in the cerebral cortex and the distribution pattern extended rostrocaudally. A weak to moderate GAL3-LI was seen in numerous cell bodies in the anterior cingulate cortex.

Septal region

An extensive and densely stained fiber network was seen throughout the entire lateral, intermediate and medial septal nuclei. The dorsal division of the lateral septum contained scarce moderately GAL3-like immunoreactive somata.

Basal ganglia

Numerous moderately GAL3-like immunoreactive cell bodies and fibers were present in the shell and core of the accumbens nucleus. The cell bodies of the subthalamic nucleus, a relay nucleus in the basal ganglia, contained weak GAL3-LI.

Amygdala and Extended Amygdala

In general, GAL3-LI was weak throughout the amygdala. Scattered cell bodies and fibers exhibited weak staining in several nuclei. Very fine GAL3-like immunoreactive fibers with scattered moderately labeled cells were detected in the central amygdaloid nucleus.

Midbrain/Mesencephalon

Labeled cells were detected within the dorsal raphe and projections from these cells were seen converging toward

the midline of the raphe. Moderately immunoreactive scattered cells were evident in the ventral tegmental area.

Brain stem

Intense staining was observed in cell bodies in the locus coeruleus.

The distribution of rat GAL3 protein in the CNS using receptor subtype selective polyclonal antibodies and tyramide signal amplification (TSA) immunocytochemistry is illustrated in Table 12. These were qualitative evaluations for the rat GAL3 receptor protein distribution based on the relative intensity of the chromogen (3,3'-diaminobenzidine) observed in individual cells at the microscopic level.

A total of 4 rat brains were analyzed for this study. As shown in Table 12, the strength of the signal obtained in various regions of the rat brain was graded as weak (+), or moderate (++) or intense(+++).

Table 12

REGION	cells	fibers	Potential Therapeutic Application
Telencephalon			
Frontal cortex	++		Anxiety/Depression
Cingulate cortex	++		Anxiety/Depression
Basal ganglia			
Accumbens nucleus	++	-	Treatment of the positive symptoms of schizophrenia Treatment of drug addiction. This region is particularly sensitive to psychoactive drugs. Anxiety/depression
Septal Region			Relief of fear
Lateral septal nucleus, dorsal	+	++	
Lateral septal nucleus, ventral	+	++	
Intermediate septal nucleus	-	++	
Medial septal nucleus		++	
Amygdala and extended Amygdala			Treatment of anxiety, panic attack, and depression. Treatment of disorders of integrated behaviors such as defense, ingestion, reproduction, and learning.
Central nucleus	++	++	Fear and anxiety

Mesencephalon			
Dorsal raphe	++	-	Depression/Analgesia
Ventral tegmental area	++	-	Depression
Brainstem/Pons/Medulla			
Locus coeruleus	+++	-	Modulation of noradrenergic transmission. Treatment of depression

The GAL3 antiserum was characterized using recombinant GAL receptors in transiently transfected COS-7 cells and Western blot analysis and the specificity of the GAL3 antiserum to recognize only the cognate receptor in vitro was established. The anatomical distribution of the GAL3 receptor protein in the rat CNS was determined using a modified immunohistochemical technique to enhance sensitivity and delectability via tyramide signal amplification (Toda et al., 1999).

The results indicate that the expression GAL3-LI was primarily found in neuronal profiles with neuropil labeling detectable in several areas. In general, the distribution of GAL3-LI is in good agreement with the reported distribution for galanin-LI, galanin binding sites, and GAL3 mRNA in the rat brain (for recent review, Branchek et al., 2000). Overall, GAL3-LI was extensively distributed throughout the brain. Paralleling the distribution of galanin binding sites GAL3-LI was observed in ventral regions of the brain.

The localization of the GAL3 protein in the dorsal raphe and locus coeruleus suggests a potential therapeutic application of galanin receptor antagonists in the treatment of depression by attenuating galanin's inhibitory tone on both of these regions.

A decrease in central serotonin (5-HT) neurotransmission has been implicated in depression. GAL3 antagonists could possibly act via GAL3 receptors on the cell bodies of dorsal raphe neurons to increase firing rate of raphe neurons thus increasing 5-HT release in the telencephalon and diencephalon. Another possible site of action for a GAL3 antagonist could be on postsynaptic GAL3 receptors in the limbic forebrain to block the putative ability of galanin to negatively regulate 5-HT_{1A} receptor transmission (Misane et al, 1998).

Unlike the dorsal raphe cells, the cells of the locus coeruleus express abundant galanin under normal conditions and it has been proposed that galanin may be released from dendrites and soma of the noradrenergic cell bodies (for review, Hökfelt et al., 1998). The ascending afferent projections of the locus coeruleus are extensive throughout the brain. Changes in the noradrenergic system have been hypothesized to be involved in depression-related behaviors and symptoms (for review, Weiss et al., 1998). The ventral tegmental area (VTA) receives projections from the locus coeruleus that have been reported to co-localize galanin and noradrenaline. It has been proposed that in certain pathological states (ex. stress induced depression) galanin released from noradrenergic terminals in the VTA

inhibits dopaminergic neurons in the region that results in decreased dopamine release in the forebrain regions, particularly the accumbens nucleus and prefrontal cortex. This decrease in dopamine release produces a decreased motor activation and anhedonia. GAL3 has been identified in all of these regions and thus presents itself as a potential therapeutic target in the treatment of depression. Drugs that would effectively decrease galanin's release in the VTA whether at the level of the locus coeruleus (somatodendritic GAL3 receptors to decrease the activity of LC cells) or in the VTA itself (presynaptically on NE/GAL terminals in the VTA or via GAL3 receptors on VTA-DA neurons to prevent the hyperpolarization VTA-DA cells by released galanin) would produce an antidepressant effect.

References

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, DC.

Amiranoff, B., et al., (1989) Galanin receptor in the rat pancreatic beta cell line Rin m 5F. Molecular characterization by chemical cross-linking. *J. Biol. Chem.*, **264**(34): 20714-20717.

Asymmetric Synthesis (1983) **Vol: 2-5,** Academic Press, Editor Morrison, J.

Bakker, R.A., et al., (2000) Constitutive activity of the histamine H1 receptor reveals inverse agonism of histamine H1 receptor antagonists. *Eur. J. Pharmacol.*, **387:** R5-R7.

Borowsky, B., et al., (1999) Cloning and characterization of the human galanin GALR2 receptor. *Peptides*, **19**: 1771-1781.

Bradford, M.M. (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of the protein-dye binding. *Anal. Biochem.*, **72:** 248-254.

Branchek, T.A., et al., (2000) Galanin receptor subtypes. *Trends in Pharm. Sci.*, **21**: 109-116.

Bryant, W.M.III, et al., (1993) *Synthetic Communications,*

23: 1617-1625.

Chen, Y., et al., (1992) Solubilization and molecular characterization of active galanin receptors from rat brain. *Biochemistry*, **31(8):** 2415-2422.

Coppola, G.M. (1987) *Journal of Heterocyclic Chemistry*, **24:** 1249.

Cullen, B. (1987) Use of eukaryotic expression technology in the functional analysis of cloned genes. *Methods Enzymol.*, **152:** 685-704.

deLigt, R.A., et al., (2000) Inverse agonism at G protein-coupled receptors: (patho)physiological relevance and implications for drug discovery. *Br. J. Pharmacol.*, **130(1):** 1-12.

De Weille, J.R., et al., (1989) Galanin inhibits dopamine secretion and activates a potassium channel in pheochromocytoma cells. *Brain Res.*, **485:** 199-203.

Detke, M.J., et al., (1995) Active behaviors in the rat forced swim test differentially produced by serotonergic and noradrenergic antidepressants. *Psychopharmacology*, **121:** 66-72.

Ennis, M. D. and Ghazal, N. B., (1992) The synthesis of (+) and (-)-flesinoxan: Application of enzymatic resolution methodology. *Tetrahedron Lett.*, **33:** 6287-6290.

File, S.E. (1985) Animal models for predicting clinical efficacy of anxiolytic drugs: social behaviour. *Neuropsychobiology*, **13:** 55-62.

File, S.E. and Pellow, S. (1984) The anxiogenic action of FG 7142 in the social interaction test is reversed by chlordiazepoxide and Ro-15-1788 but not by CGS 8216. *Archs. Int. Pharmacodyn. Ther.*, **271:** 198-205.

File, S.E. and Pellow, S. (1983) The anxiogenic action of a convulsant benzodiazepine: reversal by chlordiazepoxide. *Brain Res.*, **278:** 370-372.

File, S.E., et al., (1982) The anxiogenic action of benzodiazepine-like antagonists. *Neuropharmacology*, **21:** 1033-1037.

File, S.E. (1980) The use of social interaction as a method for detecting anxiolytic activity of chlordiazepoxide-like drugs. *J. Neurosci. Methods*, **2:** 219-238.

File, S.E. and Hyde, J.R.G. (1979) A test of anxiety that distinguishes between the actions of benzodiazepines and those of other minor tranquilisers and of stimulants. *Pharmacol. Behav. Biochem.*, **11:** 65-69.

File, S.E. and Hyde, J.R.G. (1978) Can social interaction be used to measure anxiety? *Br. J. Pharmacol.*, **62:** 19-24.

Garden, S.J., et al., (1998). *Synthetic Communications*, **28**: 1679-1689.

Glover, V. (1998) Function of endogenous monoamine oxidase inhibitors (tribulin). *J. Neural. Transm. Suppl.*, **52**: 307-13.

Gopalan, C., et al., (1993) Neurochemical evidence that the inhibitory effect of galanin on tuberoinfundibular dopamine neurons is activity dependent. *Neuroendocrinology*, **58**: 287-293.

Green, T.W. and Wuts, P.G.M. (1991) *Protection groups in Organic Synthesis*, second Edition John Wiley & Sons, New York.

Guy, A.P. and Gardner, C.R. (1985) Pharmacological characterisation of a modified social interaction model of anxiety. *Neuropsychobiology*, **13**: 194-200.

Harlow, E. and Lane, D. (1999) *Immunoblotting*. In: Barker, P. editor. Using Antibodies: A Laboratory Manual. New York: Cold Spring Harbor Laboratory Press. p 267-309.

Herrick-Davis, K., et al., (2000) Inverse agonist activity of atypical antipsychotic drugs at human 5-Hydroxytryptamine2C receptors. *J. Pharmacol. Exp. Ther.*, **295(1)**: 226-32.

Hess, B.A. Jr. and Corbino, S. (1971) *Journal of Heterocyclic Chemistry*, **8**: 161.

Hökfelt, T., et al., (1998) Galanin in Ascending Systems. *Annals of the N.Y. Acad. Sci.*, Ed. T. Hökfelt, Tamas Bartfai and J. Crawley p. 252-263.

Iversen, L. (2000) Neurotransmetter transporters: fruitful targets for CNS drug discovery. *Mol. Psychiatry*, **5(4):** 357-62.

Jansson, A., et al., (1989) Centrally administered galanin reduces dopamine utilization in the median eminence and increases dopamine utilization in the medial neostriatum of the male rat. *Acta Physiol. Scand.*, **135:** 199-200.

Javitch, J.A., et al, (1984) ^{3}H-Mazindol binding associated with neuronal dopamine and norepinephrine uptake sites. *Molecular Pharmacology*, **26**: 35-44.

Jaques, J., et al., (1981) *Enantiomer, Racemates and Resolutions*. John Wiley & Sons.

Julius, D., et al., (1988) Molecular characterization of a functional cDNA encoding the serotonin 1c receptor. *Science*, **241**: 558-564.

Kenakin, T. (1996) The classification of seven transmembrane receptors in recombinant expression systems. *Pharmacol. Rev.*, **48(3):** 413-63.

Kennett, G.A., et al., (1997) Anxiolytic-like actions of the selective 5-HT4 receptor antagonist SB-20470-A and SB-20766-A in rats. *Neuropharmacology*, **36(4-5):** 707-712.

Kirby, L.G. and Lucki, I. (1997) Interaction between the forced swimming test and fluoxetine treatment on extracellular 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in the rat. *Stress*, **2(4):** 251-263.

Leonard BE. (1996) New approaches to the treatment of depression. *J Clin Psychiatry*. **57(4):** 26-33.

Lightowler, S., et al., (1994) Anxiolytic-like effect of paroxetine in a rat social interaction test. *Pharmacol. Behav. Biochem.*, **49:** 281-285.

Lucki, I. (1997) The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. *Behav. Pharmacol.*, **8:** 523-528.

Lutz, M. and Kenakin, T. (1999) *Quantitative Molecular Pharmacology and Informatics in Drug Discovery*, John Wiley & Sons, LTD, West Sussex, England. p. 153.

Misane, I., et al., (1998) Modulation of a 5-HT1A receptor-mediated beavioral response by the neuropeptide galanin. *Ann. N.Y. Acad. Sci.*, **863:** 442-444.

Monsma, F.J. Jr., et al., (1993) Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.*, **43:** 320-327.

Nógrádi, M. (1987) *Stereoselective Synthesis*, VCH, Editor Ebel, H.

Nordstrom, O., et al., (1987) Evidence for an inhibitory effect of the peptide galanin on dopamine release from the rat median eminence. *Neurosci. Lett.*, **73:** 21-26.

Owens, M.J. (1997) Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J. Pharm. Exp. Ther.*, **283:** 1305-1322.

Otsuka, S. and Kobayashi, Y. (1964) A radioisotopic assay for monoamine oxidase determinations in human plasma. *Biochem. Pharmacol.*, **13:** 995-1006.

Page, M.E., et al., (1999) Serotonergic mediation of the effects of fluoxetine, but not desipramine, in the rat forced swim test. *Psychopharmacology*, **147:** 162-167.

Parker, E.M., et al., (1995) Cloning and characterization of the rat GALR1 galanin receptor from Rin14B insulinoma cells. *Mol. Brain Res.*, **34:** 179-189.

Paxinos, G. and Watson, C. (1986) The Rat Brain in Stereotaxic Coordinates. San Diego: Academic Press, Inc.

Porsolt, R.D. (1981) Behavioral despair. *In Enna, SJ (ed) Antidepressants: neurochemical, behavioral and clinical perspectives.* Raven Press, New York, pp. 121-139.

Porsolt, R.D., et al., (1978) Behavioral despair in rats: a new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.*, **47:** 379-391.

Porsolt, R.D., et al., (1977) Depression: a new animal model sensitive to antidepressant treatments. *Nature*, **266:** 730-732.

Razani, H., et al., (1997) 5-HT1A receptor activation: short-term effects on the mRNA expression of the 5-HT1A receptor and galanin in the raphe nuclei. *Neuroreport*, **8(16):** 3565-3570

Reneric, J.P. and Lucki, I. (1998) Antidepressant behavioral effects by dual inhibition of monoamine reuptake in the rat forced swim test. *Psychopharmacology*, **136:** 190-197.

Rodgers, R.J., et al., (1997) Animal models of anxiety: an ethological perspective. *Braz. J. Med. Biol. Res.*, **30:** 289-304.

Servin, A.L., et al., (1987) Identification and molecular characterization of galanin receptor sites in rat brain. *Biochem. Biophys. Res. Commun.*, **144(1):** 298-306.

Seutin, V., et al., (1989) Galanin decreases the activity of locus coeruleus neurons in vitro. *Euro. J. Pharmacol.* **164:** 373-376.

Smith, K.E., et al., (1998) Cloned human and rat galanin GALR3 receptors Pharmacology and activation of G-protein

inwardly rectifying K+ channels. *J. Biol. Chem.*, **273(36):** 23321-223326.

Sternberger, L.A. (1982) Neurotypy: regional individuality in rat brain detected by immunocytochemistry with monoclonal antibodies. *Proc. Natl. Acad. Sci. USA*, **79:** 1326-1330.

Tatsumi, M., et al., (1997) Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur. J. Pharmacol.*, **340(2-3):** 249-258.

Toda, Y., et al., (1999) Application of tyramide signal amplification system to immunohistochemistry: a potent method to localize antigens that are not detectable by ordinary method. *Pathol. Int.*, **49(5):** 479-483.

Treit, D. (1985) Animal models for the study of anti-anxiety agents: a review. *Neurosci. Biobehav. Rev.*, **9:** 203-222.

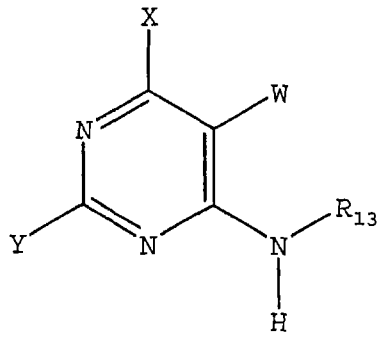
Weiss, J.M., et al., (1998) *Annals of the N.Y. Acad. Sci.*, (Ed. T. Hökfelt, Tamas Bartfai and J. Crawley) p. 364-382.

Xu, Z., et al., (1998) Galanin-5-hydroxytryptamine interactions: Electrophysiological, immunohistochemical and in situ hybridization studies on rat dorsal raphe neurons with a note on galanin R1 and R2 receptors.

Neuroscience, **87**: 79-94.

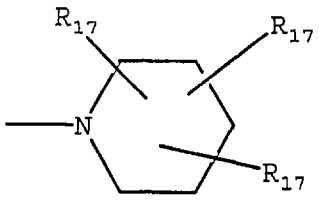
What is claimed:

1. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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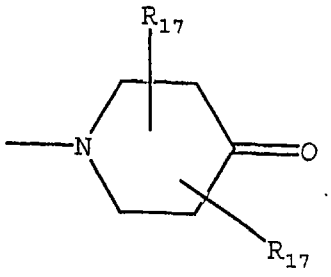

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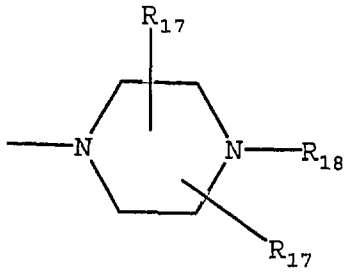


;

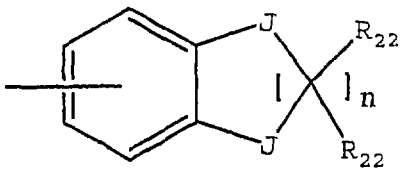
wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

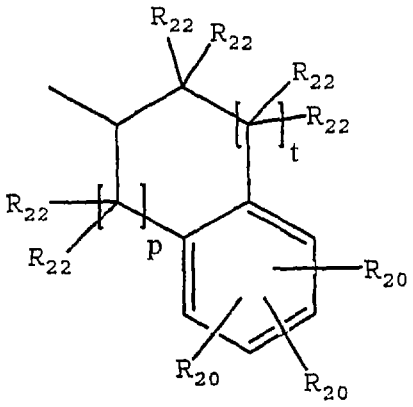
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

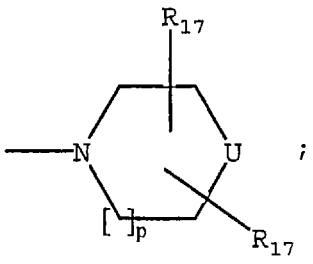


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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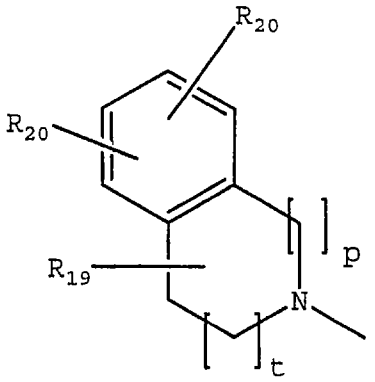
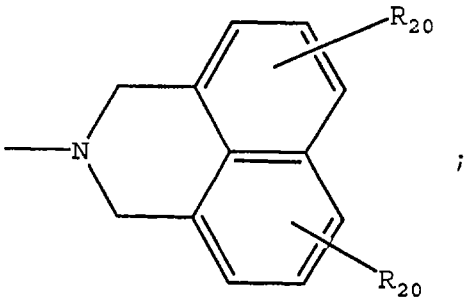


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl,

straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-

C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

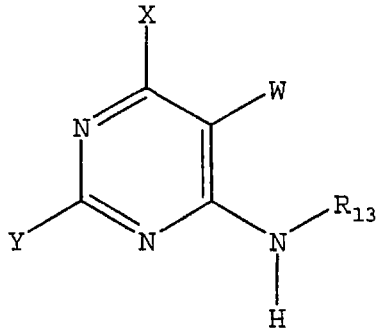
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

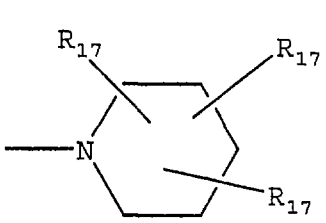
a pharmaceutically acceptable salt thereof.

2. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

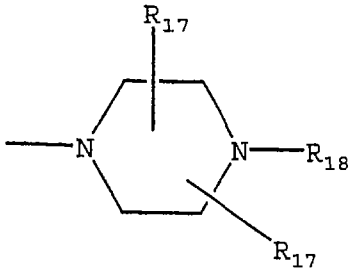


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



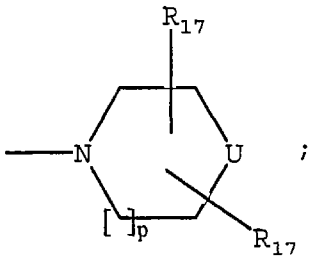
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl(C_1-C_6)alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;



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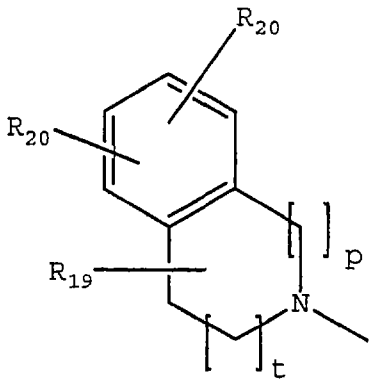
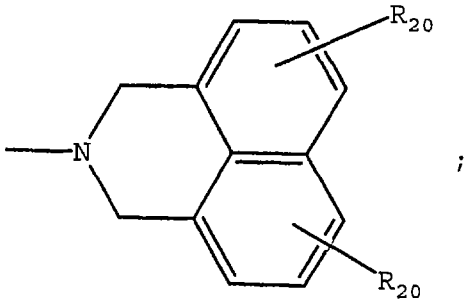


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

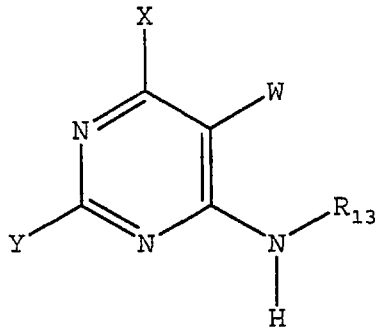
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

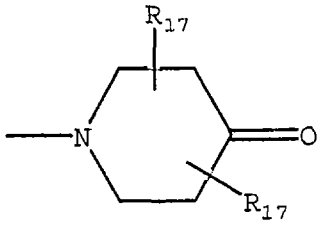
a pharmaceutically acceptable salt thereof.

3. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

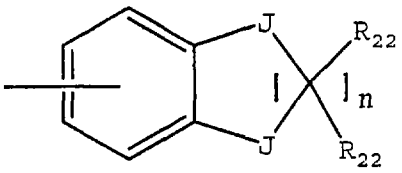
wherein X is $N(CH_3)_2$ or



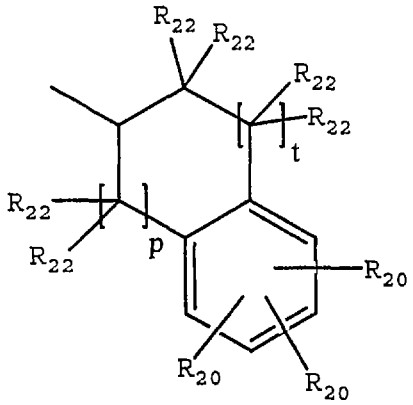
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



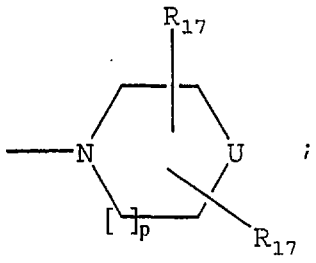
wherein Q_2 is



wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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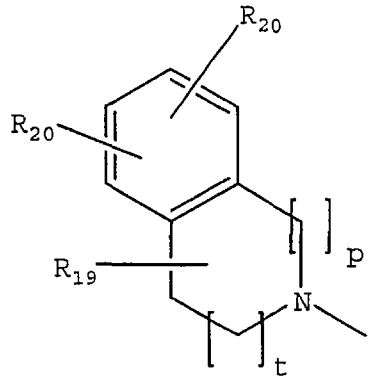
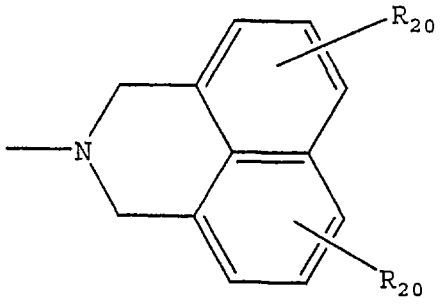


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

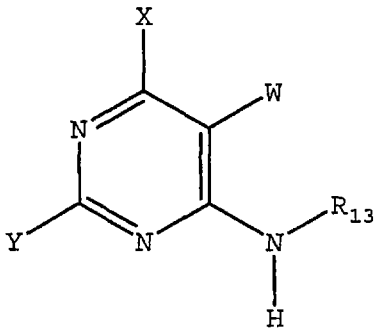
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

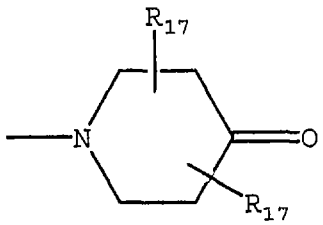
a pharmaceutically acceptable salt thereof.

4. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21},

$-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

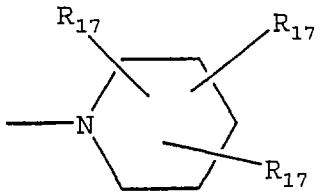
a pharmaceutically acceptable salt thereof.

5. The method of claim 1, 2, 3 or 4, wherein the compound is enantiomerically and diasteriomerically pure.

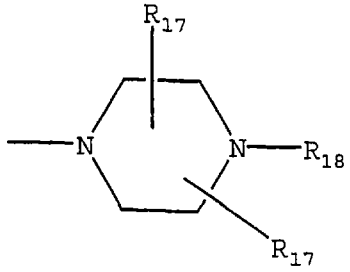
6. The method of claim 1, 2, 3 or 4, wherein the compound is enantiomerically or diasteriomerically pure.

7. The method of claim 1, 2, 3 or 4, wherein the compound can be administered orally.

8. The method of claim 1, wherein X is:



; or



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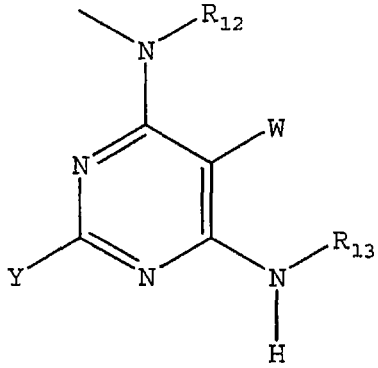
9. The method of claim 1, wherein X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

10. The method of claim 9, wherein the compound has the structure:



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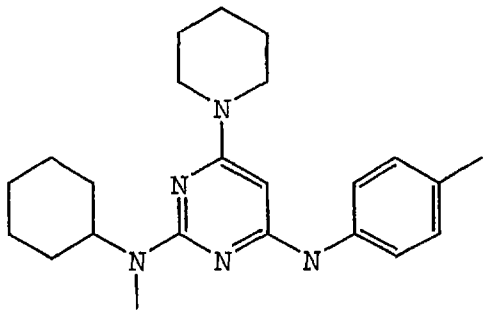
11. The method of claim 8, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

12. The method of claim 10, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

13. The method of claim 11, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

14. The method of claim 12, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

15. The method of claim 13, wherein the compound is selected from the group consisting of: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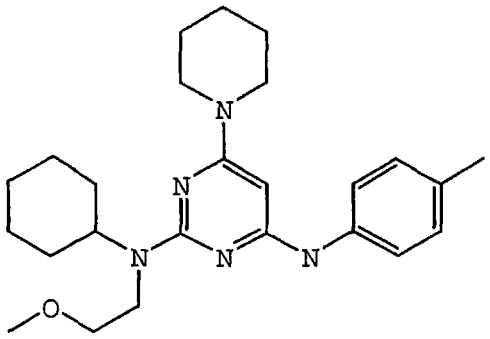
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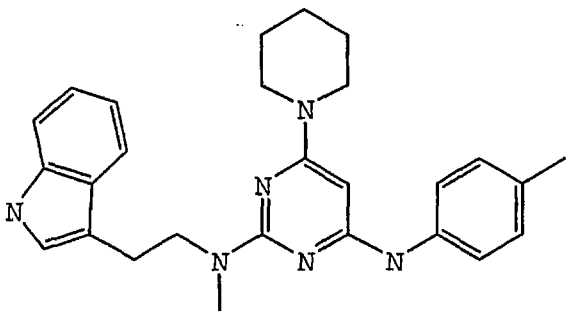
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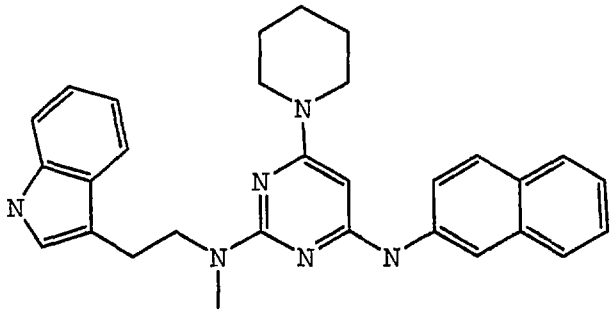

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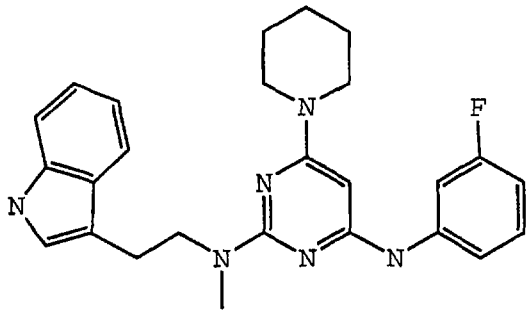

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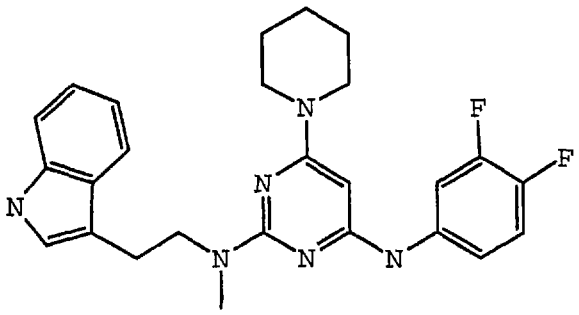

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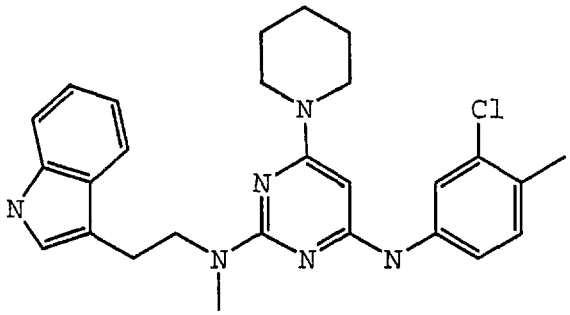
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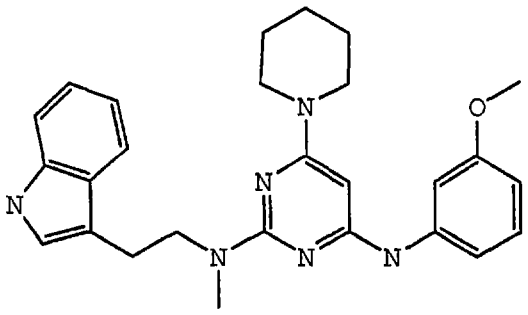
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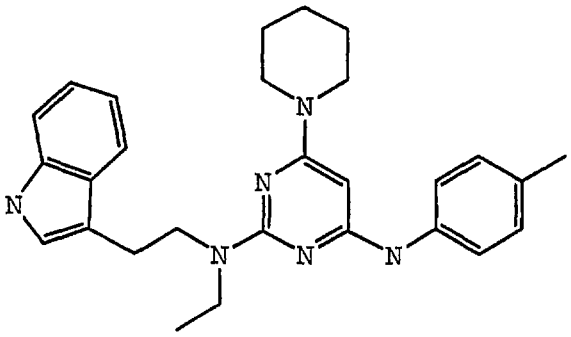
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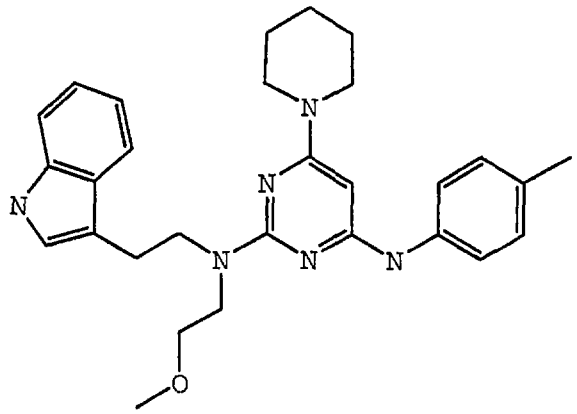

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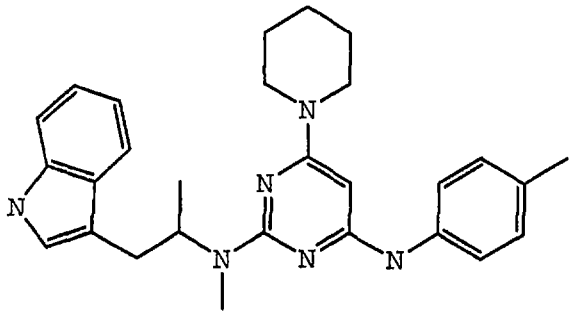

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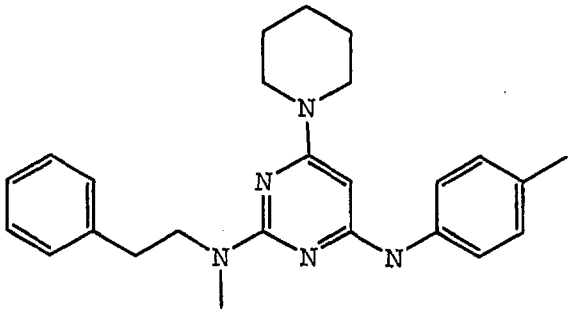

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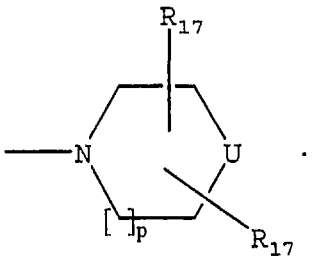
16. The method of claim 11, wherein Y is

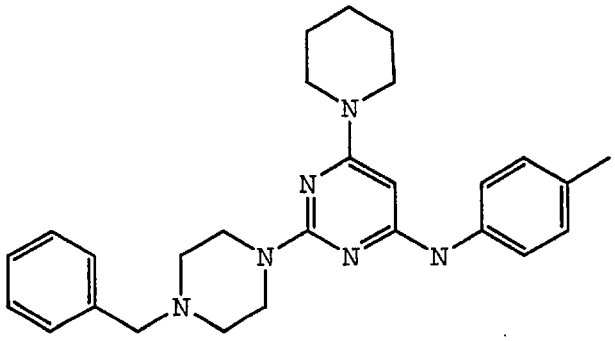


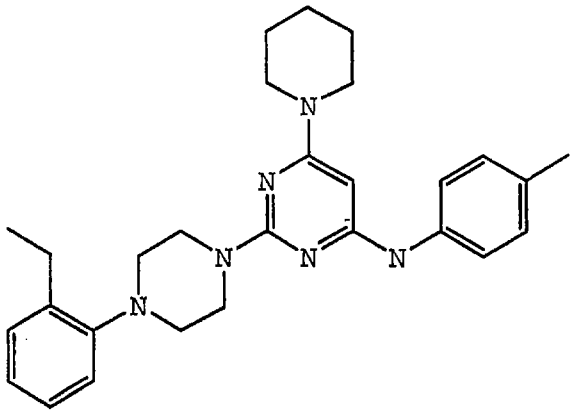
17. The method of claim 16, wherein U is NR_{16}.

18. The method of claim 17, wherein R_{16} is $(CH_2)_m$-Z.

19. The method of claim 18, wherein Z is aryl or heteroaryl.

20. The method of claim 19, wherein the compound is selected from the group consisting of:





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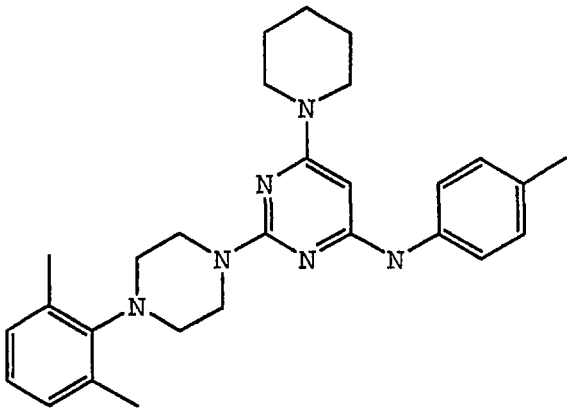

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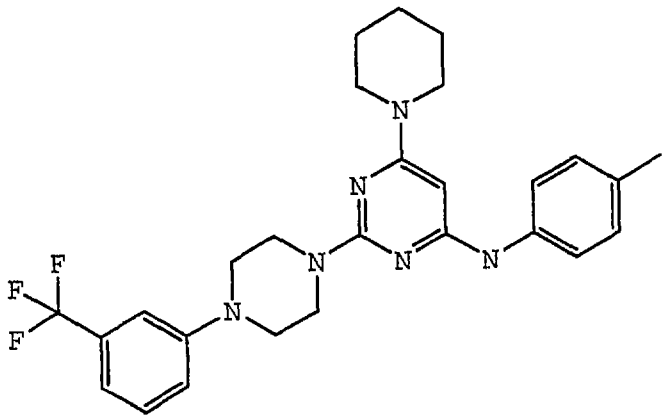

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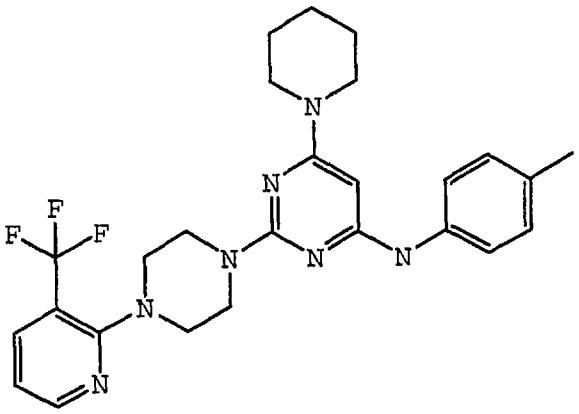
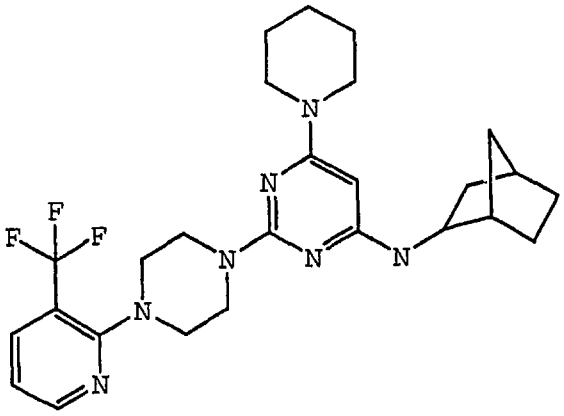
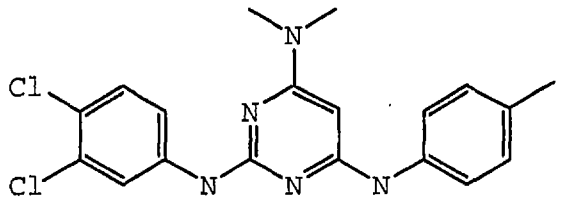


; and



21. The method of claim 12, wherein the compound is selected from the group consisting of:



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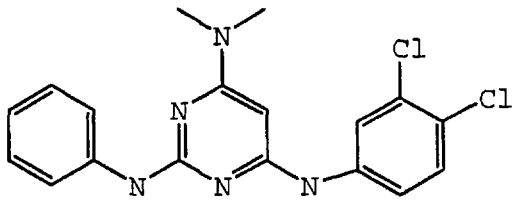

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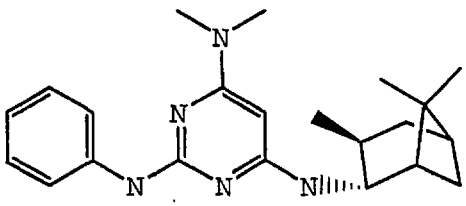

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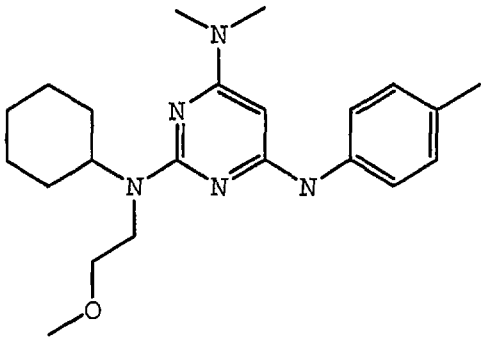

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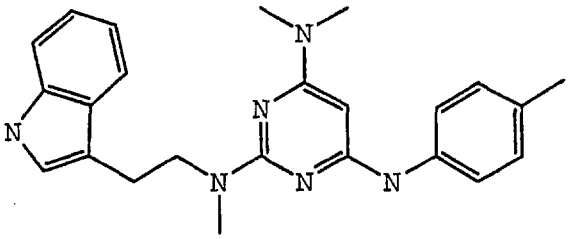
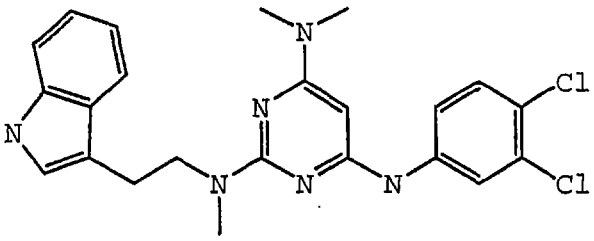
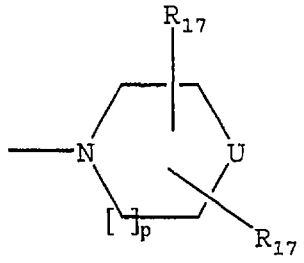


; and

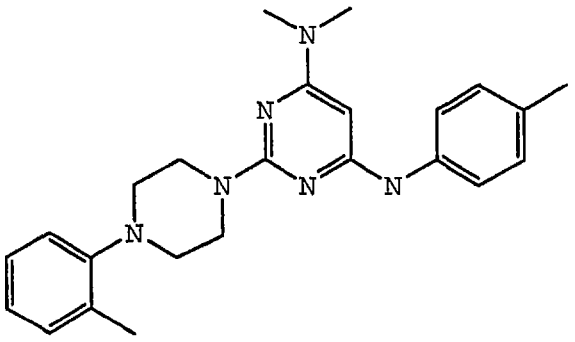


22. The method of claim 12, wherein Y is

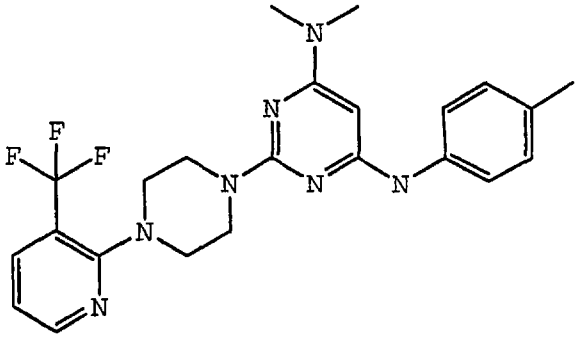


23. The method of claim 22, wherein U is NR_{16}.

24. The method of claim 23, wherein the compound is



; or



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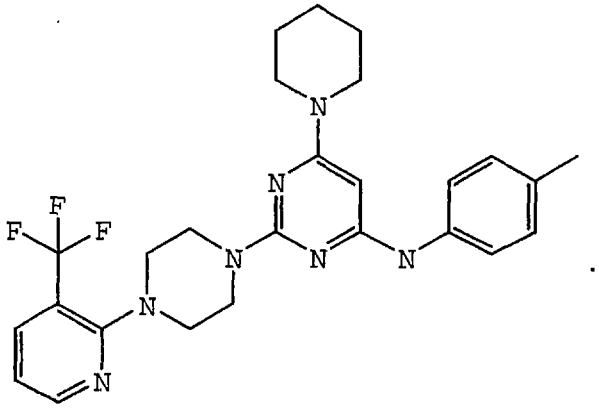
25. The method of claim 19, wherein the compound is



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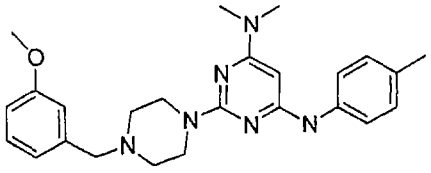
26. The method of claim 23, wherein the compound is selected from the group consisting of: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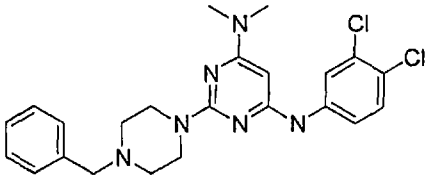
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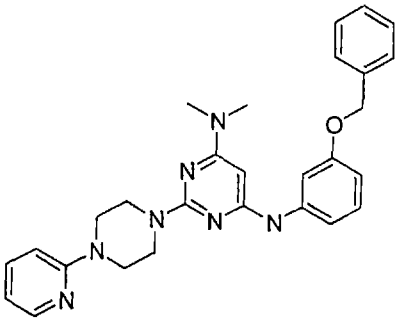
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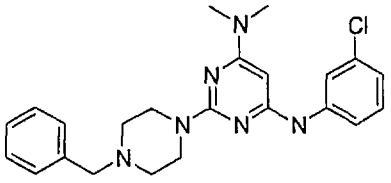
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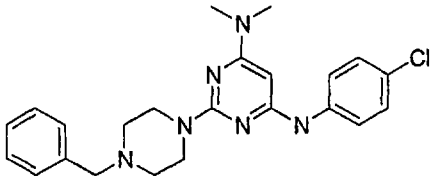
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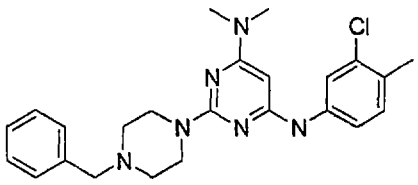
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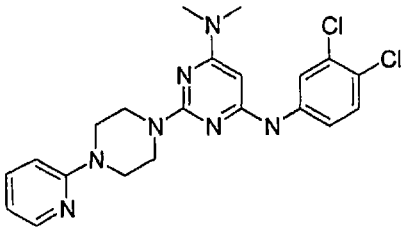
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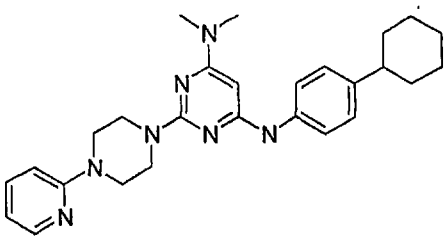
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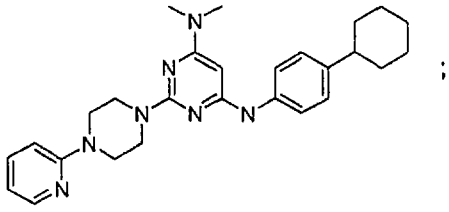
27. The method of claim 23, wherein the compound is selected from the group consisting of: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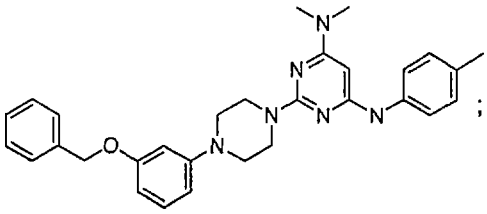
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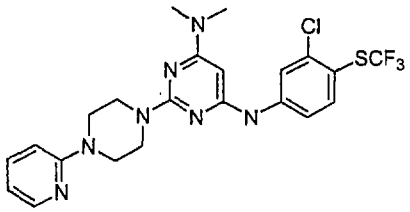
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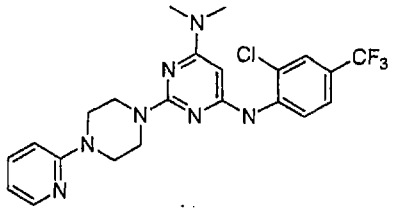
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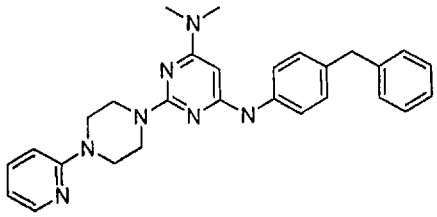
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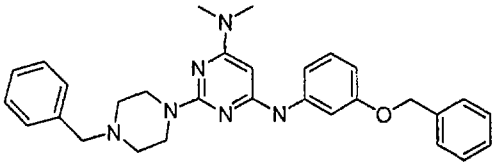

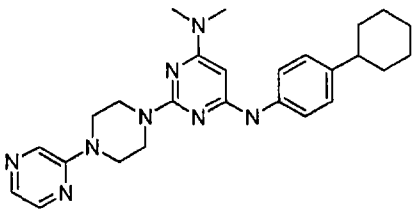
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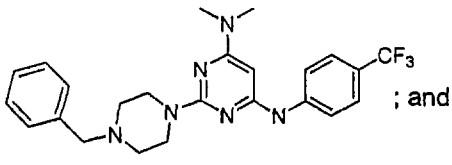
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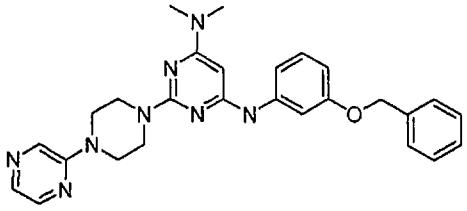
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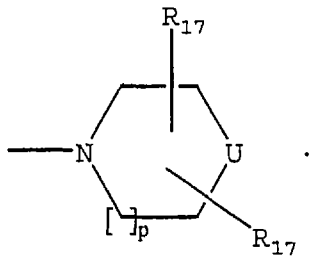
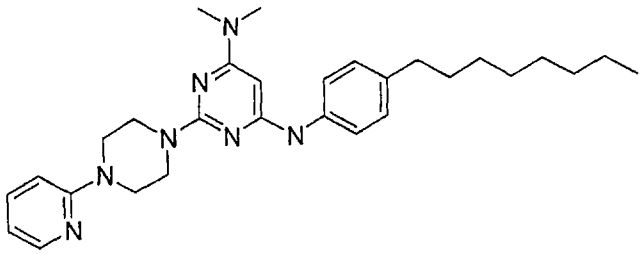
28. The method of claim 3, wherein X is $N(CH_3)_2$.

29. The method of claim 28, wherein Y is



30. The method of claim 29, wherein R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

31. The method of claim 30, wherein the compound is selected from a group consisting of: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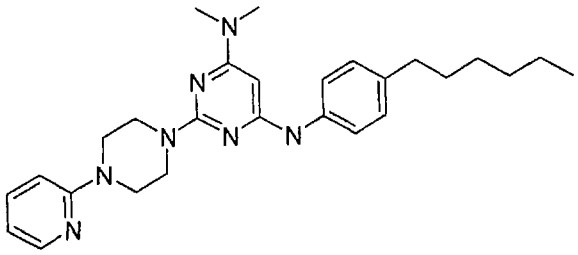
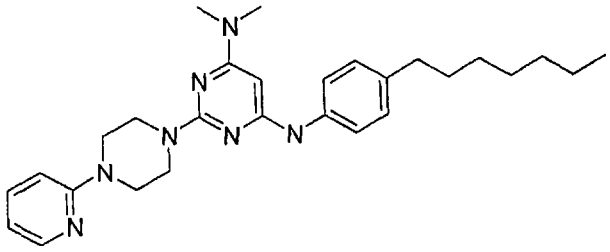

; and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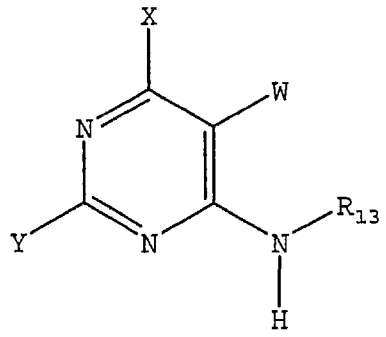
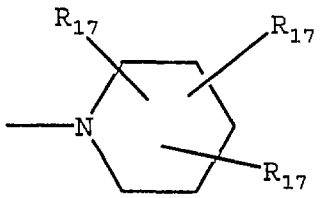
32. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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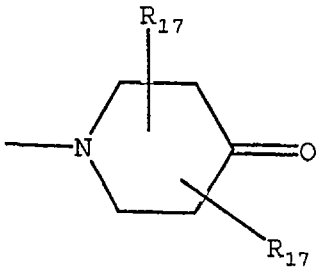
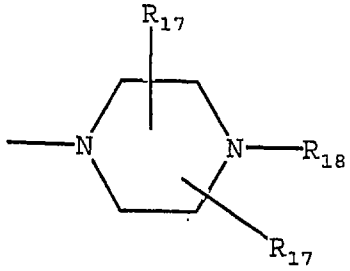


; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

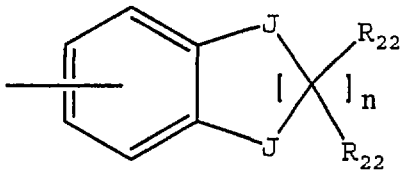
wherein R_{12} is straight chained or branched C_1-C_7 alkyl,

$(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

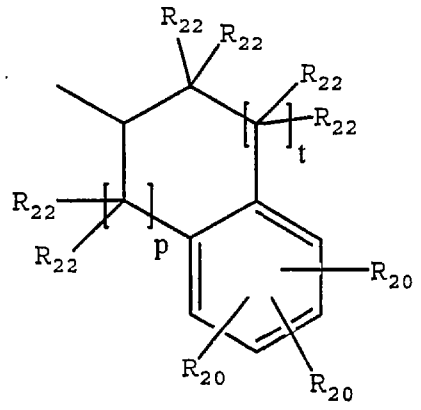
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is



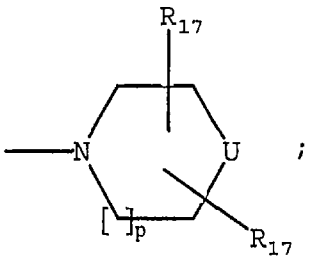
;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or

branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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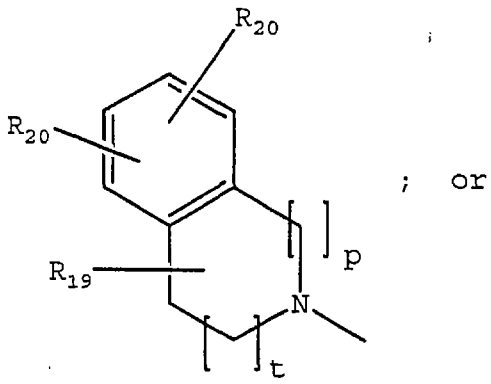
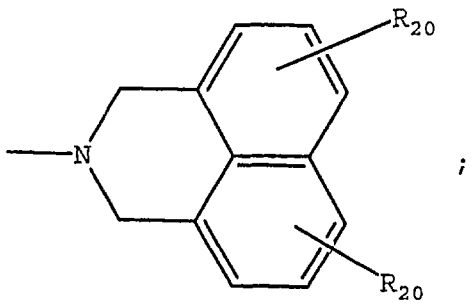


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight

chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

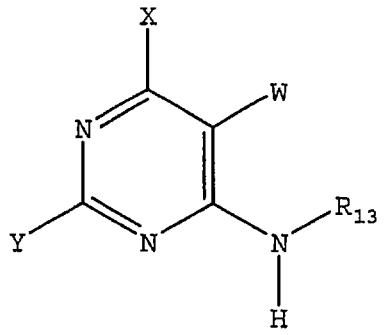
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

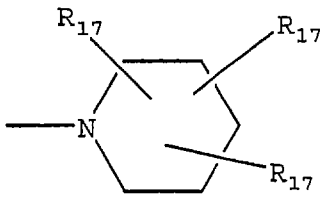
a pharmaceutically acceptable salt thereof.

33. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

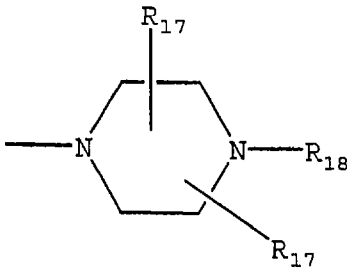


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



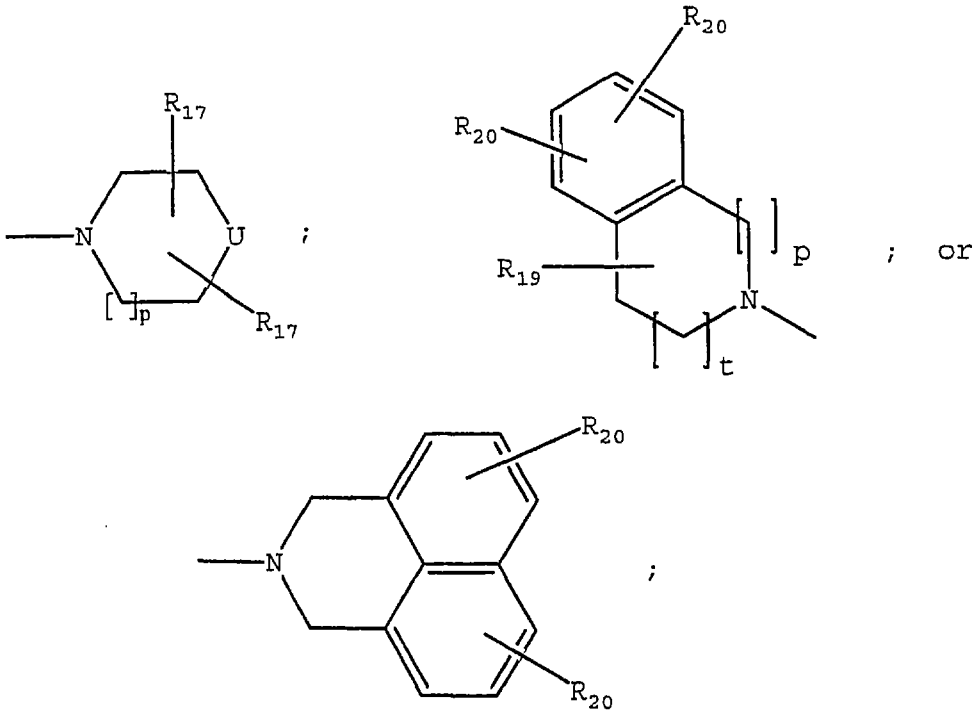
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

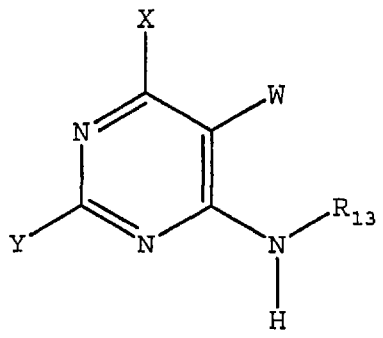
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

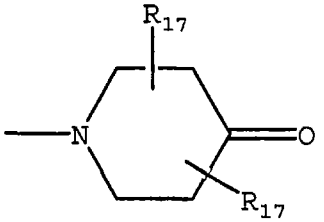
a pharmaceutically acceptable salt thereof.

34. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

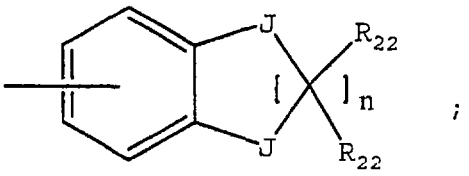


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

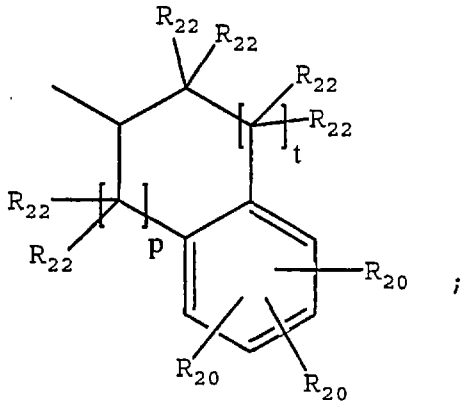
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

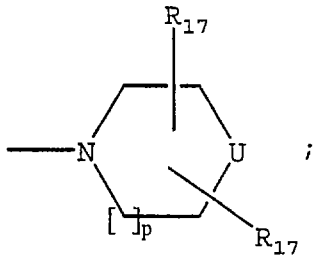


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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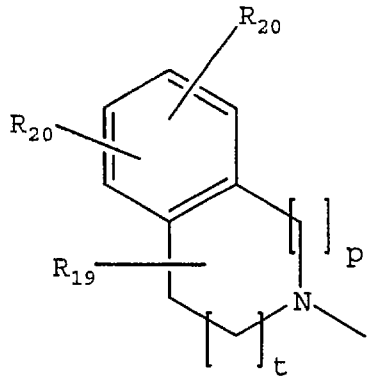
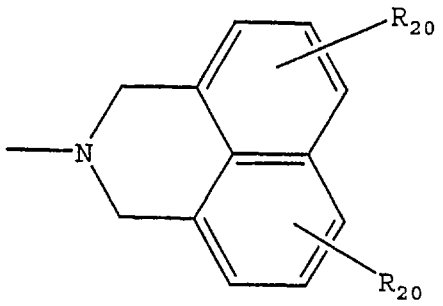


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl,

straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

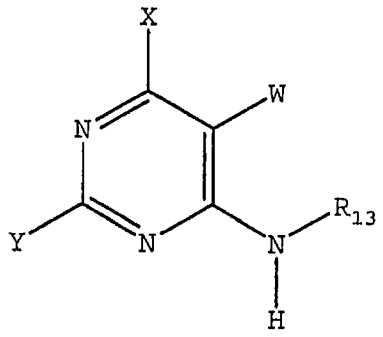
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

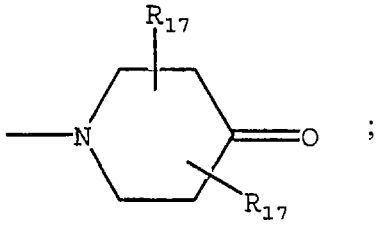
a pharmaceutically acceptable salt thereof.

35. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

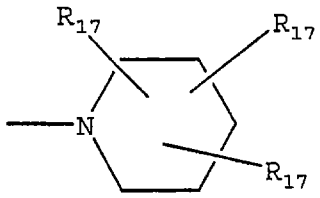
a pharmaceutically acceptable salt thereof.

36. The method of claim 32, 33, 34 or 35, wherein the compound is enantiomerically and diasteriomerically pure.

37. The method of claim 32, 33, 34 or 35, wherein the compound is enantiomerically or diasteriomerically pure.

38. The method of claim 32, 33, 34 or 35, wherein the compound can be administered orally.

39. The method of claim 32, wherein X is:



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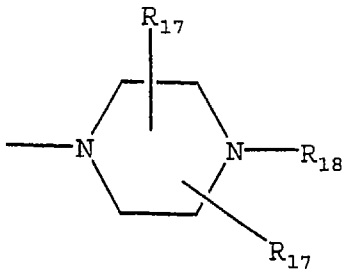
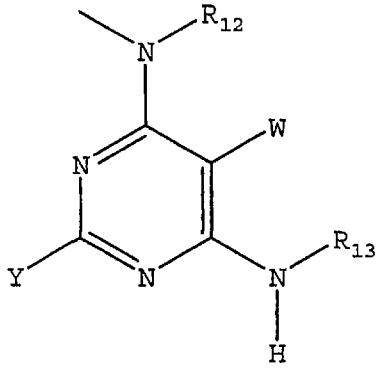


40. The method of claim 32, wherein X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

41. The method of claim 40, wherein the compound has the structure:



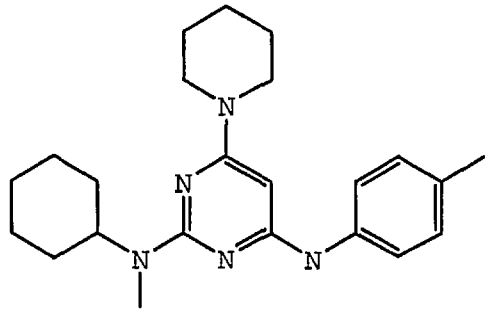
42. The method of claim 39, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

43. The method of claim 41, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

44. The method of claim 42, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

45. The method of claim 43, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

46. The method of claim 44, wherein the compound is selected from the group consisting of: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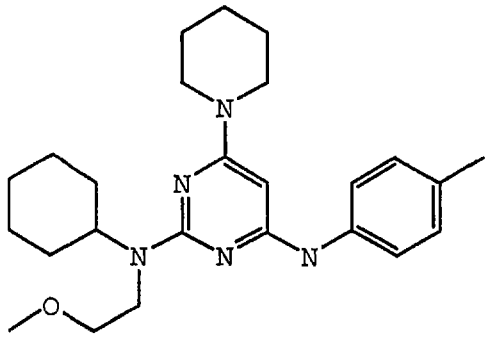
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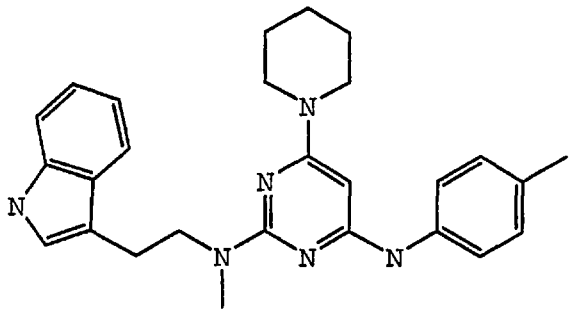
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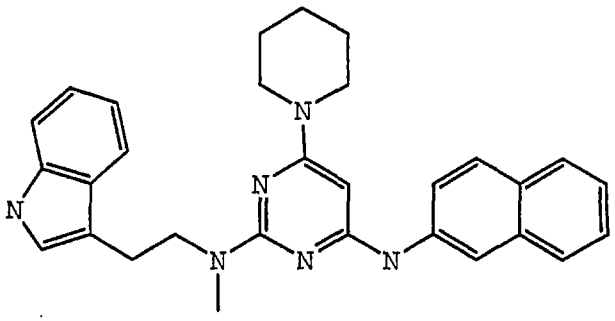

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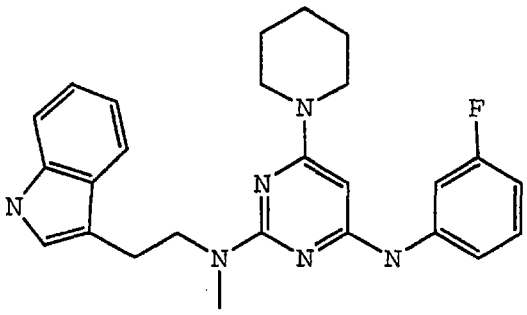

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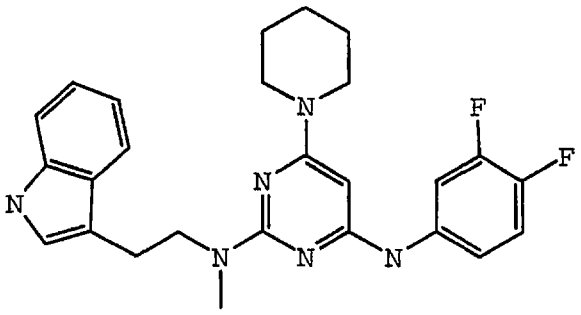

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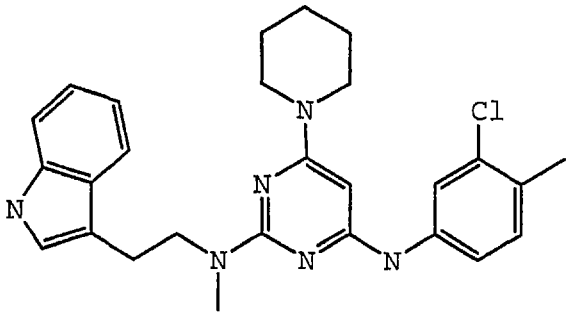
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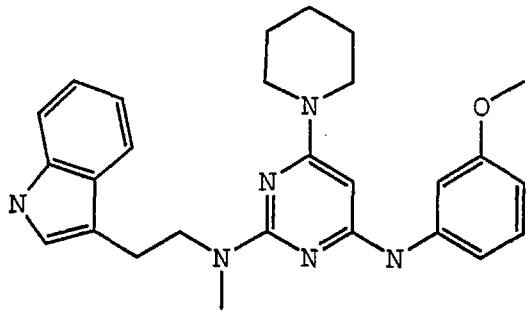
O

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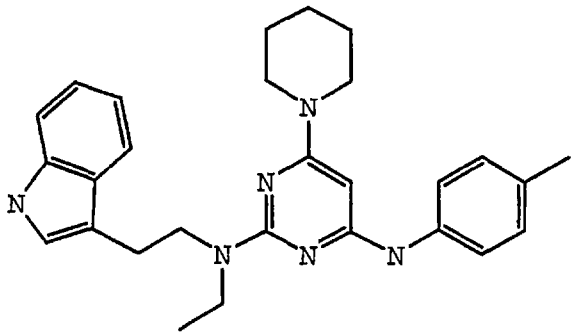

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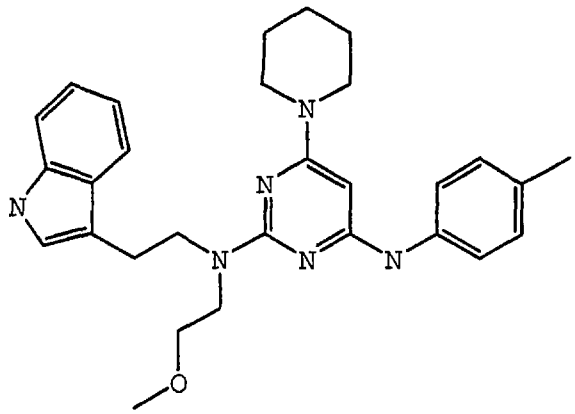

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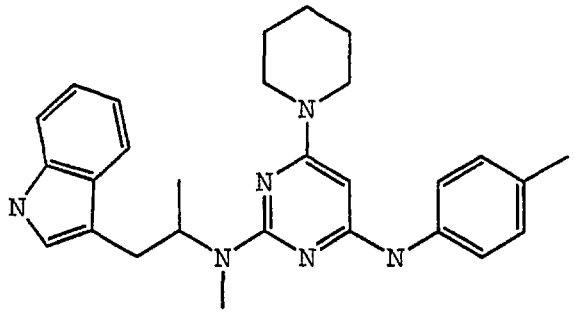
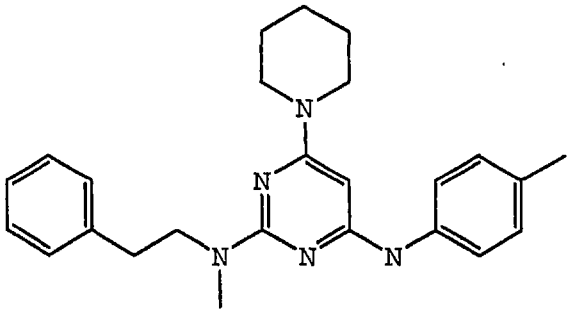


; and



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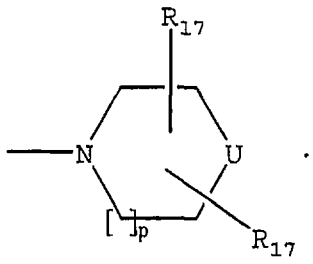
47. The method of claim 42, wherein Y is

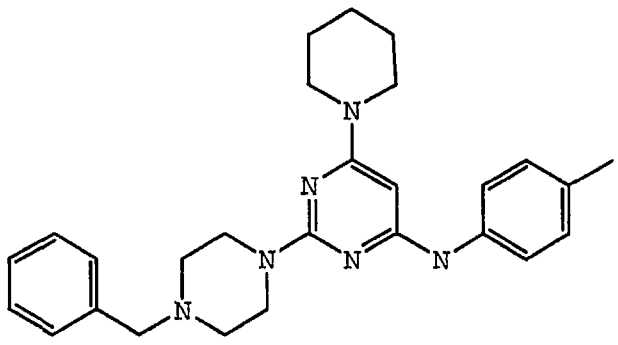


48. The method of claim 47, wherein U is NR_{16}.

49. The method of claim 48, wherein R_{16} is $(CH_2)_m$-Z.

50. The method of claim 49, wherein Z is aryl or heteroaryl.

51. The method of claim 50, wherein the compound is selected from the group consisting of:



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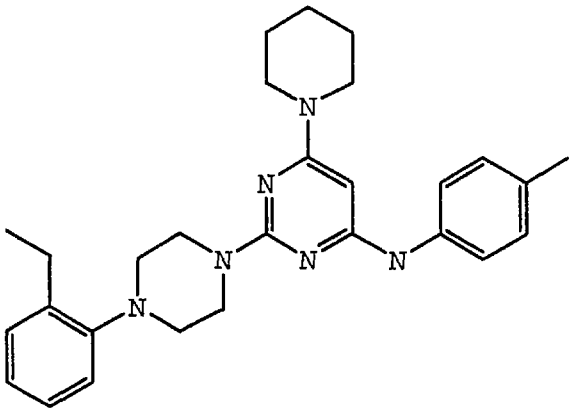

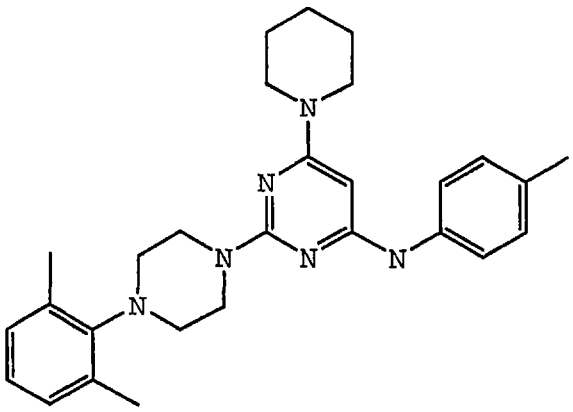

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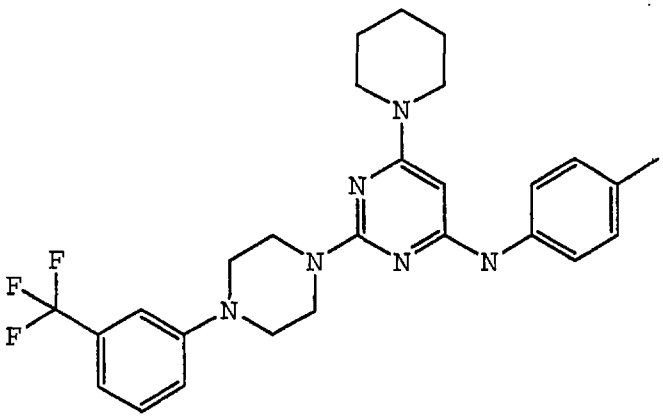

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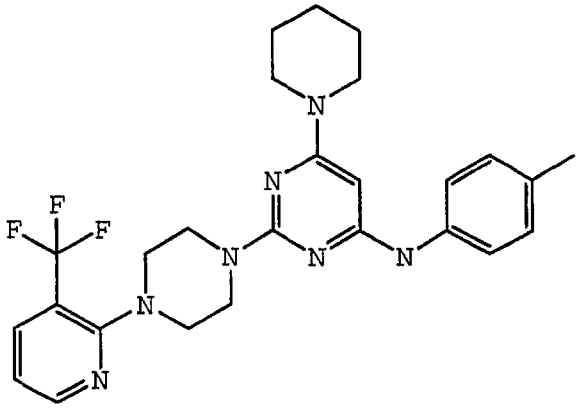
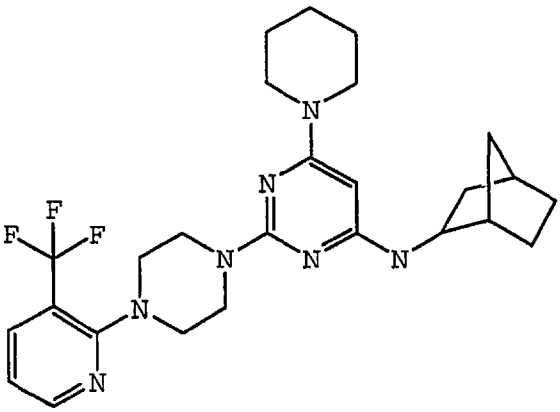
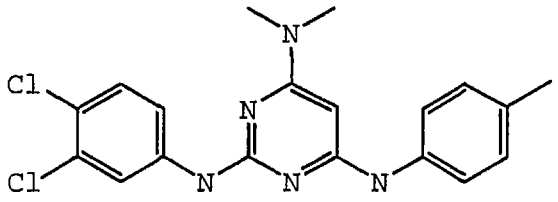


; and



52. The method of claim 43, wherein the compound is selected from the group consisting of:



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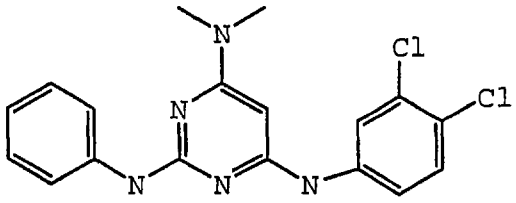
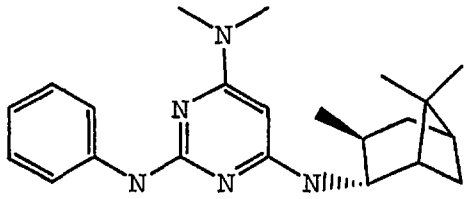


;



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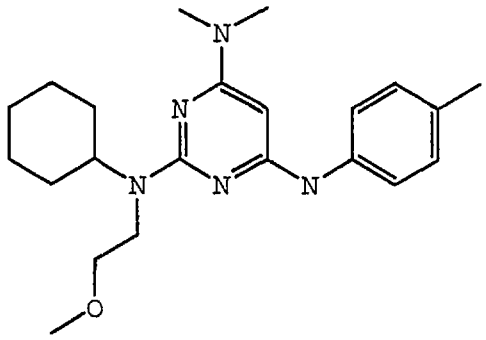

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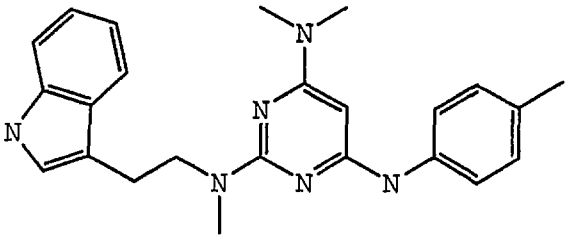
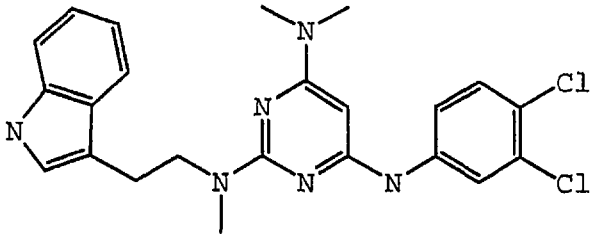
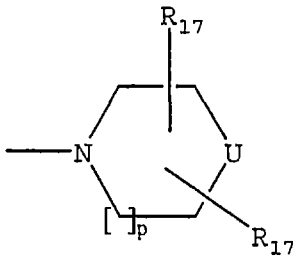


; and

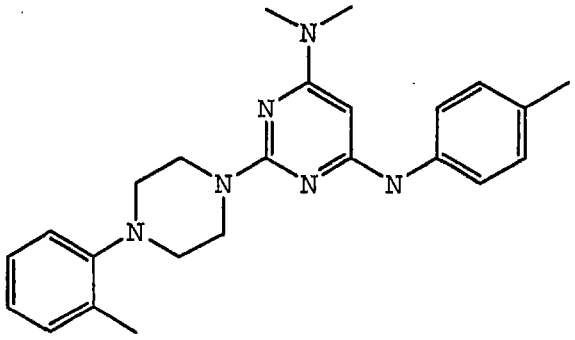


53. The method of claim 43, wherein Y is

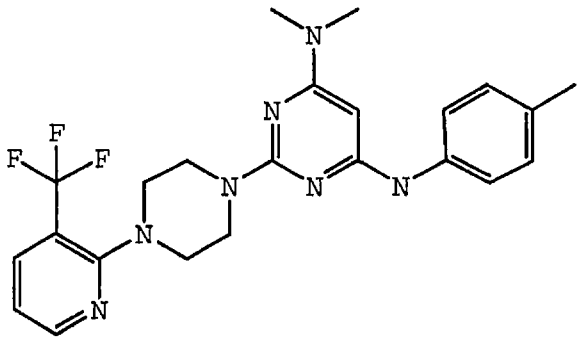


54. The method of claim 53, wherein U is NR_{16}.

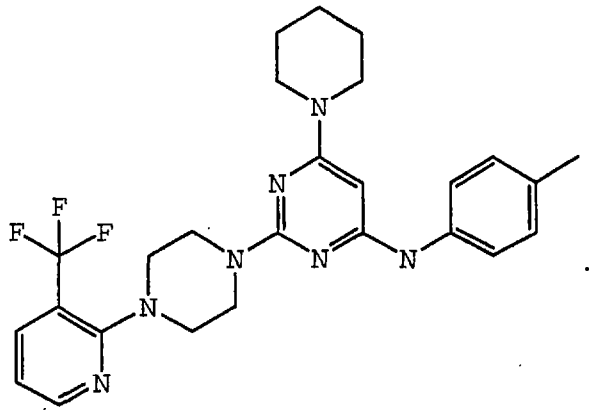
55. The method of claim 54, wherein the compound is



; or



56. The method of claim 50, wherein the compound is



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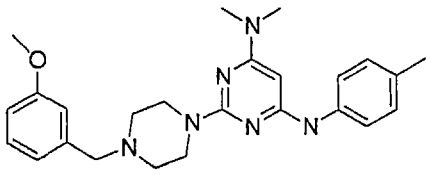
57. The method of claim 54, wherein the compound is selected from the group consisting of: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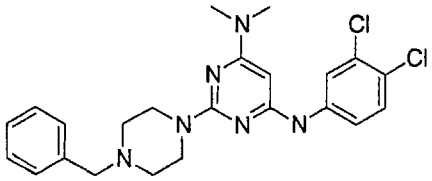
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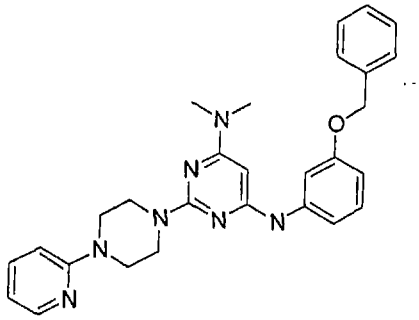
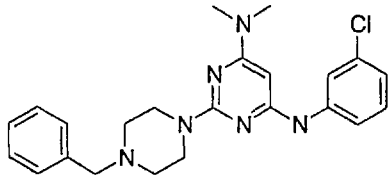
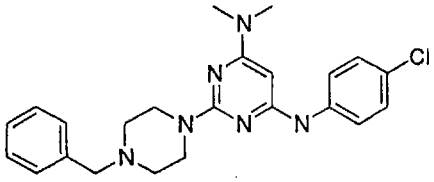

;

;

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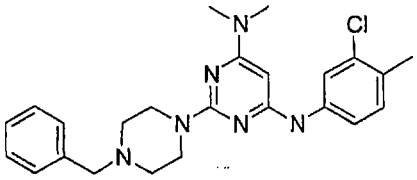
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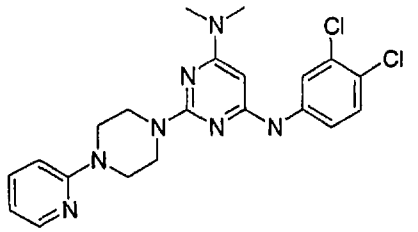
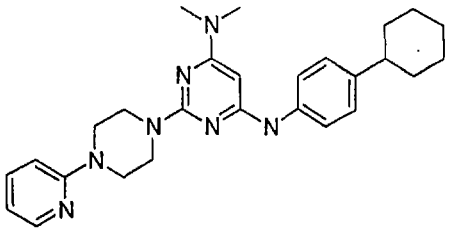

; and


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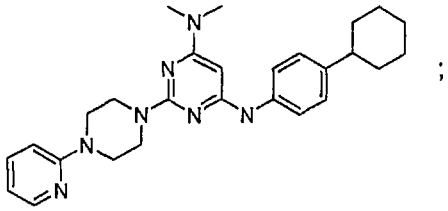
58. The method of claim 54, wherein the compound is selected from the group consisting of: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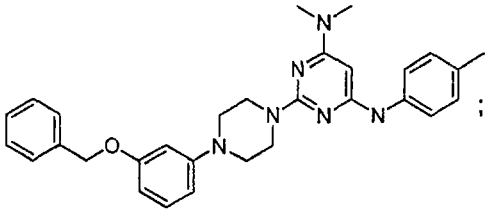
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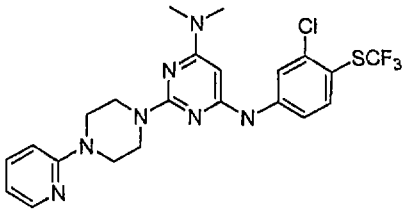
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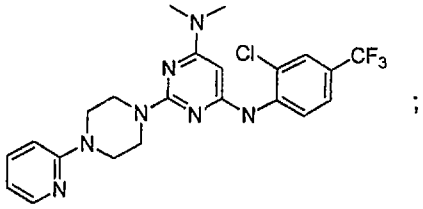
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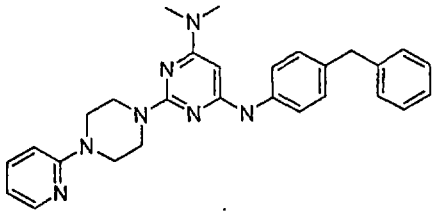
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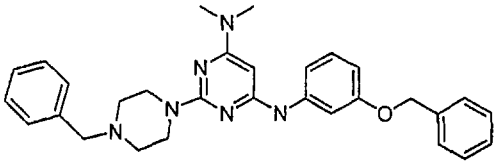

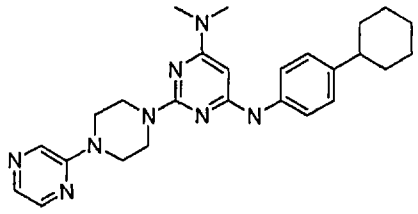
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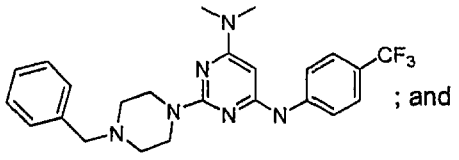
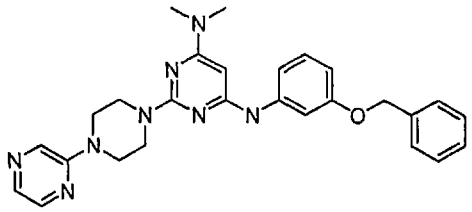
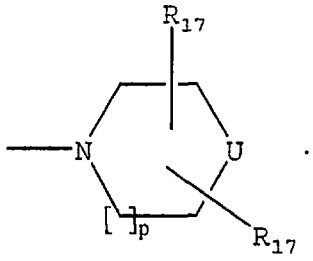

; and



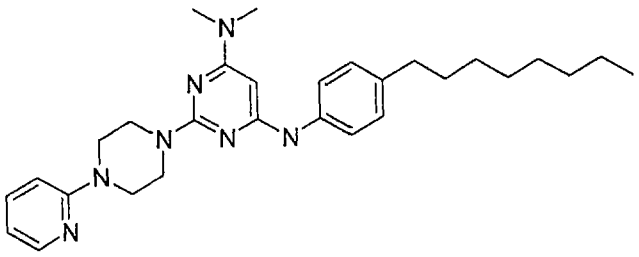
59. The method of claim 34, wherein X is $N(CH_3)_2$.

60. The method of claim 59, wherein Y is



61. The method of claim 60, wherein R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

62. The method of claim 61, wherein the compound is selected from a group consisting of: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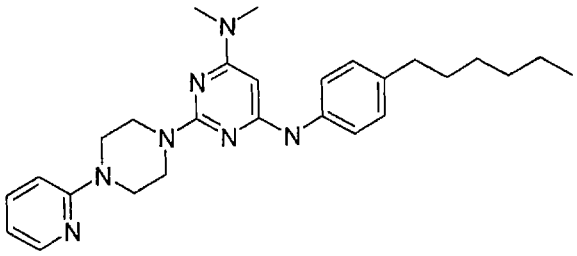
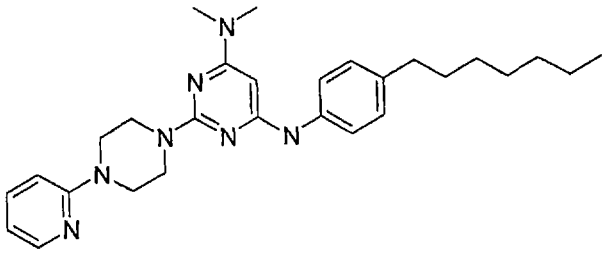
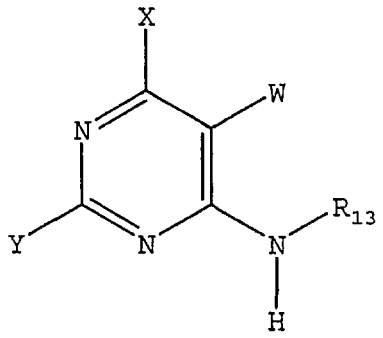

; and

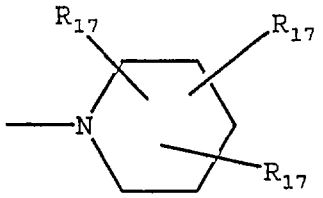


63. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

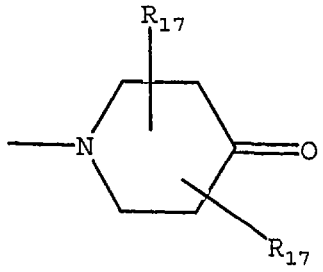


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

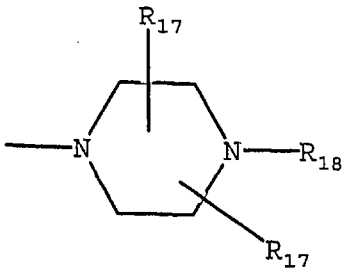
wherein X is; $NR_{11}R_{12}$;



;



; or



;

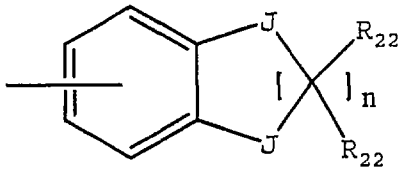
wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

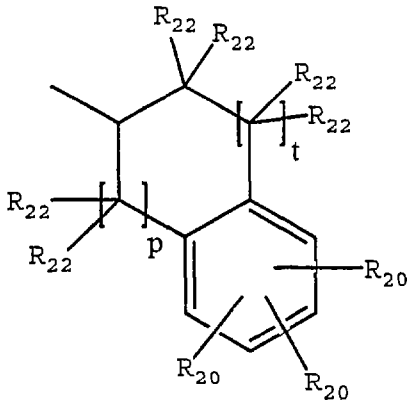
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is



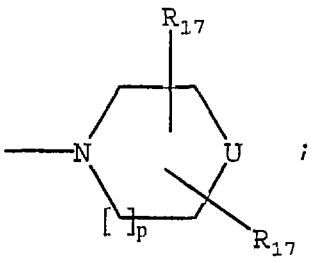
;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7

cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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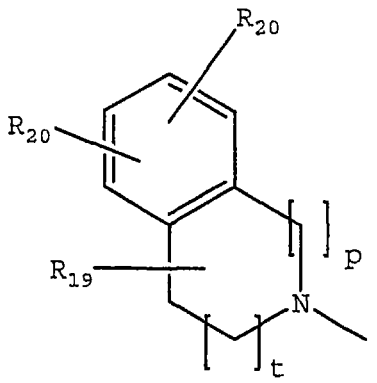
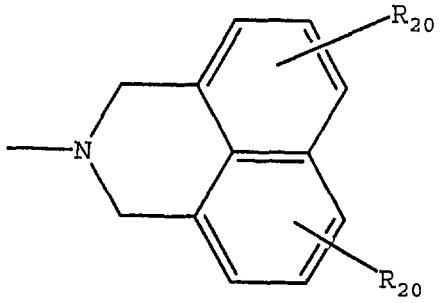


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -

$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4

straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

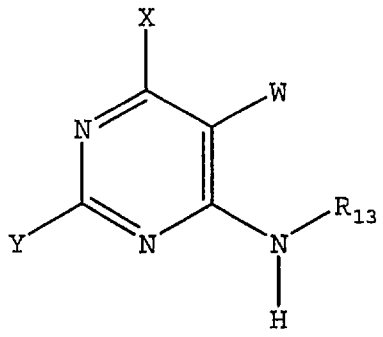
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

a pharmaceutically acceptable salt thereof.

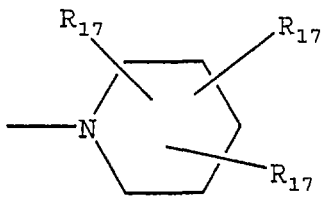
64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



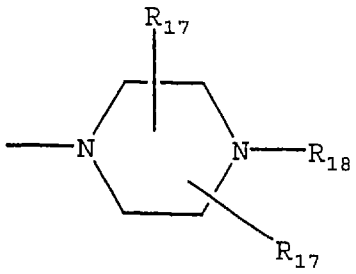
wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl,

propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



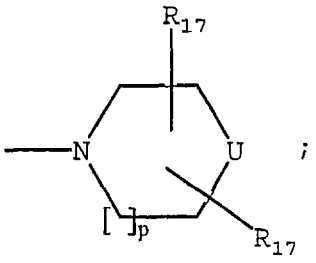
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



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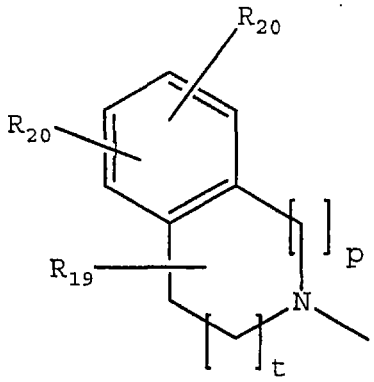
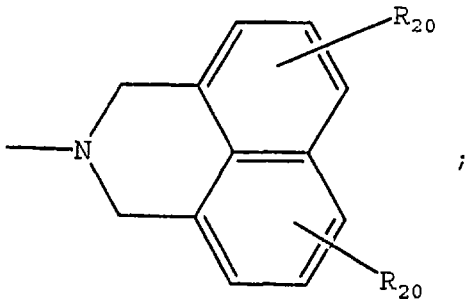


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

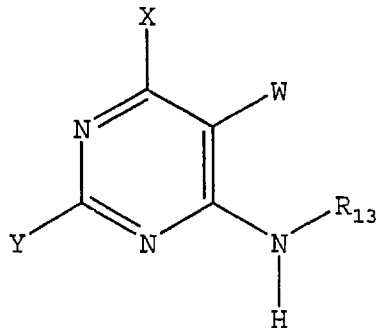
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

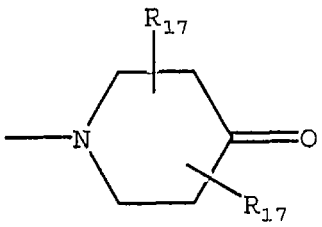
a pharmaceutically acceptable salt thereof.

65. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

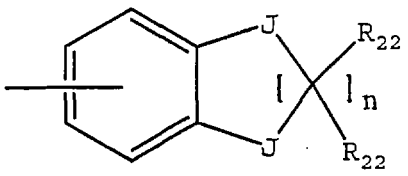
wherein X is $N(CH_3)_2$ or



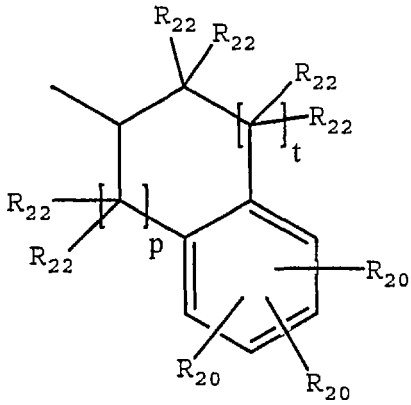
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



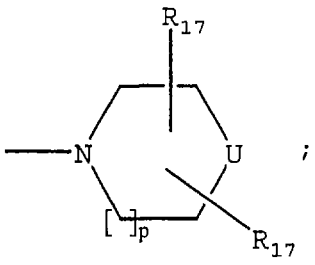
wherein Q_2 is



wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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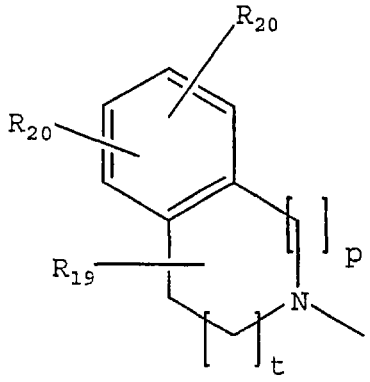
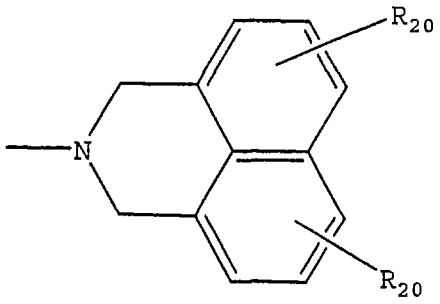


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

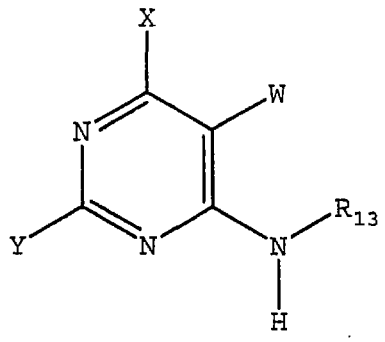
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

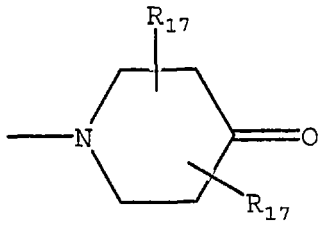
a pharmaceutically acceptable salt thereof.

66. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1\text{-}C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched $C_1\text{-}C_6$ alkyl, $(CH_2)_q\text{-}O\text{-}(CH_2)_m\text{-}CH_3$, $C_3\text{-}C_6$ cycloalkyl, or $(C(R_{19})_2)_m\text{-}Z$;

wherein R_{15} is $(C(R_{19})_2)_m\text{-}N(R_{16})_2$;

wherein Z is $C_3\text{-}C_{10}$ cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched $C_1\text{-}C_7$ alkyl, straight chained or branched $C_1\text{-}C_7$ monofluoroalkyl, straight chained or branched $C_1\text{-}C_7$ polyfluoroalkyl, straight chained or branched $C_2\text{-}C_7$ alkenyl, straight chained or branched $C_2\text{-}C_7$ alkynyl, $C_5\text{-}C_7$ cycloalkenyl, -

$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

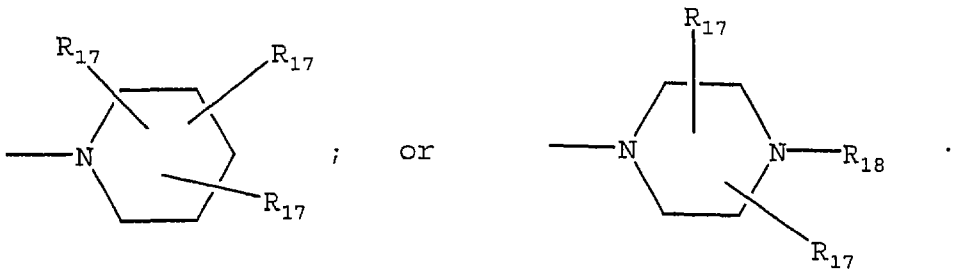
67. The pharmaceutical composition of claim 63, 64, 65 or 66, wherein the compound is enantiomerically and diasteriomerically pure.

68. The pharmaceutical composition of claim 63, 64, 65

or 66, wherein the compound is enantiomerically or diasteriomerically pure.

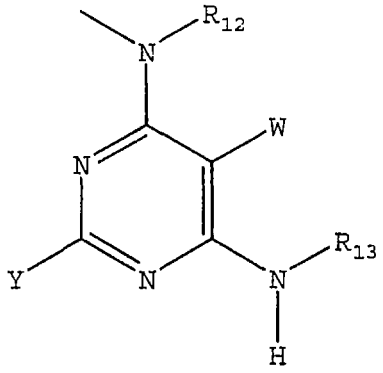
69. The pharmaceutical composition of claim 63, 64, 65 or 66,, wherein the compound can be administered orally.

70. The pharmaceutical composition of claim 63, wherein X is:



71. The pharmaceutical composition of claim 63, wherein X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

72. The pharmaceutical composition of claim 71, wherein the compound has the structure:



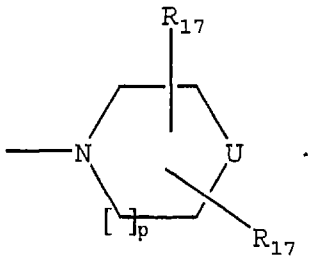
73. The pharmaceutical composition of claim 70, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

74. The pharmaceutical composition of claim 72, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

75. The pharmaceutical composition of claim 73, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

76. The pharmaceutical composition of claim 74, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

77. The pharmaceutical composition of claim 73, wherein Y is

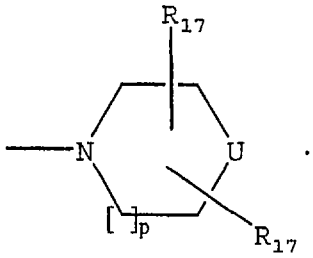


78. The pharmaceutical composition of claim 77, wherein U is NR_{16}.

79 The pharmaceutical composition of claim 78, wherein R_{16} is $(CH_2)_m$-Z.

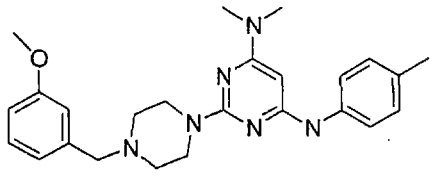
80. The pharmaceutical composition of claim 79, wherein Z is aryl or heteroaryl.

81. The pharmaceutical composition of claim 74, wherein Y is



82. The pharmaceutical composition of claim 81, wherein U is NR_{16}.

83. The pharmaceutical composition of claim 82, wherein the compound is selected from the group consisting of: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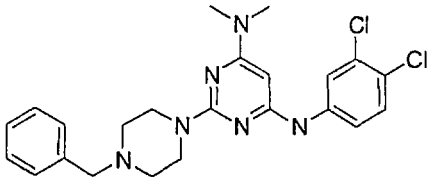
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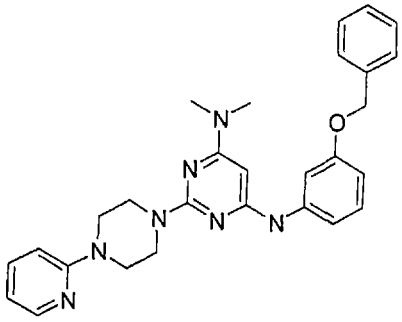
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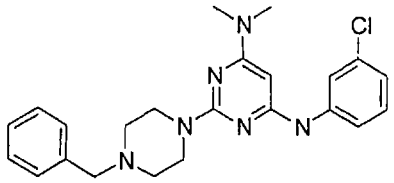
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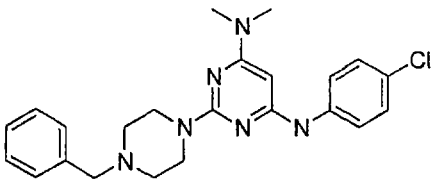
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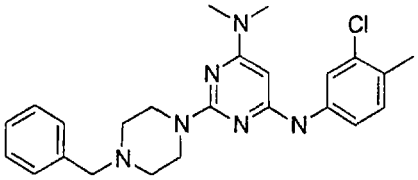
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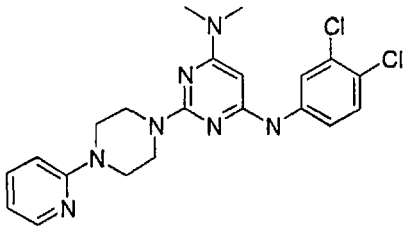
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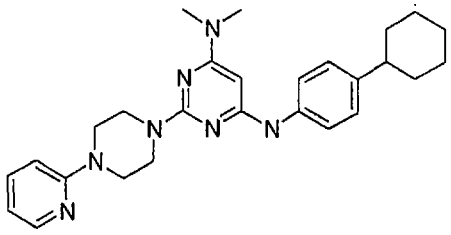
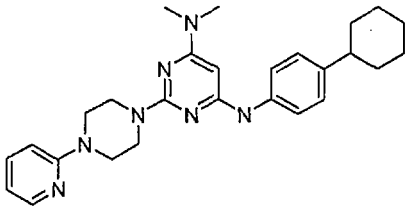

.

84. The pharmaceutical composition of claim 82, wherein the compound is selected from the group consisting of: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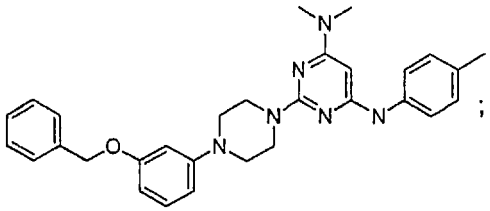
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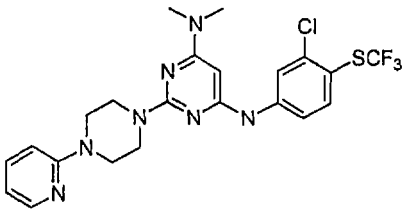
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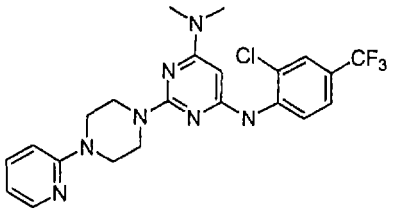
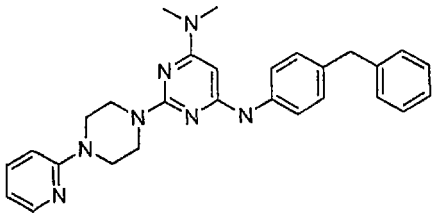

;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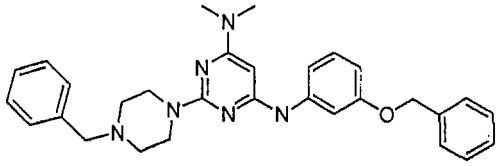
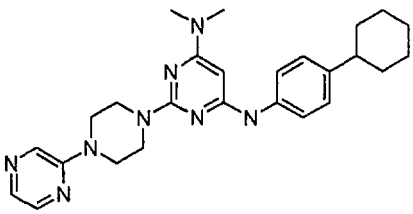
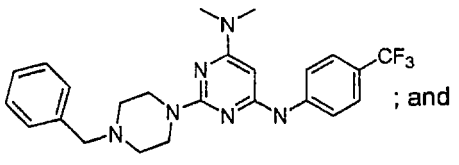
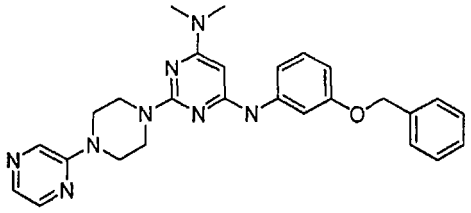


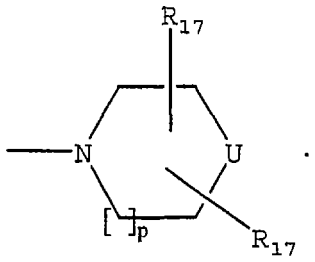

;


; and


.

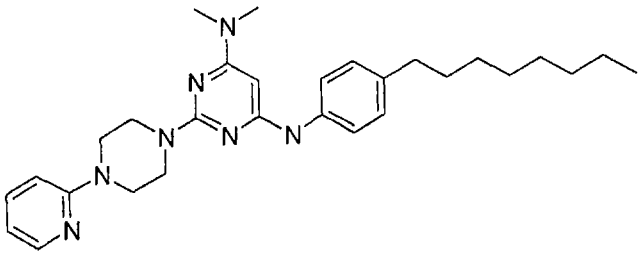
85. The pharmaceutical composition of claim 65, wherein X is $N(CH_3)_2$.

86. The pharmaceutical composition of claim 85, wherein Y is



87. The pharmaceutical composition of claim 86, wherein R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

88. The pharmaceutical composition of claim 87, wherein the compound is selected from a group consisting of: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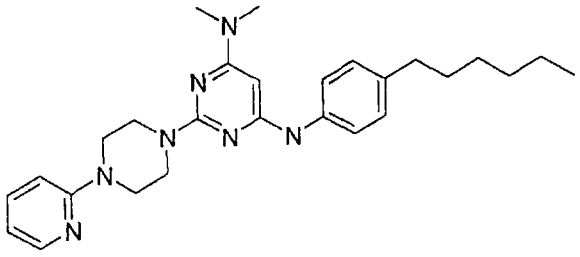
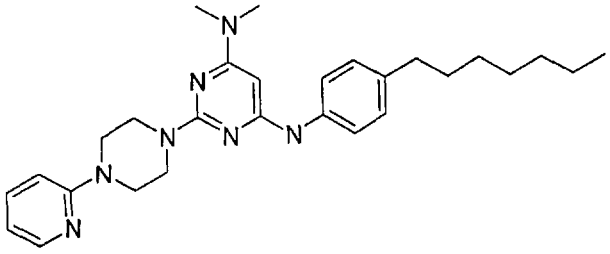
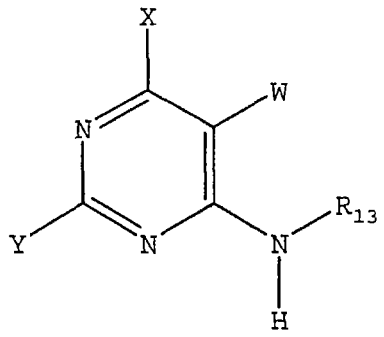

; and

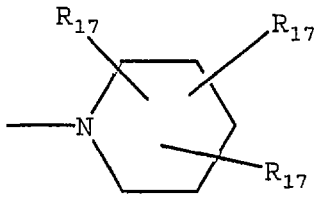

.

89. A compound having the structure:

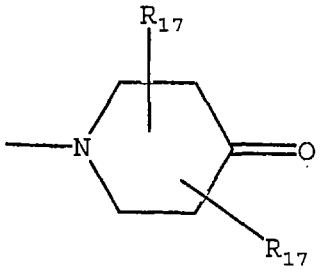


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

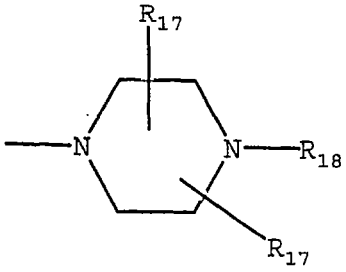
wherein X is; $NR_{11}R_{12}$;



;



; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

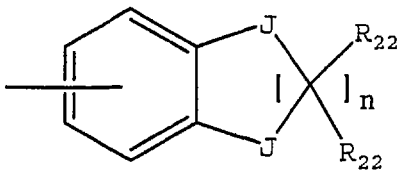
wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl,

noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

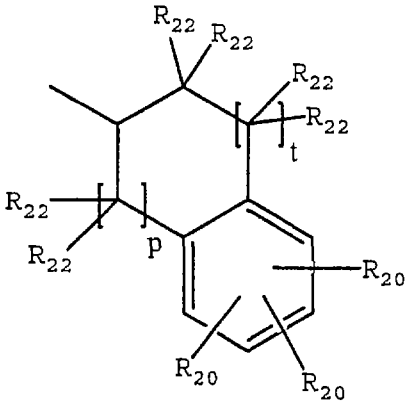
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

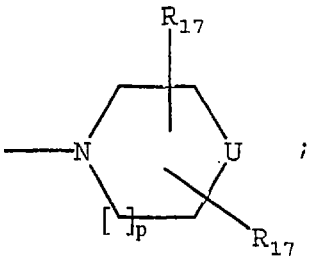


;

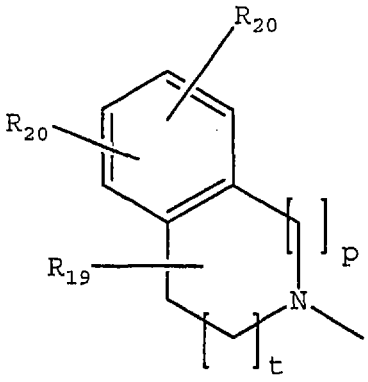
wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

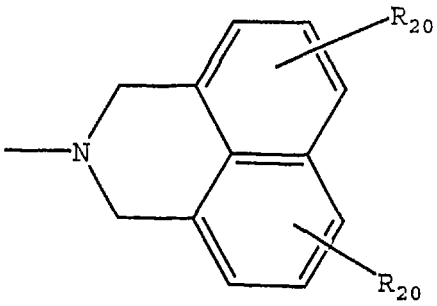
wherein Y is $NR_{14}R_{15}$;



;



; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

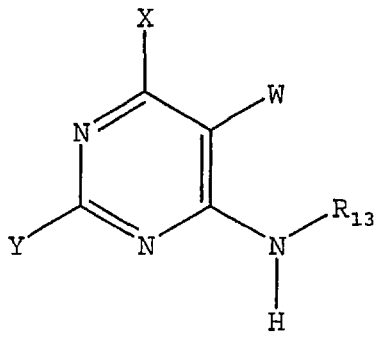
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

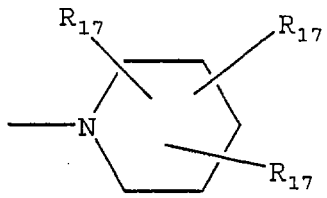
a pharmaceutically acceptable salt thereof.

90. A compound having the structure:

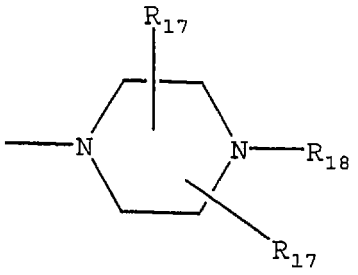


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



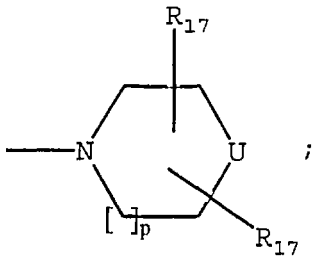
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



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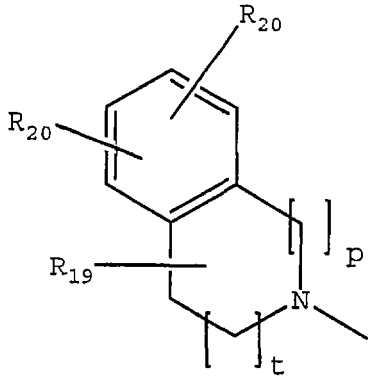
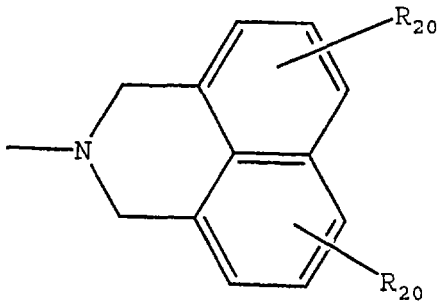


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

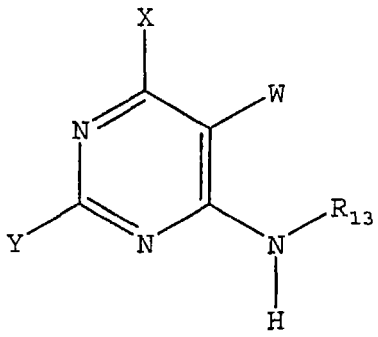
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

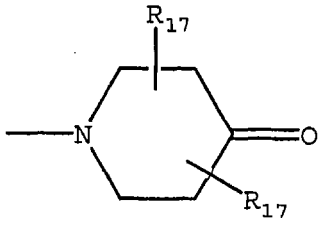
a pharmaceutically acceptable salt thereof.

91. A compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

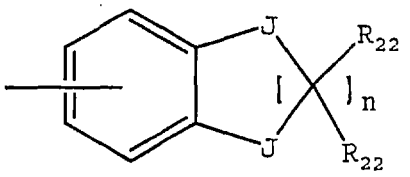


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

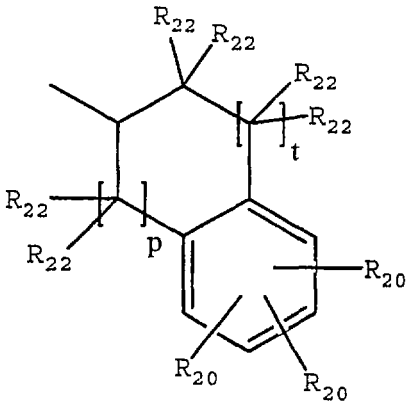
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

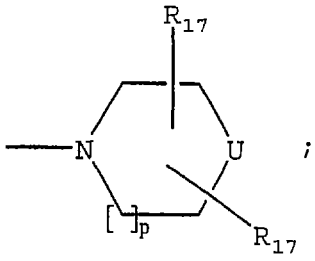


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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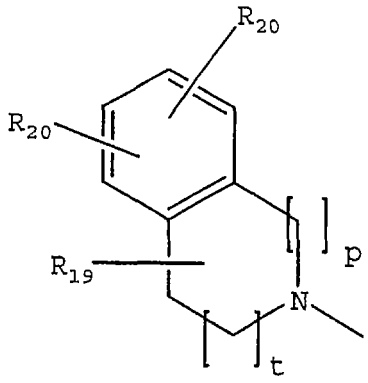

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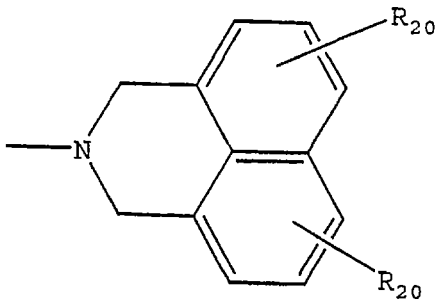


;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl,

straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

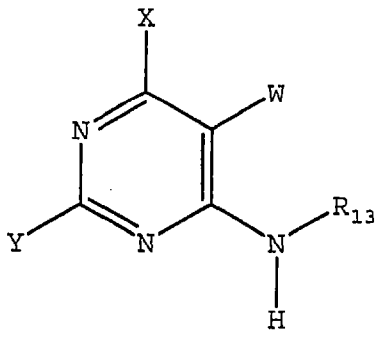
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

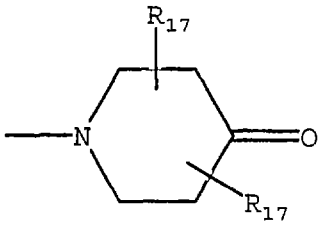
a pharmaceutically acceptable salt thereof.

92. A compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

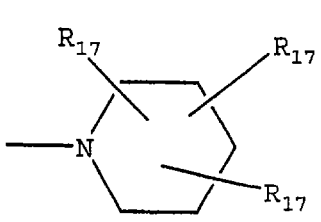
wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

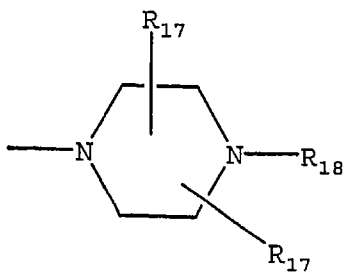
93. An enantiomerically and diasteriomerically pure compound of claim 89, 90, 91, or 92.

94. An enantiomerically or diasteriomerically pure compound of claim 89, 90, 91, or 92.

95. The compound of claim 89, wherein X is:

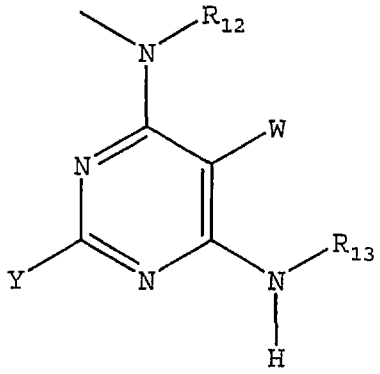


; or



96. The compound of claim 88, wherein X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

97. The compound of claim 96, wherein the compound has the structure:



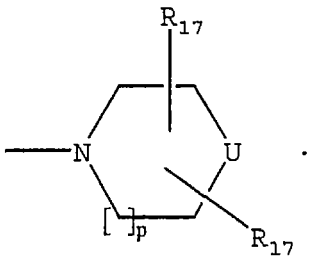
98. The compound of claim 95, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

99. The compound of claim 97, wherein R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

100. The compound of claim 98, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

101. The compound of claim 99, wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

102. The compound of claim 98, wherein Y is

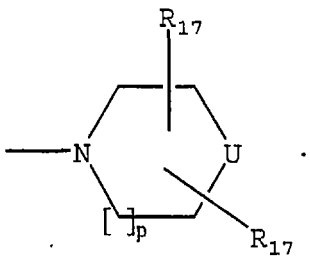


103. The compound of claim 102, wherein U is NR_{16}.

104. The compound of claim 103, wherein R_{16} is $(CH_2)_m$-Z.

105. The compound of claim 104, wherein Z is aryl or heteroaryl.

106. The compound of claim 99, wherein Y is



107. The compound of claim 106, wherein U is NR_{16}.

108. The compound of claim 107, wherein the compound is selected from the group consisting of:

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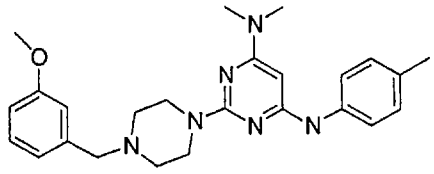
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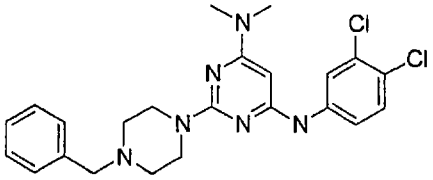
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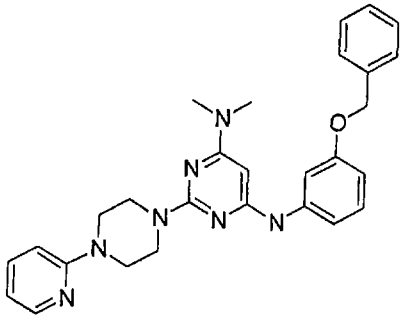
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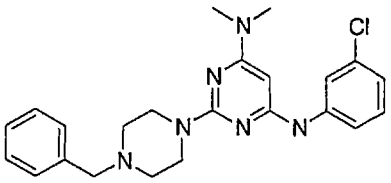
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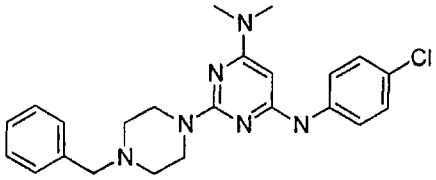
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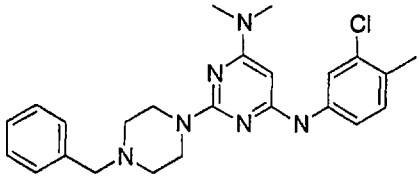
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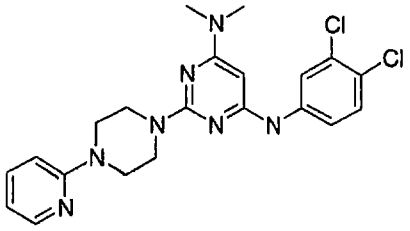
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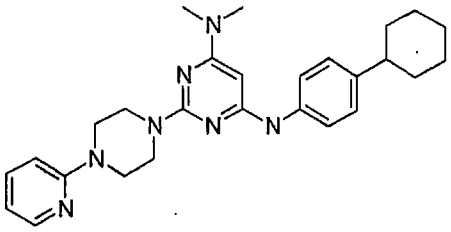
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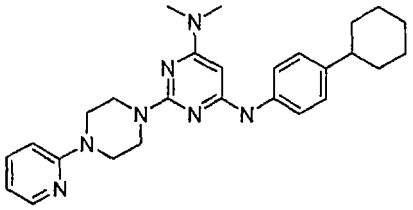
109. The compound of claim 107, wherein the compound is selected from the group consisting of: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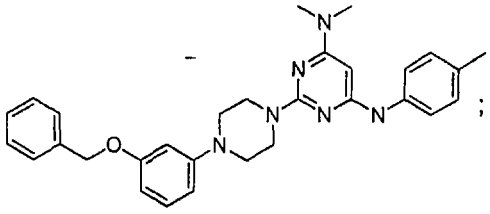
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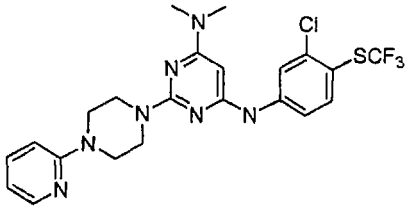
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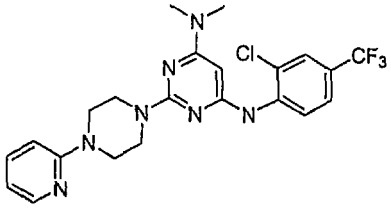
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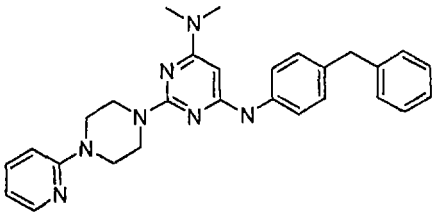
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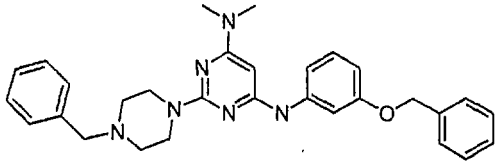
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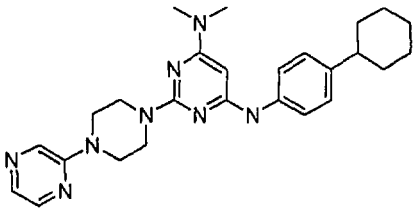
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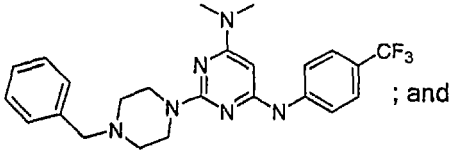
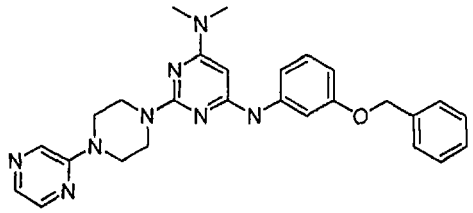

; and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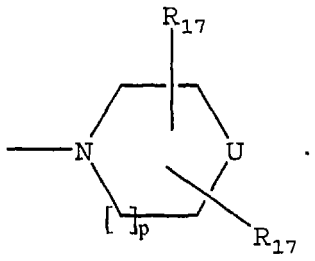
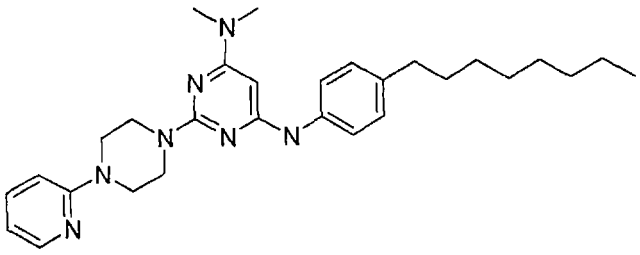
110. The compound of claim 89, wherein X is $N(CH_3)_2$.

111. The compound of claim 110, wherein Y is



111. The compound of claim 110, wherein R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

112. The compound of claim 111, wherein the compound is selected from a group consisting of: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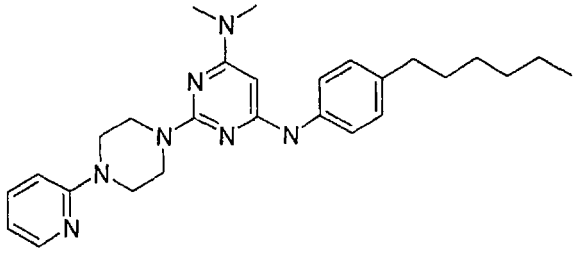
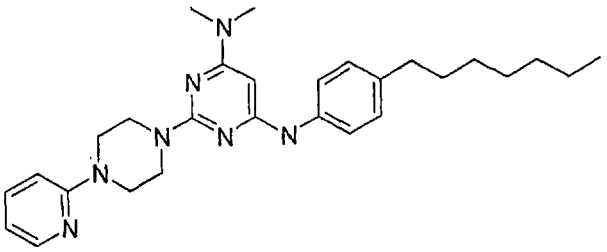

; and


.

113. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 89, 90, 91, or 92 and a pharmaceutically acceptable carrier.

114. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 89, 90, 91, or 92 and a pharmaceutically acceptable carrier.

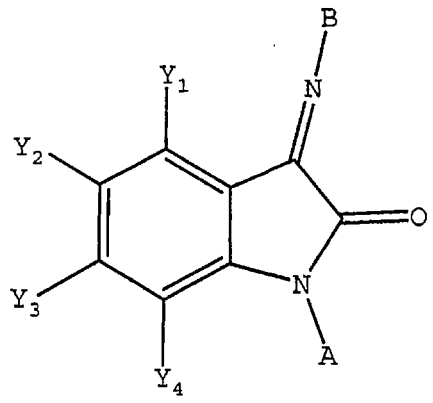
115. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 89, 90, 91, or 92 and a pharmaceutically acceptable carrier.

116. A method of treating a subject suffering from depression which comprises administering to the subject an amount of the compound of claim 89, 90, 91, or 92 effective to treat the subject's depression.

117. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of the compound of claim 89, 90, 91, or 92 effective to treat the subject's anxiety.

118. A method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of the compound of claim 89, 90, 91, or 92 effective to treat the subject's depression and anxiety.

119. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



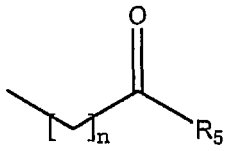
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or

branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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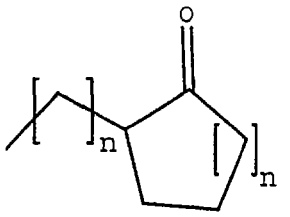

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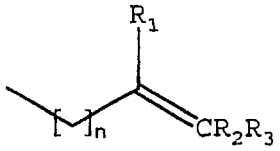
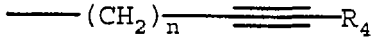
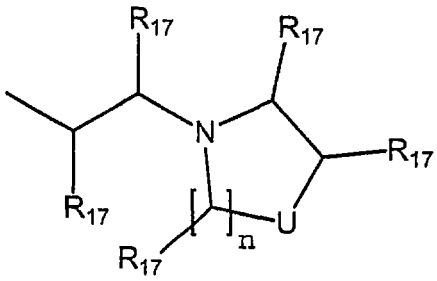


; or



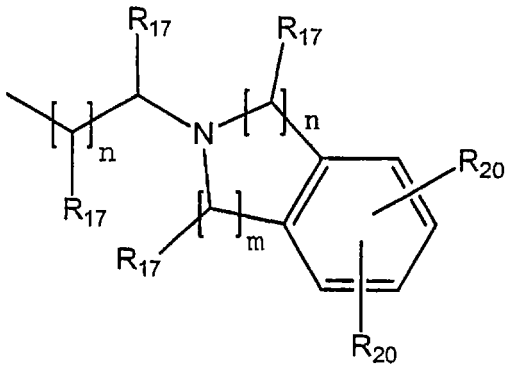
;

wherein Q_3 is



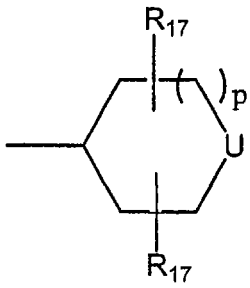
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained

or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether,

C_4-C_7 cyclic thioether, aryl, or heteroaryl;

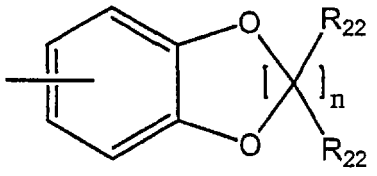
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

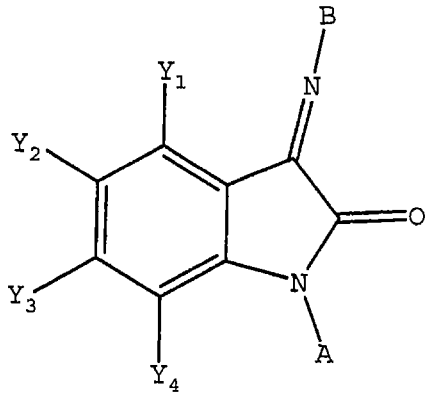


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

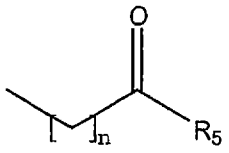
120. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;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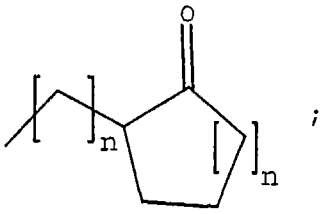
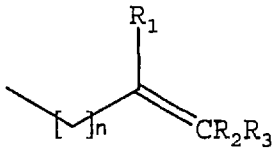
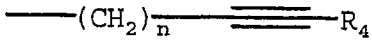

;

wherein A' is


; or 
;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7

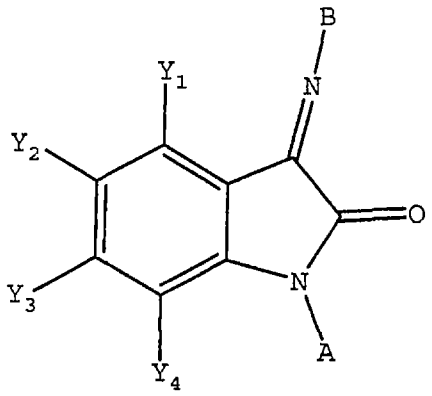
alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

121. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



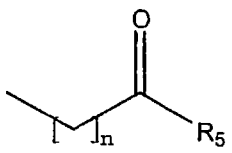
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -

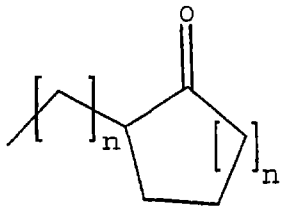
I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

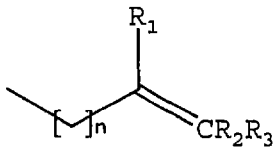
wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

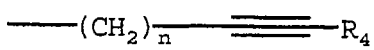
wherein A' is



;


;



; or


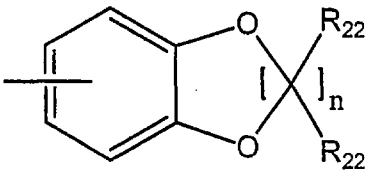
;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or

heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



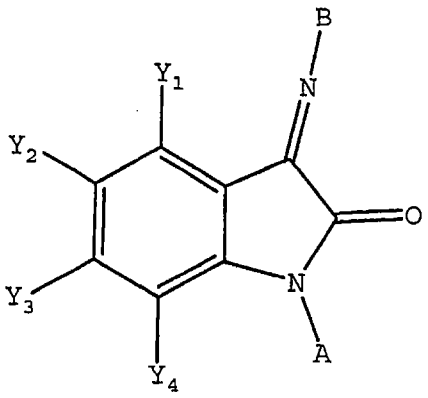
;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

122. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

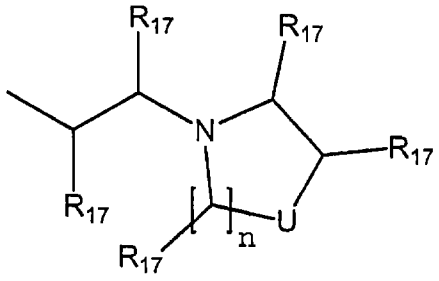


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

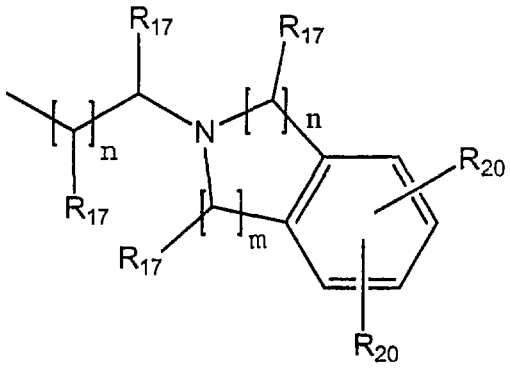
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



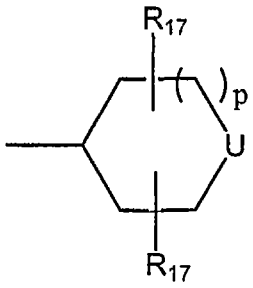
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a

methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however,

if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

123. The method of claim 119, 120, 121, or 122, wherein the compound is enantiomerically and diastereomerically pure.

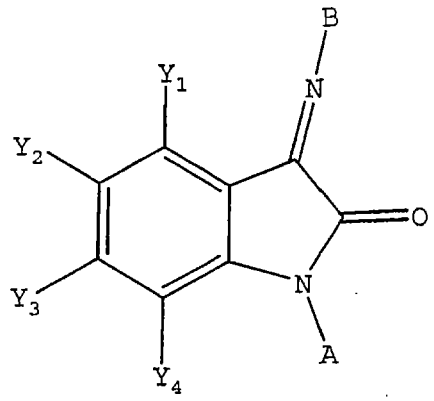
124. The method of claim 119, 120, 121, or 122, wherein the compound is enantiomerically or diastereomerically pure.

125. The method of claim 119, 120, 121, or 122, wherein the compound is a pure Z imine isomer or a pure Z alkene isomer.

126. The method of claim 119, 120, 121, or 122, wherein the compound is a pure E imine isomer or a pure E alkene isomer.

127. The method of claim 119, 120, 121, or 122, wherein the compound is administered orally.

128. The method of claim 119 or 120, wherein the compound has the structure:

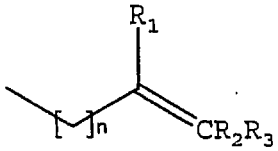


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl; and

wherein A' is



129. The method of claim 119, 120 or 122, wherein B is heteroaryl.

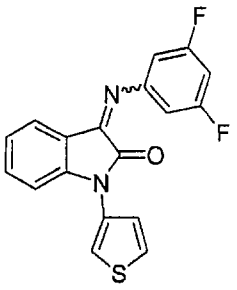
130. The method of claim 119 or 120, wherein B is aryl.

131. The method of claim 130, wherein B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

132. The method of claim 131, wherein A is aryl.

133. The method of claim 131, wherein A is heteroaryl.

134. The method of claim 133, wherein the compound is selected from the group consisting of:



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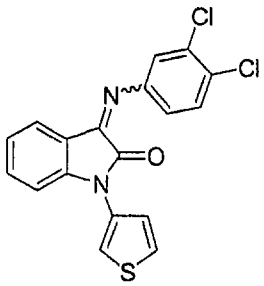
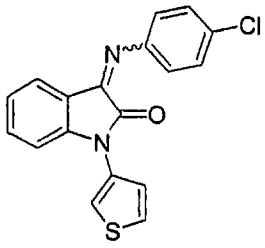
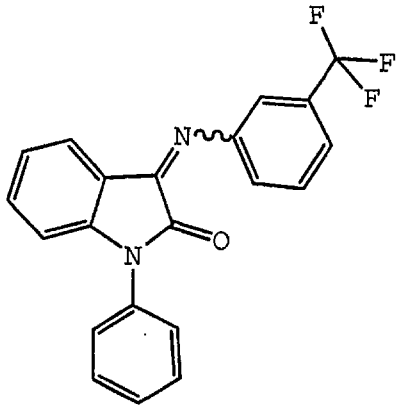


; and



.

135. The method of claim 132, wherein the compound is selected from the group consisting of:



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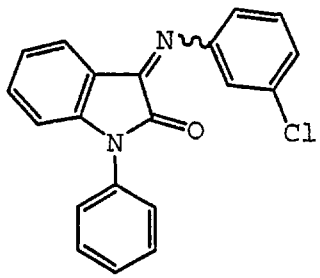

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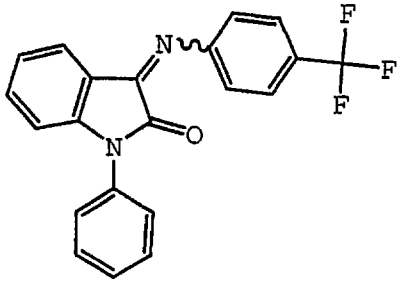

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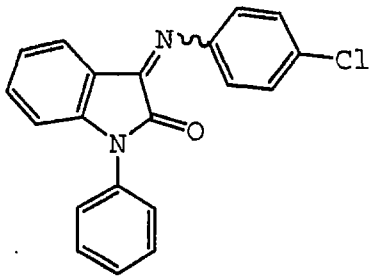

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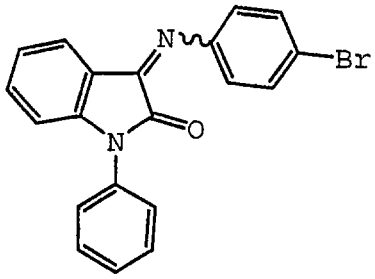

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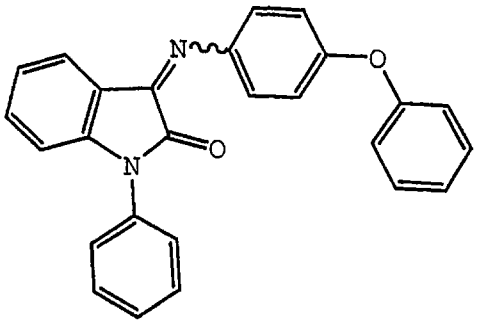
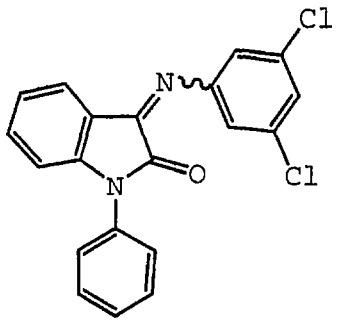
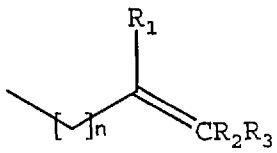


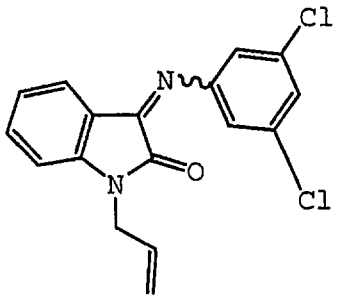
; and



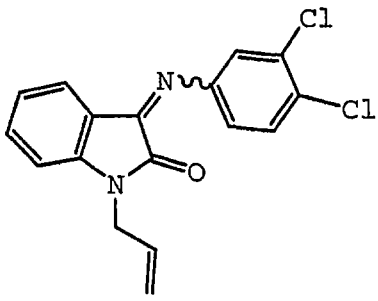
136. The method of claim 130, wherein A is A' and A' is



137. The method of claim 136, wherein the compound is:



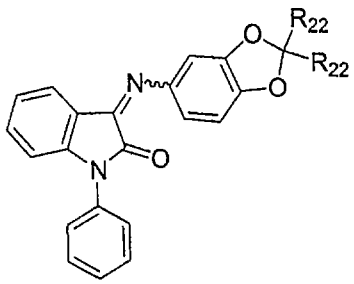
; or



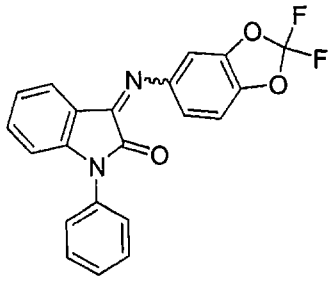
138. The method of claim 121, wherein B is Q_6.

139. The method of claim 138, wherein A is aryl.

140. The method of claim 139, wherein the compound has the structure:



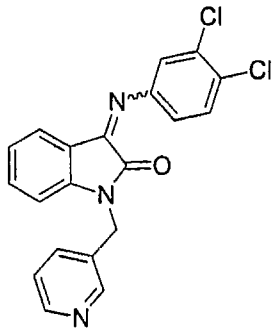
141. The method of claim 140, wherein the compound is:



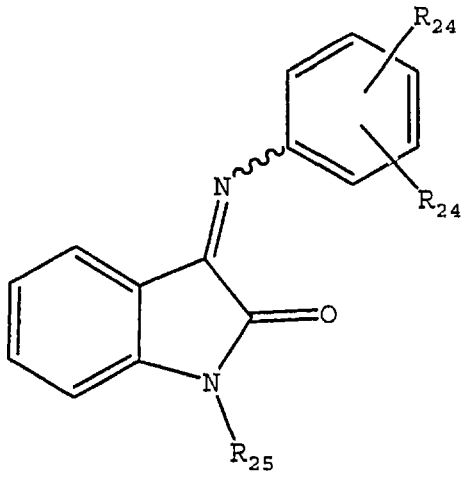
142. The method of claim 122, wherein B is aryl.

143. The method of claim 142, wherein A is (CHR_{17})-$(CHR_{17})_n$-Z.

144. The method of claim 143, wherein the compound is:



145. The method of claim 119, wherein the compound has the structure:

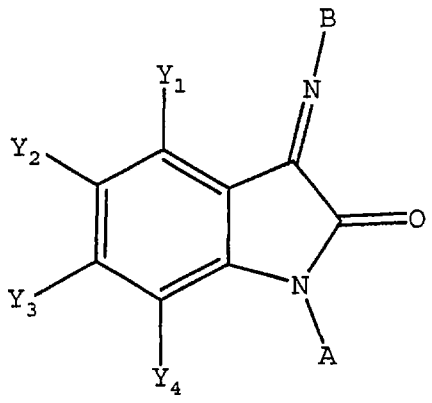


;

wherein each R_{24} is independently one or more of the following: H, F, Cl, Br, I, CF_3, OCH_3 or NO_2; and

wherein R_{25} is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br, CF_3, NO_2.

146. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



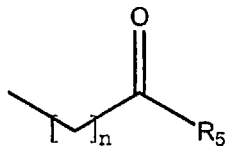
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

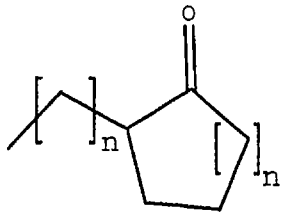
wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or

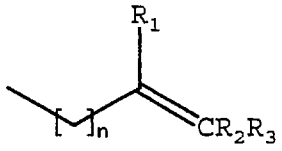
polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

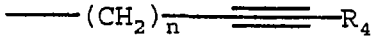
wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



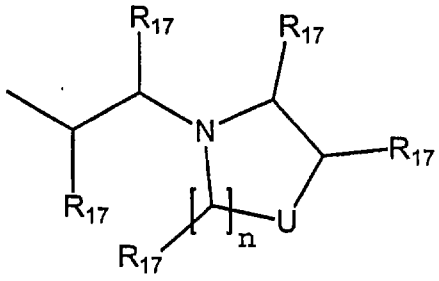
;


;


; or


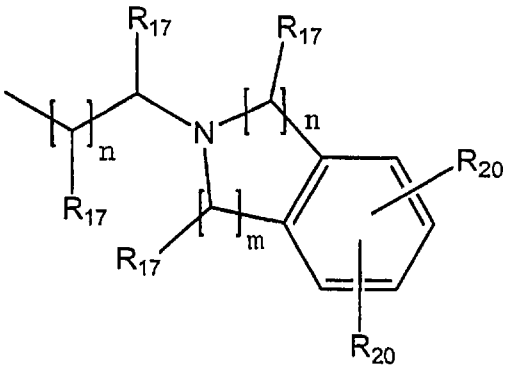
;

wherein Q_3 is



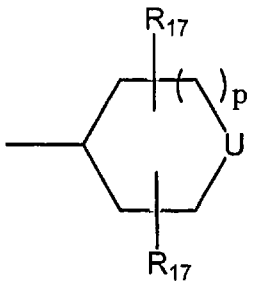
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

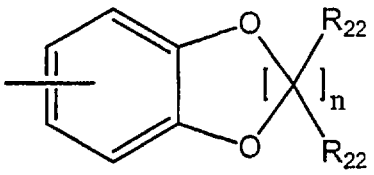
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

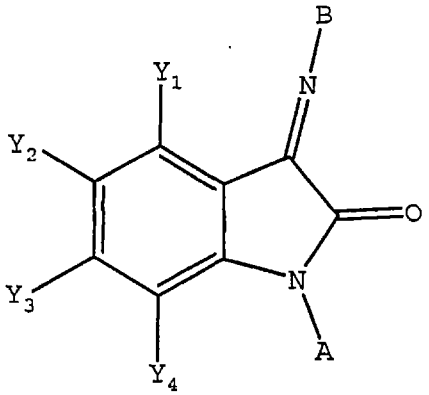


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

147. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



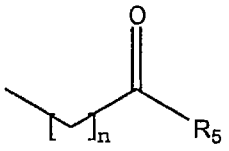
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent

carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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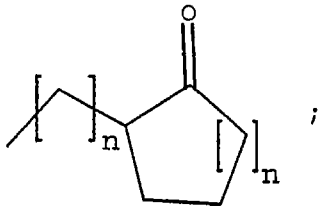

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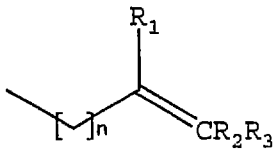
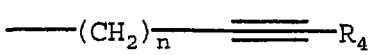


; or



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or

heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_6$ or aryl;

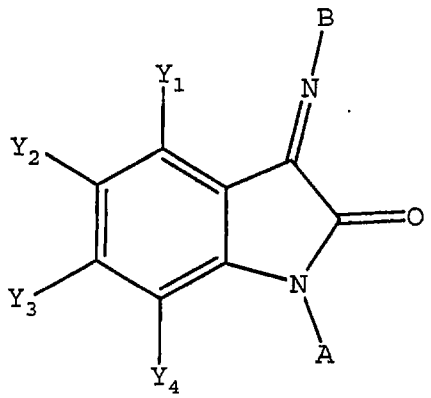
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

148. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

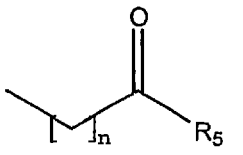


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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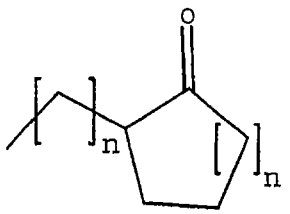

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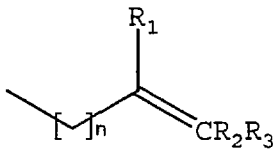
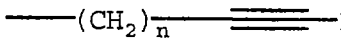


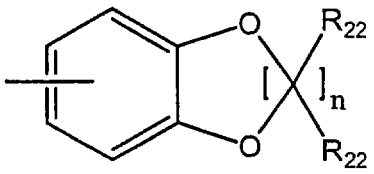
; or 

;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



;

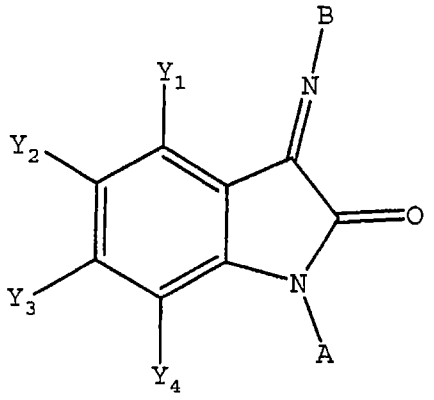
wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

149. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the

subject's anxiety wherein the compound has the structure:

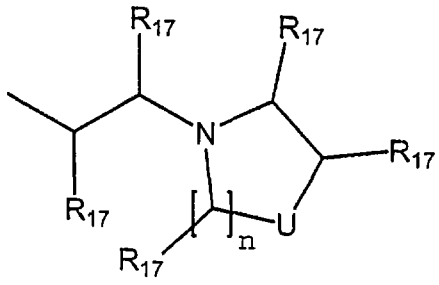


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

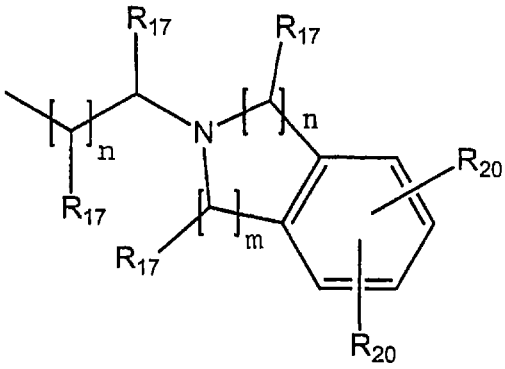
wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

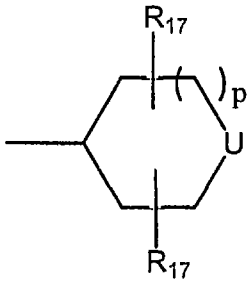
wherein Q_3 is



wherein Q_4 is



wherein Q_5 is



wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight

chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7

alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

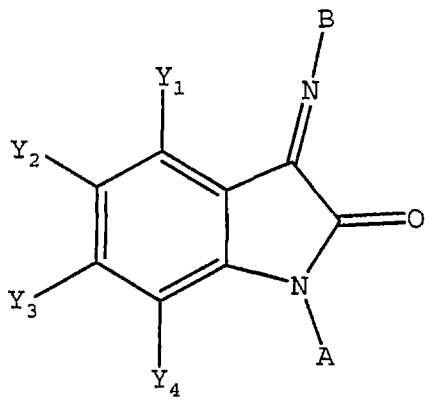
150. The method of claim 146, 147, 148, or 149, wherein the compound is enantiomerically and diastereomerically pure.

151. The method of claim 146, 147, 148, or 149, wherein the compound is enantiomerically or diastereomerically pure compound.

152. The method of claim 146, 147, 148, or 149, wherein the compound is a pure Z imine isomer or a pure Z alkene isomer.

153. The method of claim 146, 147, 148, or 149, wherein the compound is a pure E imine isomer or a pure E alkene isomer.

154. The method of claim 146 or 147, wherein the compound has the structure:

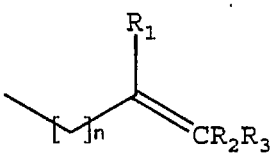


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl; and

wherein A' is



155. The method of claim 146 or 147, wherein B is heteroaryl.

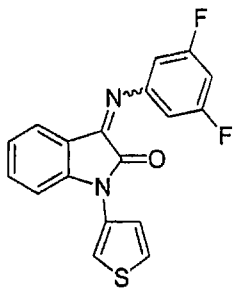
156. The method of claim 146 or 147, wherein B is aryl.

157. The method of claim 156, wherein B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

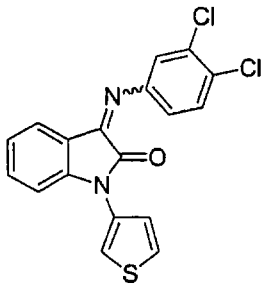
158. The method of claim 157, wherein A is aryl.

159. The method of claim 157, wherein A is heteroaryl.

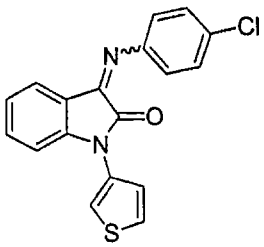
160. The method of claim 159, wherein the compound is selected from the group consisting of:



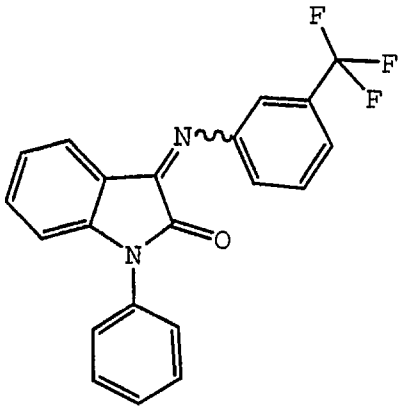
;



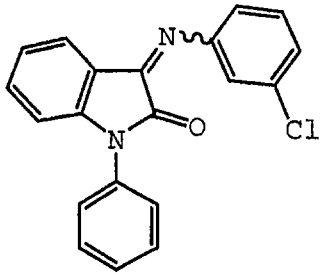
; and



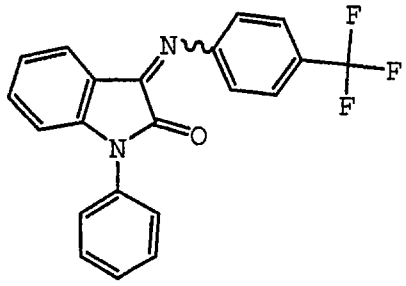
161. The method of claim 158, wherein the compound is selected from the group consisting of:



;

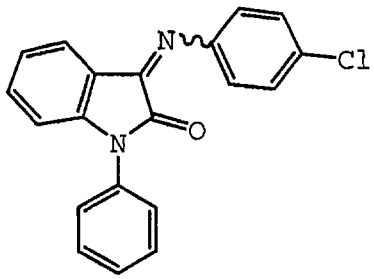


;

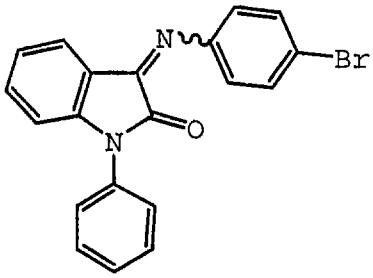


;

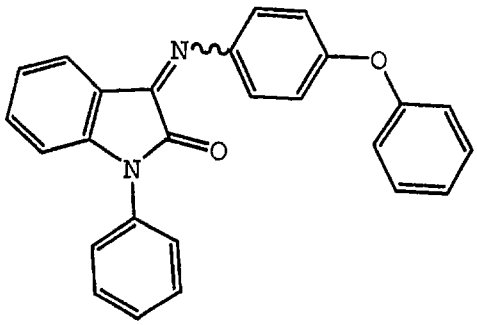
5



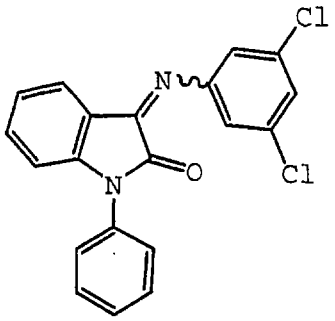
;



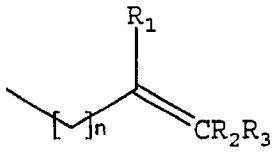
;



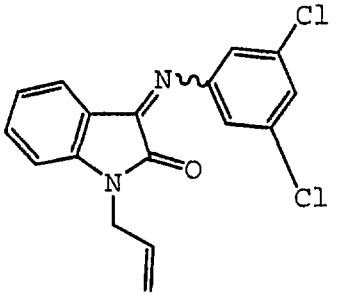
; and



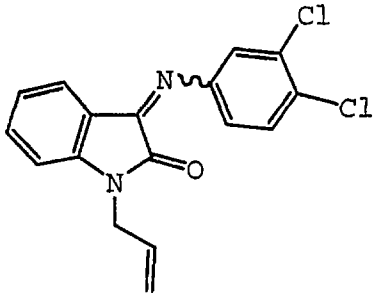
162. The method of claim 156, wherein A is A', and A' is



163. The method of claim 162, wherein the compound is:



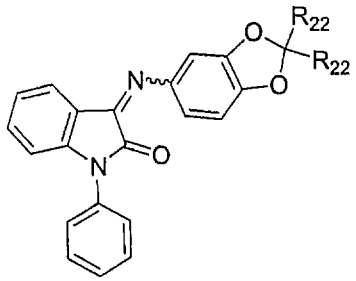
; or



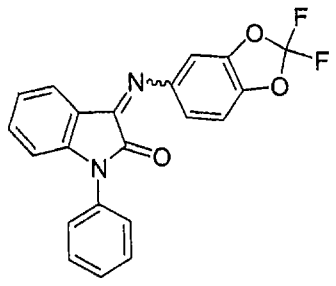
164. The method of claim 148, wherein B is Q_6.

165. The method of claim 164, wherein A is aryl.

166. The method of claim 165, wherein the compound has the structure:



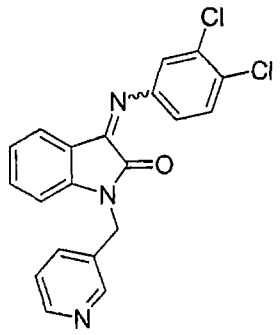
167. The method of claim 166, wherein the compound is:



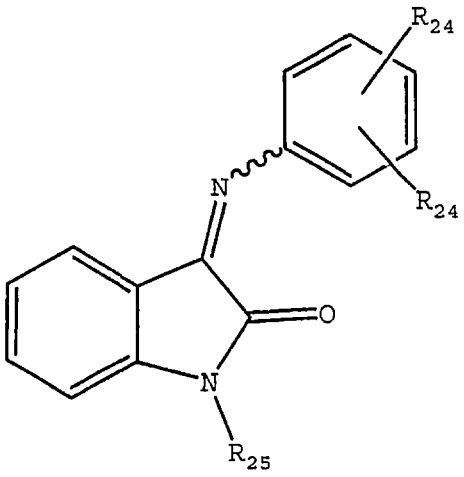
168. The method of claim 149, wherein B is aryl.

169. The method of claim 168, wherein A is (CHR_{17})-$(CHR_{17})_n$-Z.

170. The method of claim 169, wherein the compound is:



171. The method of claim 146, wherein the compound has the structure:

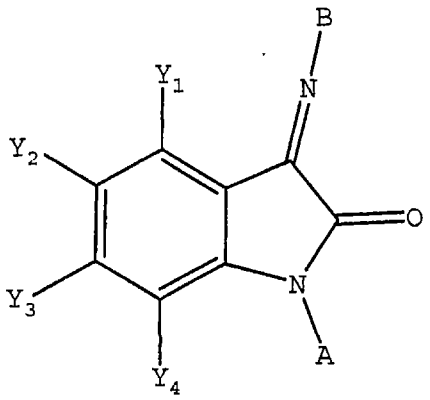


;

wherein each R_{24} is independently one or more of the following: H, F, Cl, Br, I, CF_3, OCH_3 or NO_2; and

wherein R_{25} is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br, CF_3, NO_2.

172. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



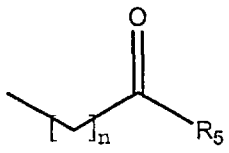
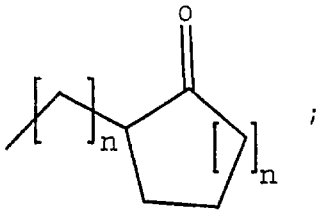
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or

polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is


;

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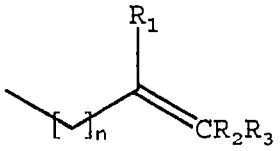
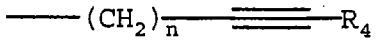
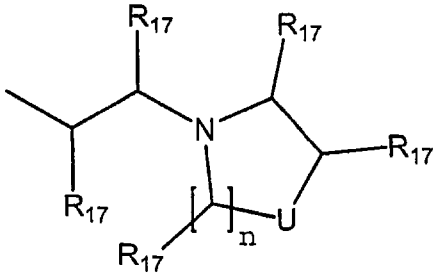
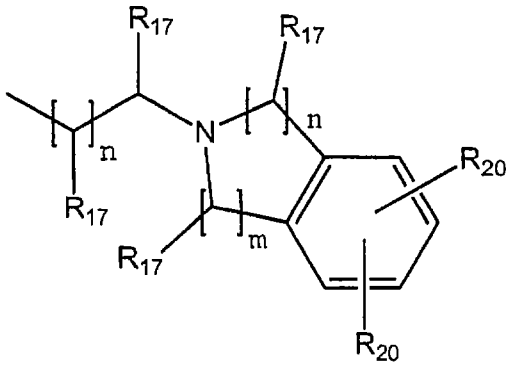

; or

;

wherein Q_3 is

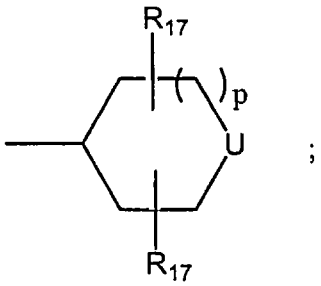

;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_6$ or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

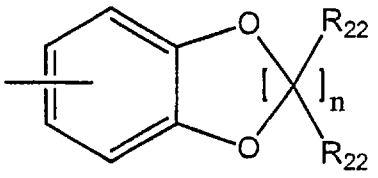
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

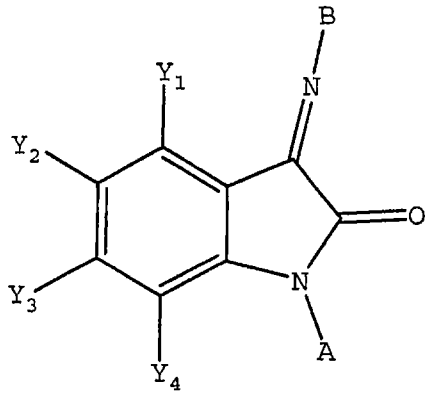


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

173. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

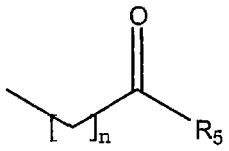


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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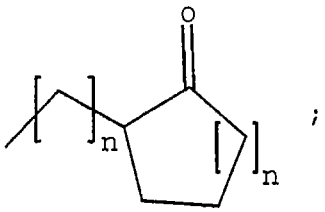

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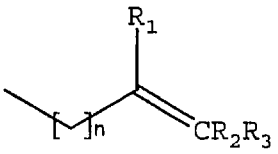
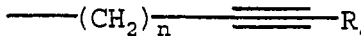


; or


;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or

heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_6$ or aryl;

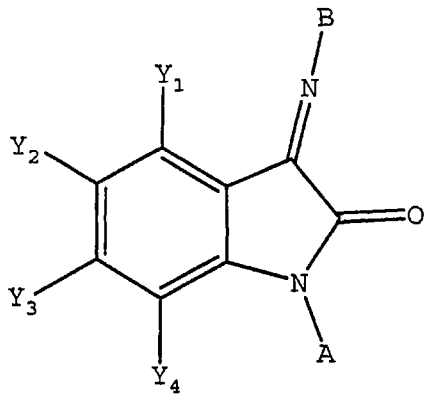
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

174. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

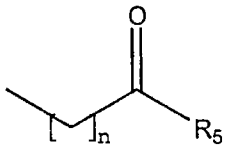


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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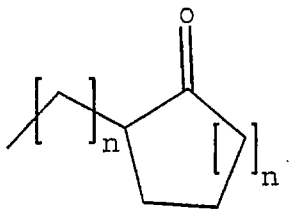

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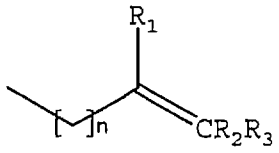
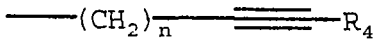


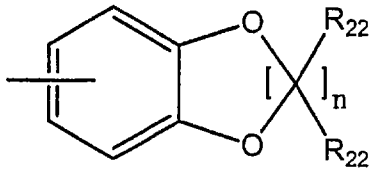
; or 

;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



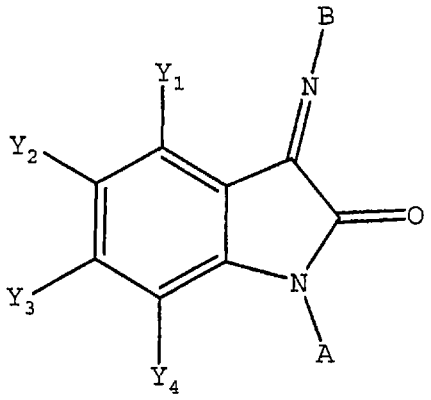
;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

175. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



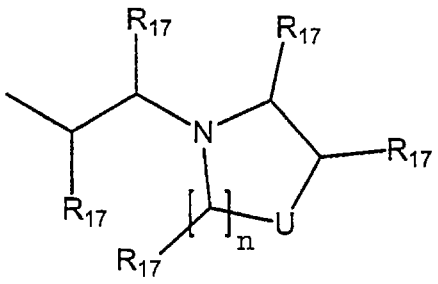
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an

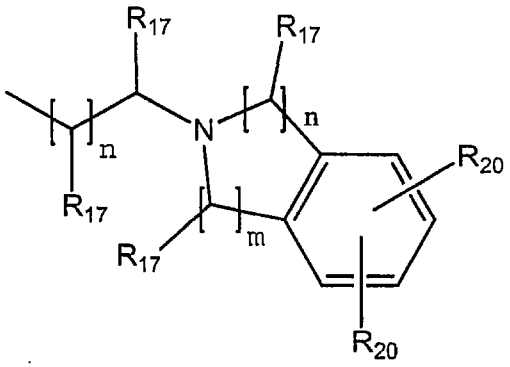
aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



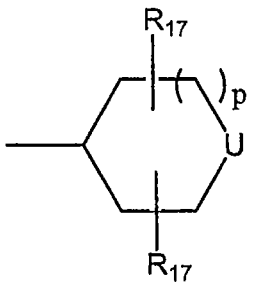
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained

or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

176. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is an enantiomerically and diastereomerically pure compound.

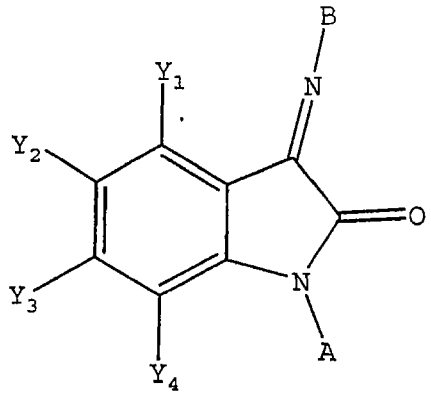
177. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is an enantiomerically or diastereomerically pure compound.

178. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is a pure Z imine isomer or a pure Z alkene isomer.

179. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is a pure E imine isomer or a pure E alkene isomer.

180. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the composition can be administered orally.

181. The pharmaceutical composition of claim 172 or 173, wherein the compound has the structure:



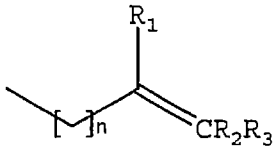
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7

alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl; and

wherein A' is



182. The pharmaceutical composition of claim 172, 173 or 175, wherein B is heteroaryl.

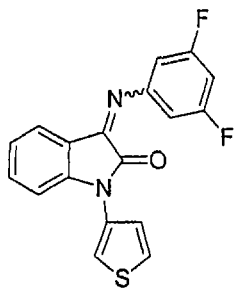
183. The pharmaceutical composition of claim 172 or 173, wherein B is aryl.

184. The pharmaceutical composition of claim 183, wherein B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, -CF_3, straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, or -$CON(R_4)_2$.

185. The pharmaceutical composition of claim 184, wherein A is aryl.

186. The pharmaceutical composition of claim 184, wherein A is heteroaryl.

187. The pharmaceutical composition of claim 186, wherein the compound is selected from the group consisting of:



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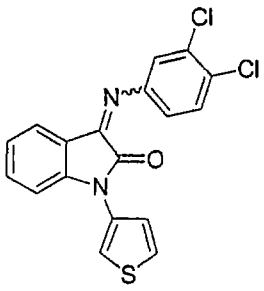
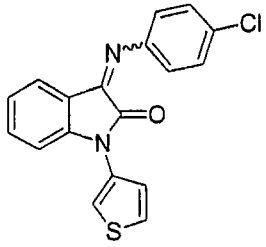


; and

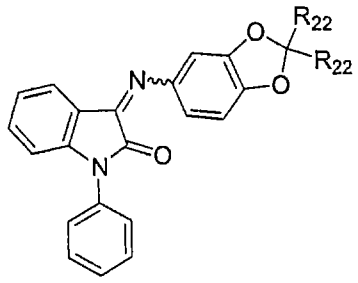


.

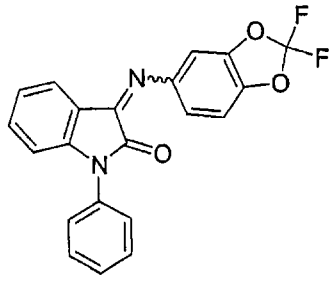
188. The pharmaceutical composition of claim 174, wherein B is Q_6.

189. The pharmaceutical composition of claim 188, wherein A is aryl.

190. The pharmaceutical composition of claim 189, wherein the compound has the structure:



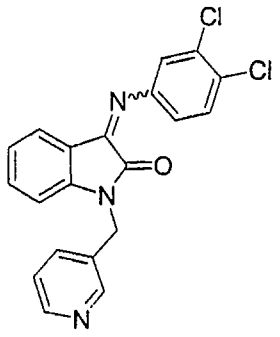
191. The pharmaceutical composition of claim 190, wherein the compound is:



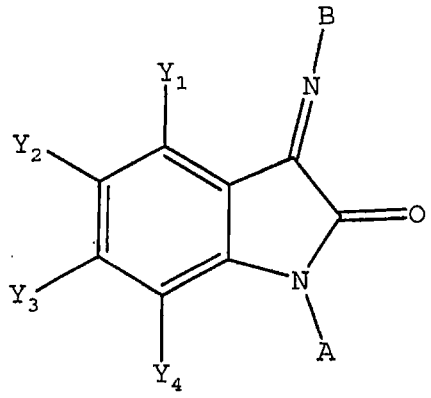
192. The pharmaceutical composition of claim 175, wherein B is aryl.

193. The pharmaceutical composition of claim 192, wherein A is $(CHR_{17})-(CHR_{17})_n-Z$.

194. The pharmaceutical composition of claim 193, wherein the compound is:



195. A compound having the structure:



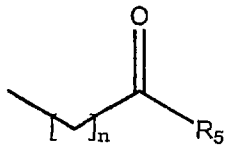
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or

any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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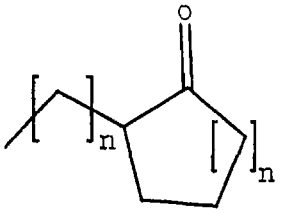

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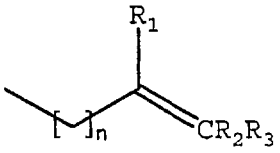
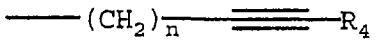
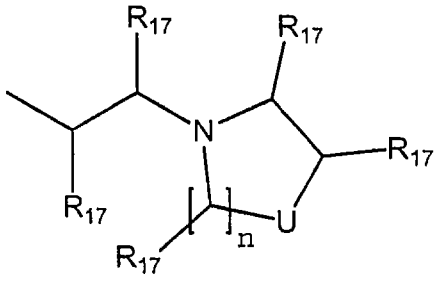


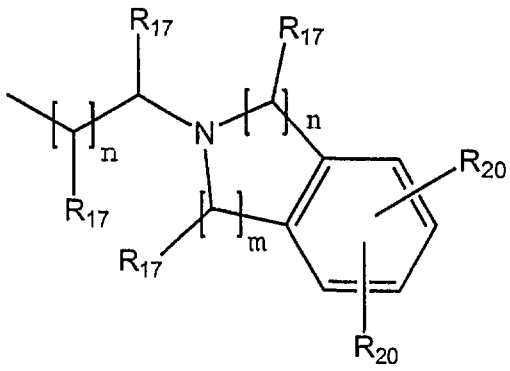
; or


;

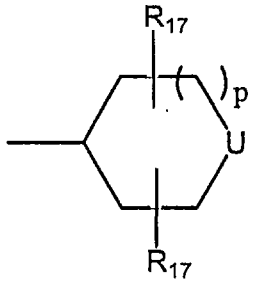
wherein Q_3 is



wherein Q_4 is



wherein Q_5 is



wherein R_1 and R_2 are each independently H, straight

chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight

chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

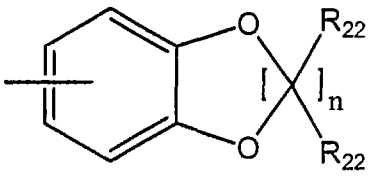
wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN,

methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

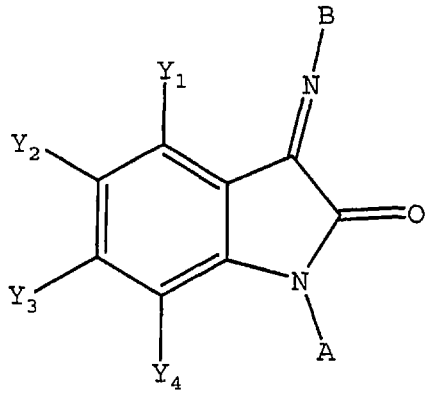


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

196. A compound having the structure:



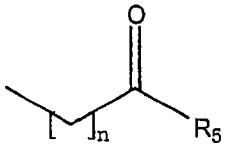
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -

I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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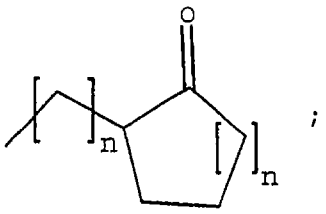

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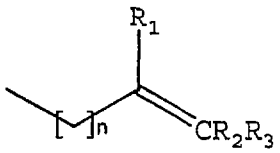
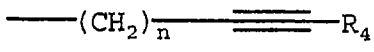


; or



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -

NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

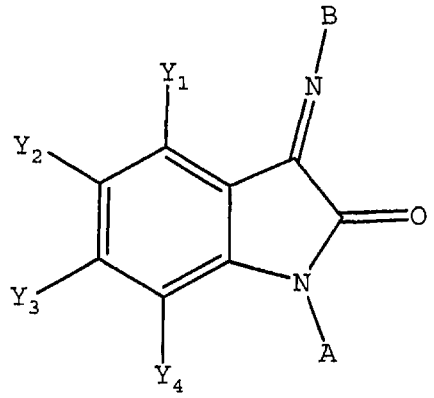
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

197. A compound having the structure:

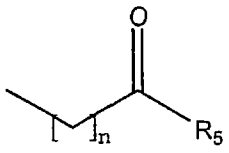
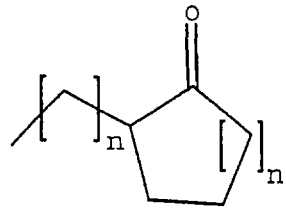


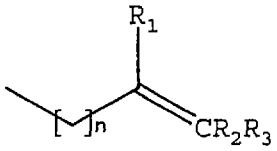
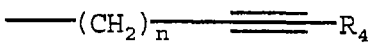
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is

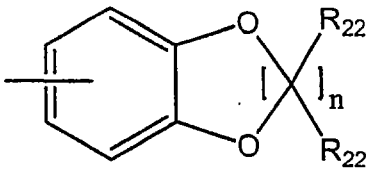
 ;  ;

 ; or  ;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

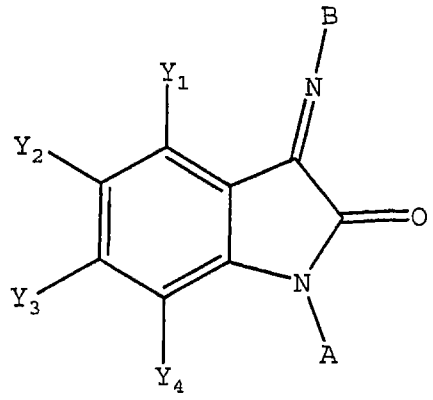
 ;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

198. A compound having the structure:

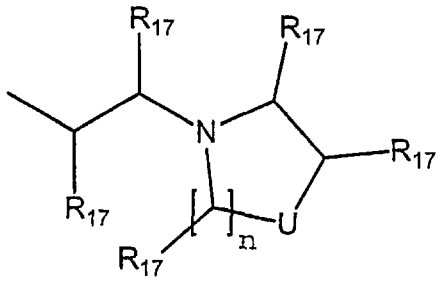


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

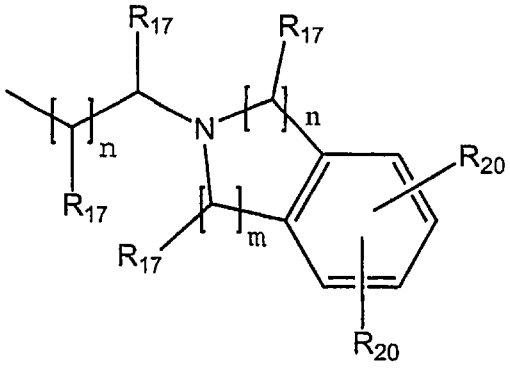
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or $(CHR_{17})-(CHR_{17})_n-Z$;

wherein Q_3 is



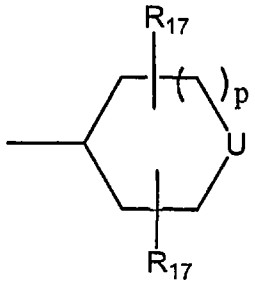
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

199. An enantiomerically and diastereomerically pure compound of claim 195, 196, 197, or 198.

200. An enantiomerically or diastereomerically pure compound of claim 195, 196, 197, or 198.

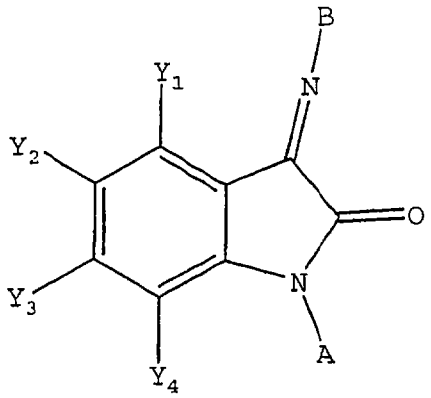
201. A pure Z imine isomer or a pure Z alkene isomer of

the compound of claim 195, 196, 197, or 198.

202. A pure E imine isomer or a pure E alkene isomer of the compound of claim 195, 196, 197, or 198.

203. The compound of claim 195, 196, 197, or 198, wherein the compound can be administered orally.

204. The compound of claim 195 or 196, wherein the compound has the structure:

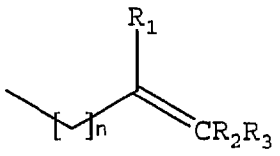


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl; and

wherein A' is



205. The compound of claim 195, 196 or 198, wherein B is heteroaryl.

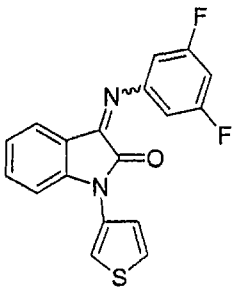
206. The compound of claim 195 or 196, wherein B is aryl.

207. The compound of claim 206, wherein B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

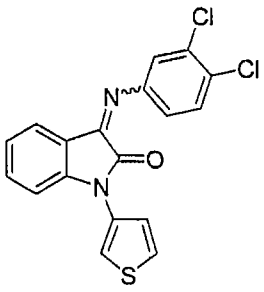
208. The compound of claim 207, wherein A is aryl.

209. The compound of claim 207, wherein A is heteroaryl.

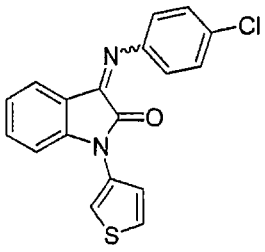
210. The compound of claim 209, wherein the compound is selected from the group consisting of:



;



; and

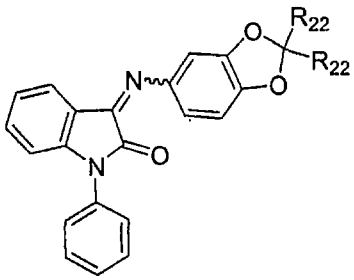


.

211. The compound of claim 197, wherein B is Q_6.

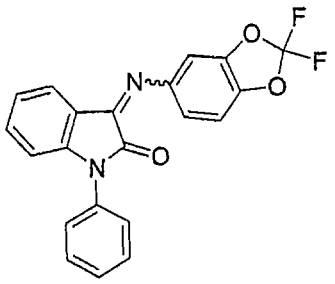
212. The compound of claim 211, wherein A is aryl.

213. The compound of claim 212, wherein the compound has the structure:



.

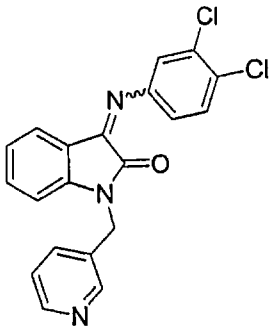
214. The compound of claim 213, wherein the compound is:



215. The compound of claim 198, wherein B is aryl.

216. The compound of claim 215, wherein A is (CHR_{17})-$(CHR_{17})_n$-Z.

217. The compound of claim 215, wherein the compound is:



218. A pure Z imine isomer of the compound of claim 195, 196, 197 or 198.

219. A pure E imine isomer of the compound of claim 195, 196, 197 or 198.

220. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 195, 196, 197 or 198, and a pharmaceutically acceptable carrier.

221. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 195, 196, 197 or 198, and a pharmaceutically acceptable carrier.

222. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 195, 196, 197 or 198, and a pharmaceutically acceptable carrier.

223. A method of treating a subject suffering from depression which comprises administering to the subject an amount of the compound of claim 195, 196, 197 or 198 effective to treat the subject's depression.

224. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of the compound of claim 195, 196, 197 or 198 effective to treat the subject's anxiety.

225. A method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of the compound of claim 195, 196, 197 or 198 effective to treat the subject's depression and anxiety.

226. A method of treating depression in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;

(b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10μM; and

(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10μM; and

(c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

227. The method of claim 226, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

228. The method of claim 227, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

229. The method of claim 228, wherein the receptor

antagonist binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

230. The method of claim 229, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

231. The method of claim 226, wherein the receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

232. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the human $5HT_{1B}$, human $5HT_{1D}$, human $5HT_{1E}$, human $5HT_{1F}$, human $5HT_{2A}$, rat $5HT_{2C}$, human $5HT_6$ and human $5HT_7$ receptors.

233. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human histamine H_1 receptor.

234. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human dopamine D_1, D_2, D_3, D_4 and D_5 receptors.

235. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human α_{1A} adrenoceptor, the human α_{1B} adrenoceptor and the human α_{1D} adrenoceptor.

236. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human α_{2A} adrenoceptor, the human α_{2B} adrenoceptor and the human α_{2C} adrenoceptor.

237. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human $5HT_4$ receptor.

238. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human $5HT_{1A}$ receptor.

239. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 30 percent.

240. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 30 percent.

241. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 15 percent.

242. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 15 percent.

243. A method of treating anxiety in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and

(b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

244. The method of claim 243, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

245. The method of claim 244, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

246. The method of claim 245, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the binding affinity

with which it binds to the human GAL1 receptor.

247. The method of claim 246, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

248. The method of claim 243, wherein the receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

249. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the human $5HT_{1B}$, human $5HT_{1D}$, human $5HT_{1E}$, human $5HT_{1F}$, human $5HT_{2A}$, rat $5HT_{2C}$, human $5HT_6$ and human $5HT_7$ receptors.

250. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human histamine H_1 receptor.

251. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human dopamine D_1, D_2, D_3, D_4 and D_5 receptors.

252. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a

binding affinity at least ten-fold higher than the binding affinity with which it binds to the human α_{1A} adrenoceptor, the human α_{1B} adrenoceptor and the human α_{1D} adrenoceptor.

253. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human α_{2A} adrenoceptor, the human α_{2B} adrenoceptor and the human α_{2C} adrenoceptor.

254. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human $5HT_4$ receptor.

255. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human $5HT_{1A}$ receptor.