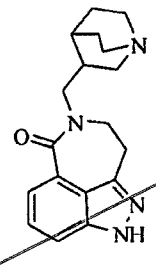
reflux until the reaction was complete by TLC and/or LC-MS. The solvent was removed under reduced pressure to give lithium 1-(2-(quinuclidin-4-ylmethylamino)ethyl)-1*H*-indazole-7-carboxylate (1.20 g, crude): ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 3.28–3.20 (m, 2H); 2.98 (t, J = 6.6 Hz, 2H), 2.81 (t, J = 7.5 Hz, 6H), 2.28 (s, 2H), 1.36 (t, J = 8.1 Hz, 6H).

[0311] Step H: Lithium 1-(2-(quinuclidin-4-ylmethylamino)ethyl)-1*H*-indazole-7-carboxylate (1.2 g, 3.6 mmol) from Step G above in THF (30 mL) was cooled in an ice bath while *N*,*N*-diisopropylethylamine (4 mL, 21.6 mmol) was added, followed by 1-propanephosphonic acid cyclic anhydride (T_3P; 50 wt% in EtOAc; 14 mL, 21.6 mmol). The reaction mixture was stirred at room temperature until the reaction was complete by TLC (overnight). The mixture was concentrated in vacuo and then purified with ISOLUTE® SCX-2 columns to give 7-(quinuclidin-4-ylmethyl)-8,9-dihydro-[1,4]diazepino[6,7,1-*hi*]indazol-6(7*H*)-one (267 mg, 24%).

Step I: 7-(Quinuclidin-4-ylmethyl)-8,9-dihydro-[1,4]diazepino[6,7,1-*hi*]indazol-6(7*H*)-one (267 mg, 0.9 mmol) from Step H above was dissolved in 1.25 M HCl in methanol and concentrated under reduced pressure to give 7-(quinuclidin-4-ylmethyl)-8,9-dihydro-[1,4]diazepino[6,7,1-*hi*]indazol-6(7*H*)-one hydrochloride as an off-white solid (299 mg, 100%): ^{1}H NMR (500 MHz, D_2O) δ 8.04 (s, 1H), 7.92 (d, J = 7.0 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 4.54 (s, 2H), 3.86 (s, 2H), 3.55 (s, 2H), 3.23 (t, J = 7.5 Hz, 6H), 1.83 (t, J = 7.5 Hz, 6H); MS (ESI+) *m/z* 311 (M+H).

~~Examples 33 and 34 – Preparation of 7-(quinuclidin-3-ylmethyl)-7,8-~~ dihydropyrazolo[3,4,5-*de*]isoquinolin-6(2*H*)-one, enantiomers A and B, hydrochloride salts



[0312] Quinuclidin-3-ylmethanamine was synthesized from quinuclidine-3-carbonitrile according to a reported method (U.S. Patent 4,853,376, which is hereby incorporated by reference in its entirety).

[0313] Step A: To a solution of methyl 3-formyl-1*H*-indazole-4-carboxylate (49.5 g, 242 mmol) was added cesium carbonate (158 g, 485 mmol) in DMF (750 mL) at 0°C. The mixture was stirred under an atmosphere of nitrogen for 15 min. To this solution were added 4-methoxybenzyl bromide (41.6 g, 267 mmol) and sodium iodide (7.3 g, 48.5 mmol). The resulting mixture continued to stir for 10 min and then warmed to room temperature and stirred for 2.5 h. The mixture was filtered to remove solid cesium carbonate and the filtrate was quenched with sat. aqueous sodium chloride (200 mL) and extracted with diethyl ether (3 × 500 mL). The combined organic layers were washed with brine (3 × 200 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 10 to 25 % ethyl acetate in hexanes) to afford methyl 3-formyl-1-(4-methoxybenzyl)-1*H*-indazole-4-carboxylate (41.8 g, 53%): ^{1}H NMR δ (300 MHz, $CDCl_3$) 10.53 (s, 1H), 7.77 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.58 (d, *J* = 9.0,1.0 Hz, 1H), 7.44 (dd, *J* = 9.0, 7.20, Hz, 1H), 7.20 (dd, *J* = 6.6, 2.1 Hz, 2H), 6.89 (dd, *J* = 6.9, 2.1 Hz, 2H), 5.68 (s, 2H), 4.01 (s, 3H), 3.77 (s, 3H); MS (ESI+) *m/z* 325 (M+H). In addition, methyl 3-formyl-2-(4-methoxybenzyl)-2*H*-indazole-4-carboxylate (24.2 g, 31%) was also isolated: ^{1}H NMR δ (300 MHz, $CDCl_3$) 10.88 (s, 1H), 8.10 (t, *J* = 7.2 Hz, 2H), 7.42 (dd, *J* = 9.0,1.0 Hz, 1H), 7.36 (dd, *J* = 9.0, 7.20, Hz, 2H), 6.82 (dd, *J* = 6.6, 2.1 Hz, 2H), 6.07 (s, 2H), 4.01 (s, 3H), 3.77 (s, 3H); MS (ESI+) *m/z* 325 (M+H).

[0314] To a –78 °C cooled suspension of (methoxymethyl)triphenylphosphonium chloride (119 g, 347 mmol) in tetrahydrofuran (1000 mL) was carefully added a solution of lithium bis(trimethylsilyl)amide (1.0M in THF, 347 mL, 347 mmol). The resulting dark red mixture was stirred at –40 °C for 30 min. To this was added a solution of methyl 3-formyl-1-(4-methoxybenzyl)-1*H*-indazole-4-carboxylate (45 g, 139 mmol) in tetrahydrofuran slowly and the mixture was stirred for 30 min. The reaction was quenched with sat. aqueous sodium chloride (500 mL) and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine (4 × 300 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by column chromatography (silica gel, 5 to 30 % ethyl acetate in hexanes) to afford

methyl 1-(4-methoxybenzyl)-3-(2-methoxyvinyl)-1*H*-indazole-4-carboxylate (40.3 g, 82%) as a yellow oil. A mixture of tetrahydrofuran (950 mL) and 6N hydrochloric acid (30 mL) was added to methyl 1-(4-methoxybenzyl)-3-(2-methoxyvinyl)-1*H*-indazole-4-carboxylate (40.3 g, 114.5 mmol) and the resulting biphasic mixture was heated to reflux for 2.5 h. The mixture was cooled to room temperature and diluted with ethyl acetate (1500 mL). The organic layer was separated and washed with brine (4 × 500 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford methyl 1-(4-methoxybenzyl)-3-(2-oxoethyl)-1*H*-indazole-4-carboxylate (30 g, 77%) as a yellow solid: ^{1}H NMR δ (300 MHz, DMSO-d_3) 9.78 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 7.2, 0.6 Hz, 1H), 7.48 (dd, J = 8.7, 7.5 Hz, 1H), 7.22–7.19 (m, 2H), 6.88–6.85 (m, 2H), 5.61 (s, 2H), 4.26 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H); MS (ESI+) *m/z* 339 (M+H).

[0315] Step C: The procedure described in Step A of Example 29 was used to convert methyl 1-(4-methoxybenzyl)-3-(2-oxoethyl)-1*H*-indazole-4-carboxylate from Step B above and quinuclidin-3-ylmethanamine to methyl 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate: ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (dd, J = 8.5, 0.7 Hz, 1H), 7.74 (dd, J = 7.2, 0.7 Hz, 1H), 7.43 (dd, J = 8.5, 7.3 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.55 (s, 2H), 3.97 (s, 3H), 3.74 (s, 3H), 3.41 (t, J = 7.1 Hz, 2H), 3.32–3.29 (m, 1H), 3.09–3.05 (m, 2H), 2.97–2.85 (m, 4H), 2.77 (dd, J = 12.0, 8.1 Hz, 1H), 2.67 (dd, J = 12.0, 7.1 Hz, 1H), 2.47–2.42 (m, 1H), 1.96–1.90 (m, 1H), 1.76–1.70 (m, 3H), 1.65–1.60 (m, 1H), 1.51–1.44 (m, 1H); MS (ESI+) *m/z* 463 (M+H).

[0316] Step D: The procedure described in Step B of Example 29 was used to convert methyl 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate from Step C above to lithium 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate: MS (ESI+) *m/z* 449 (M+H).

[0317] Step E: The procedure described in Step C of Example 29 was used to convert lithium 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate from Step D above to 2-(4-methoxybenzyl)-7-(quinuclidin-3-ylmethyl)-8,9-dihydro-2*H*-azepino[5,4,3-*cd*]indazol-6(7*H*)-one: ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.51 (dd, J = 8.4, 7.3 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.54 (s, 2H), 3.91–3.87 (m, 3H),

3.75–3.71 (m, 1H), 3.74 (s, 3H), 3.23–3.20 (m, 2H), 3.18–3.15 (m, 1H), 3.07–2.91 (m, 4H), 2.69–2.64 (m, 1H), 2.39–2.33 (m, 1H), 2.16–2.08 (m, 1H), 1.83–1.77 (m, 2H), 1.75–1.69 (m, 1H), 1.64–1.57 (m, 1H); MS (ESI+) *m/z* 431 (M+H).

[0318] Step F: A solution of 2-(4-methoxybenzyl)-7-(quinuclidin-3-ylmethyl)-8,9-dihydro-2*H*-azepino[5,4,3-*cd*]indazol-6(7*H*)-one (219 mg, 0.51 mmol) in trifluoroacetic acid (3 mL) was subjected to microwave irradiation at 130 °C for 18 min. The mixture was diluted with methanol and concentrated in vacuo. The resulting residue was converted to the free base by elution through an SCX-2 cartridge and then purified by column chromatography (silica gel, (12%–100% solvent mixture B in methylene chloride; solvent mixture B = 70:27:3 methylene chloride/methanol/concentrated ammonium hydroxide) to afford 7-(quinuclidin-3-ylmethyl)-8,9-dihydro-2*H*-azepino[5,4,3-*cd*]indazol-6(7*H*)-one (140 mg, 88%) as a colorless oil: MS (ESI+) *m/z* 311 (M+H).

[0319] Step G: 7-(quinuclidin-3-ylmethyl)-8,9-dihydro-2*H*-azepino[5,4,3-*cd*]indazol-6(7*H*)-one from Step F above was resolved by preparative chiral HPLC (CHIRALCEL OD column, using 80:20:0.1 heptane/isopropanol/diethylamine as the eluent) to give enantiomers A and B.

[0320] Step H: The procedure described in Step D of Example 29 was used to convert 7-(quinuclidin-3-ylmethyl)-8,9-dihydro-2*H*-azepino[5,4,3-*cd*]indazol-6(7*H*)-one, enantiomer A (absolute stereochemistry unknown) from Step G above to the corresponding hydrochloride salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.3 Hz, 1H), 3.94–3.88 (m, 4H), 3.56–3.51 (m, 1H), 3.45–3.29 (m, 5H), 3.26–3.23 (m, 2H), 2.69–2.62 (m, 1H), 2.36 (br s, 1H), 2.10 (br s, 1H), 2.06–1.98 (m, 2H), 1.94–1.88 (m, 1H); MS (ESI+) *m/z* 311 (M+H).

[0321] Step I: The procedure described in Step D of Example 29 was used to convert 7-(quinuclidin-3-ylmethyl)-8,9-dihydro-2*H*-azepino[5,4,3-*cd*]indazol-6(7*H*)-one, enantiomer B (absolute stereochemistry unknown) from Step G above to the corresponding hydrochloride salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.3 Hz, 1H), 3.94–3.88 (m, 4H), 3.56–3.51 (m, 1H), 3.45–3.29 (m, 5H), 3.26–3.23 (m, 2H), 2.69–2.62 (m, 1H), 2.36 (br s, 1H), 2.10 (br s, 1H), 2.06–1.98 (m, 2H), 1.94–1.88 (m, 1H); MS (ESI+) *m/z* 311 (M+H).

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a five- to seven-membered heterocyclic ring, which comprises from 1 to 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and is optionally substituted from 1 to 4 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^6 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^7 and R^8 are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —C(O)R^6, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

n is 1 or 2;

p is 0, 1, 2, or 3; and

q is 0, 1, or 2;

~~or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.~~

2. The compound according to claim 1, wherein Q has an empirical ~~formula $C_{7-10}N_{1-2}$.~~

3. The compound according to claim 1, wherein Q is an azabicycloheptane, azabicyclooctane, or azabicyclononane.

4. The compound according to claim 3, wherein Q is quinuclidine.

16. A method of treating a disease or condition which is susceptible to treatment with a 5-HT_3 receptor modulator comprising:

selecting a patient with a disease or condition which is susceptible to treatment with a 5-HT_3 receptor modulator; and

administering to the patient a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

17. The method according to claim 16, wherein the disease or condition is selected from the group consisting of general anxiety disorders, social phobias, vertigo, obsessive-compulsive disorders, panic disorders, post-traumatic stress disorders, bulimia nervosa, drug withdrawal effects, alcohol dependency, pain, sleep related central apneas, chronic fatigue syndrome, Parkinson's Disease Psychosis, schizophrenia, cognitive decline and defects in schizophrenia, Parkinson's Disease, Huntington's Chorea, presenile dementias, Alzheimer's Disease, obesity, substance abuse disorders, dementia associated with neurodegenerative disease, cognition deficits, fibromyalgia syndrome, rosacea, cardiovascular disorders mediated by serotonin, chemotherapy induced nausea and vomiting, post-operative induced nausea and vomiting, radiation induced nausea and vomiting, gastrointestinal disorders, irritable bowel syndrome, gastroesophageal reflux disease, Burkitt's lymphoma, bronchial asthma, pruritus, migraine, and epilepsy.

18. The method according to claim 16, wherein the compound according to claim 1 or pharmaceutically acceptable salt thereof is a 5-HT_3 receptor antagonist.

19. The method according to claim 16, wherein the compound according to claim 1 or pharmaceutically acceptable salt thereof is a 5-HT_3 partial agonist.

20. The method according to claim 16 further comprising:

administering to the patient a therapeutically effective amount of a schizophrenia adjunct.

21. The method according to claim 20, wherein the schizophrenia adjunct is selected from the group consisting of valproate, levomepromazine, alprazolam, haloperidol, chlorpromazine, risperidone, paliperidone, olanzapine, ziprasidone, quetiapine, clozapine, lithium carbonate, diazepam, carbamazepine, selective serotonin re-uptake inhibitors, tricyclic antidepressants, and combinations thereof

22. The method according to claim 16 further comprising:

administering to the patient a therapeutically effective amount of a Parkinson's Disease adjunct.

23. The method according to claim 22, wherein the Parkinson's Disease adjunct is selected from the group consisting of transdermal rotigotine, rasagiline, safinamide, levodopa, carbidopa, dopamine agonists, COMT inhibitors, MAO-B inhibitors, amantadine, anticholinergic agents, and combinations thereof

24. A method of treating irritable bowel syndrome comprising:

selecting a patient with irritable bowel syndrome; and

administering to the patient a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

25. The method according to claim 24 further comprising:

administering to the patient a therapeutically effective amount of a second serotonin 5-HT_3 receptor modulator or a serotonin 5-HT_4 receptor modulator.

26. The method according to claim 25, wherein the second serotonin 5-HT_3 receptor modulator or serotonin 5-HT_4 receptor modulator is selected from the group consisting of Alosetron, renzapride, cilansetron, Tegaserod, Prucalopride, ondansetron, and combinations thereof.

27. The method according to claim 24 further comprising:

administering to the patient a therapeutically effective amount of a therapeutic agent selected from the group consisting of somatostatin analogs, muscarinic receptor antagonists, laxatives, antispasmodics, antidepressants, antidiarrheal agents, prokinetic agents, peripheral opiate narcotic antagonists, and combinations thereof.

28. A method of treating emesis comprising:

selecting a patient with emesis; and

administering to the patient a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

29. The method according to claim 28 further comprising:

administering to the patient a therapeutically effective amount of one or more other anti-emetic compounds.

30. The method according to claim 29, wherein the one or more other anti-emetic compounds are selected from the group consisting of dexamethasone, alosetron, alprazolam, aprepitant, dimenhydrinate, diphenhydramine, dolasetron, tetrahydrocannabinol, nabilone, dronabinol, droperidol, granisetron, haloperidol, lorazepam, metoclopramide, midazolam, olanzapine, ondansetron, palonosetron, proclorperazine, promethazine, tropisetron, and combinations thereof.

31. A method of treating CNS diseases or conditions comprising:

selecting a patient with a CNS disease or condition; and

administering to the patient a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

32. The method according to claim 31, wherein the CNS disease or condition is selected from the group consisting of schizophrenia and Parkinson's disease.

33. A compound of formula II:

from the group consisting of nitrogen, oxygen, and sulfur, and is optionally substituted from 1 to 4 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^6 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^7 and R^8 are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —C(O)R^6, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

n is 0, 1, or 2, with the provisos that: (1) when Z is N, then n is 1 or 2; and (2) when Z is C, then n is 0, 1, or 2;

p is 0, 1, 2, or 3; and

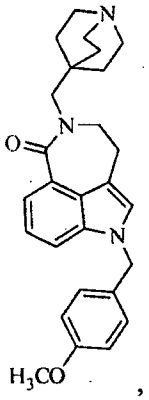
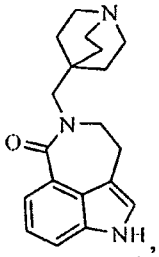
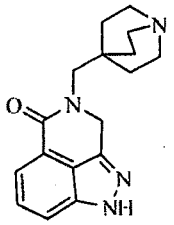
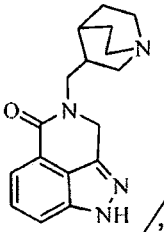
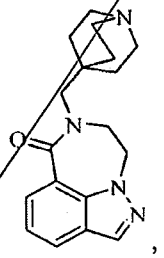
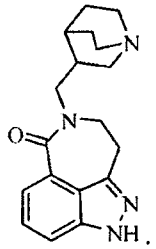
q is 0, 1, or 2;

~~or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.~~

34. The compound according to claim 33, wherein Q has an empirical ~~formula $C_{7-10}N_{1-2}$.~~

35. The compound according to claim 33, wherein Q is an azabicycloheptane, azabicyclooctane, or azabicyclononane.

36. The compound according to claim 35, wherein Q is quinuclidine.


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49. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 33 and a pharmaceutically acceptable carrier.

50. A method of treating a disease or condition which is susceptible to treatment with a 5-HT_3 receptor modulator comprising:

selecting a patient with a disease or condition which is susceptible to treatment with a 5-HT_3 receptor modulator; and

administering to the patient a therapeutically effective amount of a compound according to claim 33 or a pharmaceutically acceptable salt thereof.

51. The method according to claim 50, wherein the disease or condition is selected from the group consisting of general anxiety disorders, social phobias, vertigo, obsessive-compulsive disorders, panic disorders, post-traumatic stress disorders, bulimia nervosa, drug withdrawal effects, alcohol dependency, pain, sleep related central apneas, chronic fatigue syndrome, Parkinson's Disease Psychosis, schizophrenia, cognitive decline and defects in schizophrenia, Parkinson's Disease,

Huntington's Chorea, presenile dementias, Alzheimer's Disease, obesity, substance abuse disorders, dementia associated with neurodegenerative disease, cognition deficits, fibromyalgia syndrome, rosacea, cardiovascular disorders mediated by serotonin, chemotherapy induced nausea and vomiting, post-operative induced nausea and vomiting, radiation induced nausea and vomiting, gastrointestinal disorders, irritable bowel syndrome, gastroesophageal reflux disease, Burkitt's lymphoma, bronchial asthma, pruritus, migraine, and epilepsy.

52. The method according to claim 50, wherein the compound according to claim 33 or pharmaceutically acceptable salt thereof is a 5-HT_3 receptor antagonist.

53. The method according to claim 50, wherein the compound according to claim 33 or pharmaceutically acceptable salt thereof is a 5-HT_3 partial agonist.

54. The method according to claim 50 further comprising:

administering to the patient a therapeutically effective amount of a schizophrenia adjunct.

55. The method according to claim 54, wherein the schizophrenia adjunct is selected from the group consisting of valproate, levomepromazine, alprazolam, haloperidol, chlorpromazine, risperidone, paliperidone, olanzapine, ziprasidone, quetiapine, clozapine, lithium carbonate, diazepam, carbamazepine, selective serotonin re-uptake inhibitors, tricyclic antidepressants, and combinations thereof

56. The method according to claim 50 further comprising:

administering to the patient a therapeutically effective amount of a Parkinson's Disease adjunct.

57. The method according to claim 56, wherein the Parkinson's Disease adjunct is selected from the group consisting of transdermal rotigotine,

rasagiline, safinamide, levodopa, carbidopa, dopamine agonists, COMT inhibitors, MAO-B inhibitors, amantadine, anticholinergic agents, and combinations thereof

58. A method of treating irritable bowel syndrome comprising:
selecting a patient with irritable bowel syndrome; and
administering to the patient a therapeutically effective amount of a compound according to claim 33 or a pharmaceutically acceptable salt thereof.

59. The method according to claim 58 further comprising:
administering to the patient a therapeutically effective amount of a second serotonin 5-HT_3 receptor modulator or a serotonin 5-HT_4 receptor modulator.

60. The method according to claim 59, wherein the second serotonin 5-HT_3 receptor modulator or serotonin 5-HT_4 receptor modulator is selected from the group consisting of Alosetron, renzapride, cilansetron, Tegaserod, Prucalopride, ondansetron, and combinations thereof.

61. The method according to claim 58 further comprising:
administering to the patient a therapeutically effective amount of a therapeutic agent selected from the group consisting of somatostatin analogs, muscarinic receptor antagonists, laxatives, antispasmodics, antidepressants, antidiarrheal agents, prokinetic agents, peripheral opiate narcotic antagonists, and combinations thereof.

62. A method of treating emesis comprising:
selecting a patient with emesis; and
administering to the patient a therapeutically effective amount of a compound according to claim 33 or a pharmaceutically acceptable salt thereof.

63. The method according to claim 62 further comprising:
administering to the patient a therapeutically effective amount of one or more other anti-emetic compounds.

64. The method according to claim 63, wherein the one or more other anti-emetic compounds are selected from the group consisting of dexamethasone, alosetron, alprazolam, aprepitant, dimenhydrinate, diphenhydramine, dolasetron, tetrahydrocannabinol, nabilone, dronabinol, droperidol, granisetron, haloperidol, lorazepam, metoclopramide, midazolam, olanzapine, ondansetron, palonosetron, proclorperazine, promethazine, tropisetron, and combinations thereof.

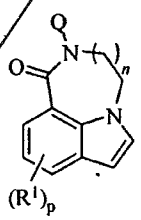
65. A method of treating CNS diseases or conditions comprising:

selecting a patient with a CNS disease or condition; and

administering to the patient a therapeutically effective amount of a compound according to claim 33 or a pharmaceutically acceptable salt thereof.

66. The method according to claim 65, wherein the CNS disease or condition is selected from the group consisting of schizophrenia and Parkinson's disease.

67. A process of preparing a product compound of formula Ia:

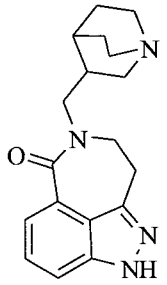


formula Ia

wherein:

Q is a saturated, bicyclic, heterocyclic amine, wherein the saturated, bicyclic, heterocyclic amine comprises at least two atoms between the amide nitrogen of the compound of formula I and any amine nitrogen of Q and wherein the saturated, bicyclic, heterocyclic amine is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from the group consisting of C_1-C_3 alkyl, halogen, —CN, —OR^7, and —NR^7R^8;

Examples 33 and 34 - Preparation of 5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1H-azepino[5,4,3-cd]indazol-6(3H)-one, enantiomers A and B, hydrochloride salts



[0312] Quinuclidin-3-ylmethanamine was synthesized from quinuclidine-3-carbonitrile according to a reported method (U.S. Patent 4,853,376, which is hereby incorporated by reference in its entirety).

[0313] Step A: To a solution of methyl 3-formyl-1*H*-indazole-4-carboxylate (49.5 g, 242 mmol) was added cesium carbonate (158 g, 485 mmol) in DMF (750 mL) at 0°C. The mixture was stirred under an atmosphere of nitrogen for 15 min. To this solution were added 4-methoxybenzyl bromide (41.6 g, 267 mmol) and sodium iodide (7.3 g, 48.5 mmol). The resulting mixture continued to stir for 10 min and then warmed to room temperature and stirred for 2.5 h. The mixture was filtered to remove solid cesium carbonate and the filtrate was quenched with sat. aqueous sodium chloride (200 mL) and extracted with diethyl ether (3 × 500 mL). The combined organic layers were washed with brine (3 × 200 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 10 to 25 % ethyl acetate in hexanes) to afford methyl 3-formyl-1-(4-methoxybenzyl)-1*H*-indazole-4-carboxylate (41.8 g, 53%): ^{1}H NMR δ (300 MHz, $CDCl_3$) □10.53 (s, 1H), 7.77 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.58 (d, *J* = 9.0,1.0 Hz, 1H), 7.44 (dd, *J* = 9.0, 7.20, Hz, 1H), 7.20 (dd, *J* = 6.6, 2.1 Hz, 2H), 6.89 (dd, *J* = 6.9, 2.1 Hz, 2H), 5.68 (s, 2H), 4.01 (s, 3H), 3.77 (s, 3H); MS (ESI+) *m/z* 325 (M+H). In addition, methyl 3-formyl-2-(4-methoxybenzyl)-2*H*-indazole-4-carboxylate (24.2 g, 31%) was also isolated: ^{1}H NMR δ (300 MHz, $CDCl_3$) □10.88 (s, 1H), 8.10 (t, *J* = 7.2 Hz, 2H), 7.42 (dd, *J* = 9.0,1.0 Hz, 1H), 7.36 (dd, *J* = 9.0, 7.20, Hz, 2H), 6.82 (dd, *J* = 6.6, 2.1 Hz, 2H), 6.07 (s, 2H), 4.01 (s, 3H), 3.77 (s, 3H); MS (ESI+) *m/z* 325 (M+H).

[0314] To a –78 °C cooled suspension of (methoxymethyl)triphenylphosphonium chloride (119 g, 347 mmol) in tetrahydrofuran (1000 mL) was carefully added a solution of lithium bis(trimethylsilyl)amide (1.0M in THF, 347 mL, 347 mmol). The resulting dark red mixture was stirred at –40 °C for 30 min. To this was added a solution of methyl 3-formyl-1-(4-methoxybenzyl)-1*H*-indazole-4-carboxylate (45 g, 139 mmol) in tetrahydrofuran slowly

and the mixture was stirred for 30 min. The reaction was quenched with sat. aqueous sodium chloride (500 mL) and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine (4 × 300 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by column chromatography (silica gel, 5 to 30 % ethyl acetate in hexanes) to afford methyl 1-(4-methoxybenzyl)-3-(2-methoxyvinyl)-1*H*-indazole-4-carboxylate (40.3 g, 82%) as a yellow oil. A mixture of tetrahydrofuran (950 mL) and 6N hydrochloric acid (30 mL) was added to methyl 1-(4-methoxybenzyl)-3-(2-methoxyvinyl)-1*H*-indazole-4-carboxylate (40.3 g, 114.5 mmol) and the resulting biphasic mixture was heated to reflux for 2.5 h. The mixture was cooled to room temperature and diluted with ethyl acetate (1500 mL). The organic layer was separated and washed with brine (4 × 500 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford methyl 1-(4-methoxybenzyl)-3-(2-oxoethyl)-1*H*-indazole-4-carboxylate (30 g, 77%) as a yellow solid: ^{1}H NMR δ (300 MHz, DMSO-d_3) □9.78 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 7.2, 0.6 Hz, 1H), 7.48 (dd, J = 8.7, 7.5 Hz, 1H), 7.22–7.19 (m, 2H), 6.88–6.85 (m, 2H), 5.61 (s, 2H), 4.26 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H); MS (ESI+) *m/z* 339 (M+H).

[0315] Step C: The procedure described in Step A of Example 29 was used to convert methyl 1-(4-methoxybenzyl)-3-(2-oxoethyl)-1*H*-indazole-4-carboxylate from Step B above and quinuclidin-3-ylmethanamine to methyl 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate: ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (dd, J = 8.5, 0.7 Hz, 1H), 7.74 (dd, J = 7.2, 0.7 Hz, 1H), 7.43 (dd, J = 8.5, 7.3 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.55 (s, 2H), 3.97 (s, 3H), 3.74 (s, 3H), 3.41 (t, J = 7.1 Hz, 2H), 3.32–3.29 (m, 1H), 3.09–3.05 (m, 2H), 2.97–2.85 (m, 4H), 2.77 (dd, J = 12.0, 8.1 Hz, 1H), 2.67 (dd, J = 12.0, 7.1 Hz, 1H), 2.47–2.42 (m, 1H), 1.96–1.90 (m, 1H), 1.76–1.70 (m, 3H), 1.65–1.60 (m, 1H), 1.51–1.44 (m, 1H); MS (ESI+) *m/z* 463 (M+H).

[0316] Step D: The procedure described in Step B of Example 29 was used to convert methyl 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate from Step C above to lithium 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate: MS (ESI+) *m/z* 449 (M+H).

[0317] Step E: The procedure described in Step C of Example 29 was used to convert lithium 1-(4-methoxybenzyl)-3-(2-(quinuclidin-3-ylmethylamino)ethyl)-1*H*-indazole-4-carboxylate from Step D above to 1-(4-methoxybenzyl)-5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1*H*-azepino[5,4,3-*cd*]indazol-6(3*H*)-one: ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, J

= 7.2 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 2H), 3.91–3.87 (m, 3H), 3.75–3.71 (m, 1H), 3.74 (s, 3H), 3.23–3.20 (m, 2H), 3.18–3.15 (m, 1H), 3.07–2.91 (m, 4H), 2.69–2.64 (m, 1H), 2.39–2.33 (m, 1H), 2.16–2.08 (m, 1H), 1.83–1.77 (m, 2H), 1.75–1.69 (m, 1H), 1.64–1.57 (m, 1H); MS (ESI+) *m/z* 431 (M+H).

[0318] Step F: A solution of 1-(4-methoxybenzyl)-5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1*H*-azepino[5,4,3-*cd*]indazol-6(3*H*)-one (219 mg, 0.51 mmol) in trifluoroacetic acid (3 mL) was subjected to microwave irradiation at 130 °C for 18 min. The mixture was diluted with methanol and concentrated in vacuo. The resulting residue was converted to the free base by elution through an SCX-2 cartridge and then purified by column chromatography (silica gel, (12%–100% solvent mixture B in methylene chloride; solvent mixture B = 70:27:3 methylene chloride/methanol/concentrated ammonium hydroxide) to afford 5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1H-azepino[5,4,3-cd]indazol-6(3H)-one (140 mg, 88%) as a colorless oil: MS (ESI+) *m/z* 311 (M+H).

[0319] Step G: 5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1H-azepino[5,4,3-cd]indazol-6(3H)-one from Step F above was resolved by preparative chiral HPLC (CHIRALCEL OD column, using 80:20:0.1 heptane/isopropanol/diethylamine as the eluent) to give enantiomers A and B.

[0320] Step H: The procedure described in Step D of Example 29 was used to convert 5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1H-azepino[5,4,3-cd]indazol-6(3H)-one, enantiomer A (absolute stereochemistry unknown) from Step G above to the corresponding hydrochloride salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.3 Hz, 1H), 3.94–3.88 (m, 4H), 3.56–3.51 (m, 1H), 3.45–3.29 (m, 5H), 3.26–3.23 (m, 2H), 2.69–2.62 (m, 1H), 2.36 (br s, 1H), 2.10 (br s, 1H), 2.06–1.98 (m, 2H), 1.94–1.88 (m, 1H); MS (ESI+) *m/z* 311 (M+H).

[0321] Step I: The procedure described in Step D of Example 29 was used to convert 5-(quinuclidin-3-ylmethyl)-4,5-dihydro-1H-azepino[5,4,3-cd]indazol-6(3H)-one, enantiomer B (absolute stereochemistry unknown) from Step G above to the corresponding hydrochloride salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.3 Hz, 1H), 3.94–3.88 (m, 4H), 3.56–3.51 (m, 1H), 3.45–3.29 (m, 5H), 3.26–3.23 (m, 2H), 2.69–2.62 (m, 1H), 2.36 (br s, 1H), 2.10 (br s, 1H), 2.06–1.98 (m, 2H), 1.94–1.88 (m, 1H); MS (ESI+) *m/z* 311 (M+H).

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a five- to seven-membered heterocyclic ring, which comprises from 1 to 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and is optionally substituted from 1 to 4 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^6 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^7 and R^8 are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —C(O)R^6, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

n is 1 or 2;

p is 0, 1, 2, or 3; and

q is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. The compound according to claim 1, wherein Q has an empirical formula $C_{7\text{-}10}H_{12\text{-}19}N_{1\text{-}2}$.

3. The compound according to claim 1, wherein Q is an azabicycloheptane, azabicyclooctane, or azabicyclononane.

4. The compound according to claim 3, wherein Q is quinuclidine.

16. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of a disease or condition which is susceptible to treatment with a 5-HT_3 receptor modulator.

17. The use of the compound according to claim 16, wherein the disease or condition is selected from the group consisting of general anxiety disorders, social phobias, vertigo, obsessive-compulsive disorders, panic disorders, post-traumatic stress disorders, bulimia nervosa, drug withdrawal effects, alcohol dependency, pain, sleep related central apneas, chronic fatigue syndrome, Parkinson's Disease Psychosis, schizophrenia, cognitive decline and defects in schizophrenia, Parkinson's Disease, Huntington's Chorea, presenile dementias, Alzheimer's Disease, obesity, substance abuse disorders, dementia associated with neurodegenerative disease, cognition deficits, fibromyalgia syndrome, rosacea, cardiovascular disorders mediated by serotonin, chemotherapy induced nausea and vomiting, post-operative induced nausea and vomiting, radiation induced nausea and vomiting, gastrointestinal disorders, irritable bowel syndrome, gastroesophageal reflux disease, Burkitt's lymphoma, bronchial asthma, pruritus, migraine, and epilepsy.

18. The use of the compound according to claim 16, wherein the compound according to claim 1 or pharmaceutically acceptable salt thereof is a 5-HT_3 receptor antagonist.

19. The use of the compound according to claim 16, wherein the compound according to claim 1 or pharmaceutically acceptable salt thereof is a 5-HT_3 partial agonist.

20. The use of the compound according to claim 16 further comprising:
a therapeutically effective amount of a schizophrenia adjunct.

21. The use of the compound according to claim 20, wherein the schizophrenia adjunct is selected from the group consisting of valproate, levomepromazine, alprazolam, haloperidol, chlorpromazine, risperidone, paliperidone, olanzapine, ziprasidone, quetiapine, clozapine, lithium carbonate, diazepam, carbamazepine, selective serotonin re-uptake inhibitors, tricyclic antidepressants, and combinations thereof

22. The use of the compound according to claim 16 further comprising: a therapeutically effective amount of a Parkinson's Disease adjunct.

23. The use of the compound according to claim 22, wherein the Parkinson's Disease adjunct is selected from the group consisting of transdermal rotigotine, rasagiline, safinamide, levodopa, carbidopa, dopamine agonists, COMT inhibitors, MAO-B inhibitors, amantadine, anticholinergic agents, and combinations thereof

24. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of irritable bowel syndrome.

25. The use of the compound according to claim 24 further comprising: a therapeutically effective amount of a second serotonin 5-HT_3 receptor modulator or a serotonin 5-HT_4 receptor modulator.

26. The use of the compound according to claim 25, wherein the second serotonin 5-HT_3 receptor modulator or serotonin 5-HT_4 receptor modulator is selected from the group consisting of Alosetron, renzapride, cilansetron, Tegaserod, Prucalopride, ondansetron, and combinations thereof.

27. The use of the compound according to claim 24 further comprising:

a therapeutically effective amount of a therapeutic agent selected from the group consisting of somatostatin analogs, muscarinic receptor antagonists, laxatives, antispasmodics, antidepressants, antidiarrheal agents, prokinetic agents, peripheral opiate narcotic antagonists, and combinations thereof.

28. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of emesis.

29. The use of the compound according to claim 28 further comprising:

a therapeutically effective amount of one or more other anti-emetic compounds.

30. The use of the compound according to claim 29, wherein the one or more other anti-emetic compounds are selected from the group consisting of dexamethasone, alosetron, alprazolam, aprepitant, dimenhydrinate, diphenhydramine, dolasetron, tetrahydrocannabinol, nabilone, dronabinol, droperidol, granisetron, haloperidol, lorazepam, metoclopramide, midazolam, olanzapine, ondansetron, palonosetron, proclorperazine, promethazine, tropisetron, and combinations thereof.

31. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of CNS diseases or conditions.

32. The use of the compound according to claim 31, wherein the CNS disease or condition is selected from the group consisting of schizophrenia and Parkinson's disease.

33. A compound of formula II:

from the group consisting of nitrogen, oxygen, and sulfur, and is optionally substituted from 1 to 4 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^6 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^7 and R^8 are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —C(O)R^6, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

n is 0, 1, or 2, with the provisos that: (1) when Z is N, then n is 1 or 2; and (2) when Z is C, then n is 0, 1, or 2;

p is 0, 1, 2, or 3; and

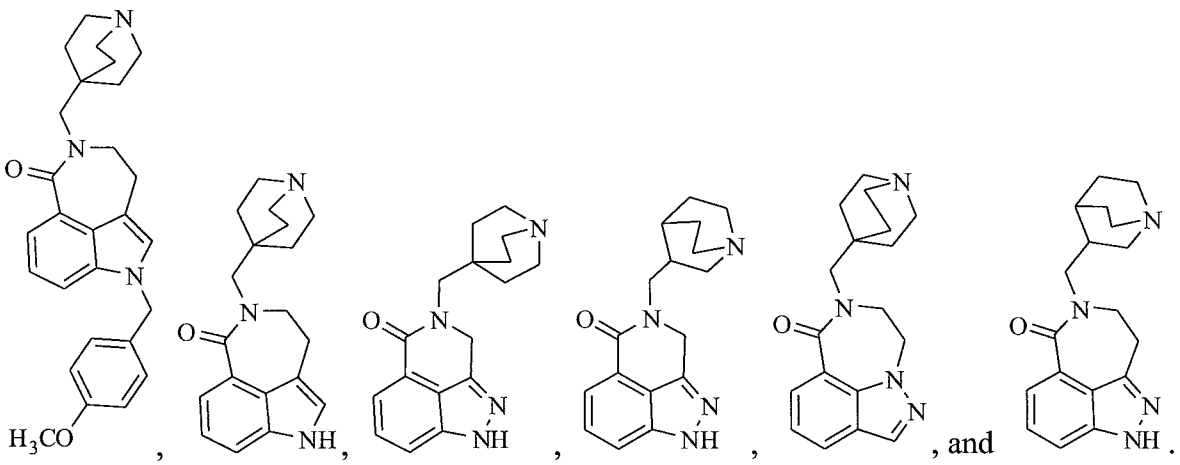
q is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

34. The compound according to claim 33, wherein Q has an empirical formula $C_{7\text{-}10}H_{12\text{-}19}N_{1\text{-}2}$.

35. The compound according to claim 33, wherein Q is an azabicycloheptane, azabicyclooctane, or azabicyclononane.

36. The compound according to claim 35, wherein Q is quinuclidine.



49. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 33 and a pharmaceutically acceptable carrier.

50. Use of a compound according to claim 33 in the manufacture of a medicament for the treatment of a disease or condition which is susceptible to treatment with a 5-HT_3 receptor modulator.

51. The use of the compound according to claim 50, wherein the disease or condition is selected from the group consisting of general anxiety disorders, social phobias, vertigo, obsessive-compulsive disorders, panic disorders, post-traumatic stress disorders, bulimia nervosa, drug withdrawal effects, alcohol dependency, pain, sleep related central apneas, chronic fatigue syndrome, Parkinson's Disease Psychosis, schizophrenia, cognitive decline and defects in schizophrenia, Parkinson's Disease, Huntington's Chorea, presenile dementias, Alzheimer's Disease, obesity, substance abuse disorders, dementia associated with neurodegenerative disease, cognition deficits, fibromyalgia syndrome, rosacea, cardiovascular disorders mediated by serotonin, chemotherapy induced nausea and vomiting, post-operative induced nausea and vomiting, radiation induced nausea and vomiting,

gastrointestinal disorders, irritable bowel syndrome, gastroesophageal reflux disease, Burkitt's lymphoma, bronchial asthma, pruritus, migraine, and epilepsy.

52. The use of the compound according to claim 50, wherein the compound according to claim 33 or pharmaceutically acceptable salt thereof is a 5-HT_3 receptor antagonist.

53. The use of the compound according to claim 50, wherein the compound according to claim 33 or pharmaceutically acceptable salt thereof is a 5-HT_3 partial agonist.

54. The use of the compound according to claim 50 further comprising: a therapeutically effective amount of a schizophrenia adjunct.

55. The use of the compound according to claim 54, wherein the schizophrenia adjunct is selected from the group consisting of valproate, levomepromazine, alprazolam, haloperidol, chlorpromazine, risperidone, paliperidone, olanzapine, ziprasidone, quetiapine, clozapine, lithium carbonate, diazepam, carbamazepine, selective serotonin re-uptake inhibitors, tricyclic antidepressants, and combinations thereof

56. The use of the compound according to claim 50 further comprising: a therapeutically effective amount of a Parkinson's Disease adjunct.

57. The use of the compound according to claim 56, wherein the Parkinson's Disease adjunct is selected from the group consisting of transdermal rotigotine, rasagiline, safinamide, levodopa, carbidopa, dopamine agonists, COMT inhibitors, MAO-B inhibitors, amantadine, anticholinergic agents, and combinations thereof

58. Use of a compound according to claim 33 in the manufacture of a medicament for the treatment of irritable bowel syndrome.

59. The use of the compound according to claim 58 further comprising:

a therapeutically effective amount of a second serotonin 5-HT_3 receptor modulator or a serotonin 5-HT_4 receptor modulator.

60. The use of the compound according to claim 59, wherein the second serotonin 5-HT_3 receptor modulator or serotonin 5-HT_4 receptor modulator is selected from the group consisting of Alosetron, renzapride, cilansetron, Tegaserod, Prucalopride, ondansetron, and combinations thereof.

61. The use of the compound according to claim 58 further comprising:

a therapeutically effective amount of a therapeutic agent selected from the group consisting of somatostatin analogs, muscarinic receptor antagonists, laxatives, antispasmodics, antidepressants, antidiarrheal agents, prokinetic agents, peripheral opiate narcotic antagonists, and combinations thereof.

62. Use of a compound according to claim 33 in the manufacture of a medicament for the treatment of emesis.

63. The use of the compound according to claim 62 further comprising:

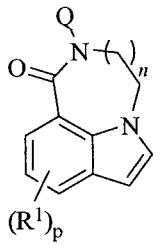
a therapeutically effective amount of one or more other anti-emetic compounds.

64. The use of the compound according to claim 63, wherein the one or more other anti-emetic compounds are selected from the group consisting of dexamethasone, alosetron, alprazolam, aprepitant, dimenhydrinate, diphenhydramine, dolasetron, tetrahydrocannabinol, nabilone, dronabinol, droperidol, granisetron, haloperidol, lorazepam, metoclopramide, midazolam, olanzapine, ondansetron, palonosetron, proclorperazine, promethazine, tropisetron, and combinations thereof.

65. Use of a compound according to claim 33 in the manufacture of a medicament for the treatment of CNS diseases or conditions.

66. The use of the compound according to claim 65, wherein the CNS disease or condition is selected from the group consisting of schizophrenia and Parkinson's disease.

67. A process of preparing a product compound of formula Ia:



formula Ia

wherein:

Q is a saturated, bicyclic, heterocyclic amine, wherein the saturated, bicyclic, heterocyclic amine comprises at least two atoms between the amide nitrogen of the compound of formula I and any amine nitrogen of Q and wherein the saturated, bicyclic, heterocyclic amine is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from the group consisting of C_1-C_3 alkyl, halogen, —CN, —OR^7, and —NR^7R^8;