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RESEARCH ARTICLE

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Synthesis and antiemetic activity of 1,2,3,9-tetrahydro-9-methyl-3-(4-substituted-piperazin-1-ylmethyl)-4*H*-carbazol-4-one derivatives

Abstract 5-HT_3 receptor antagonists, such as Ondansetron, are used for anti-emesis after chemotherapy, radiotherapy and operations. Some Ondansetron analogs possessing piperazine ring as side chains were synthesized in our lab. Thus, one of the two carbonyl groups of starting material 1,3-cyclohexandione (**1**) was condensed with phenylhydrazine hydrochloride to form monophenylhydrazone (**2**). 1,2,3,9-Tetrahydro-4*H*-carbazol-4-one (**3**) was prepared from **2** *via* cyclization and rearranged in the presence of $ZnCl_2$. Through a methylation reaction, compound **3** was converted to 1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one (**4**). 3-Dimethylaminomethyl substituted compound (**5**) was synthesized from **4** by a Mannich reaction in glacial acetic acid. Nine novel 1,2,3,9-tetrahydro-9-methyl-3-(4-substituted-piperazin-1-ylmethyl)- 4*H*-carbazol-4-one derivatives (**6a**–**6i)** were synthesized through nucleophilic substitution reaction of **5** with piperazines. The structures of all the target compounds were determined by elemental analysis, IR, MS, ^1H NMR and ^{13}C NMR spectra. The results of preliminary pharmacological test show that part of the novel compounds have antiemetic activity comparable to that of the control Ondansetron.

Keywords 5-HT_3 receptor antagonist, 1, 2, 3, 9-tetrahydro-4*H*-carbazol-4-one, Mannich reaction, antiemetic

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1 Introduction

Ondansetron (Fig. 1), 1,2,3,9-tetrahydro-9-methyl-3-(2-methyl-1*H*-imidazol-1-ylmethyl)-4*H*-carbazol-4-one hydrochloride dihydrate is a potent, highly selective and competitive 5-HT_3 receptor antagonist [1]. Ondansetron can reduce the incidence of emetic episodes induced by radiation, cyclophosphamide, and cisplatin-based chemotherapies, has no extrapyramidal effects and is well tolerated by patients who are receiving radiotherapy or chemotherapy. The pharmacologic and therapeutic use of Ondansetron have been the subject of several previous reviews focusing primarily on the use of the drug for prevention of chemotherapy induced nausea and vomiting in adult patients [1–5]. The other review provides an overview of the pharmacology of Ondansetron and its good efficacy in children for the prevention of acute nausea and vomiting associated with moderately or highly emetogenic chemotherapy and/or radiation therapy, particularly when combined with dexamethasone. Ondansetron is thus a suitable clinical option [6]. In summary, Ondansetron is an antiemetic agent available for use in adults and children.

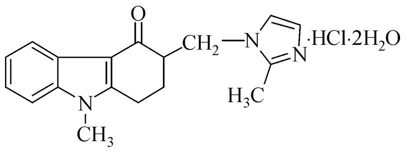

Fig. 1 Ondansetron

In the last few years, extensive studies have been carried out on anti-emetic agents. A series of 5-HT_3 receptor antagonists were developed following Ondansetron, but there have been no marked progress on antiemetic activity. The study on the structure-activity relationships of 5-HT_3 receptor antagonists indicates that the basic pharmacophores are an aromatic ring, a carbonyl group which is at the same flat surface with the aromatic ring, an alkali center and there should be a definitive distance between the carbonyl group and the alkali center [7]. It is well known that piperazine group not only possesses wide biological activities, but also regulates the lipid/water partition coefficient (lg *P*) of pharmaceuticals. This led us to design and synthesize a series of novel carbazole derivatives **6a**–**6i** which possess piperazine ring as side chains. Herein, we report the synthesis and antiemetic activity of these new compounds.

2 Experimental

2.1 Synthesis

Melting points were determined on YRT-3 melting point apparatus and uncorrected. The IR spectra were recorded on a Nicolet Impact 400 FTIR with KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 MHz) instrument with tetramethylsilane (TMS) as the internal standard in $CDCl_3$ (chemical shift in δ parts per million). Mass spectra were measured on a Shimadzu GCMS QP-5000 instrument at 70 eV. Elemental microanalysis (C, H, and N) was performed on an Element Analyzer MOD-1106 instrument for vacuum-dried samples. Chemicals were purchased from commercial suppliers and used without further purification.

2.1.1 1,3-Cyclohexandione monophenylhydrazone (**2**)

A mixture of **1** (10 g, 0.09 mol), phenylhydrazine hydrochloride (13 g, 0.09 mol), sodium acetic acid (7.2 g, 0.09 mol), ethanol 95% (50 mL) and H_2O (150 mL) was added to a flask, stirred for 20 min, filtered, washed with 95% ethanol, crystallized and dried to give 1,3-cyclohexandione monophenylhydrazone (**2**, 15.3 g, 85%) as a white solid. mp 168–178°C, Ref. [8] mp 189–192°C.

2.1.2 1,2,3,9-Tetrahydro-4H-carbazol-4-one (**3**)

1,3-Cyclohexandione monophenylhydrazone (**2**, 6.1 g, 0.03 mol) was dissolved in acetic acid (50 mL). The resulting solution was refluxed for 5 h with $ZnCl_2$ as the catalytic agent, after evaporating the solvent in a rotary evaporator under reduced pressure. Ice-water (80 mL) was added to the residue, while the product was crystallized, filtered, washed with acetonitrile, and dried to give 1,2,3,9-tetrahydro-4*H*-carbazol-4-one (**3**, 2.8 g, 51%) as a light yellow solid. mp 222–224°C, Ref. [9] mp 219–221°C.

2.1.3 1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one (**4**)

1,2,3,9-Tetrahydro-4*H*-carbazol-4-one (**3**, 18.5 g, 0.1 mol) was dissolved in acetone, while dimethyl sulfate (25 g, 0.2 mol) and potassium hydroxide 40% (50 mL) were added. The mixture was stirred for 20 min, filtered, washed with water, crystallized, and dried to give 1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one (**4**, 18.8 g, 94%) as a yellow solid. mp 196–199°C, Ref. [10] mp 178–183°C.

2.1.4 1,2,3,9-Tetrahydro-9-methyl-3-dimethylaminomethyl-4H-carbazol-4-one (**5**)

A mixture of **4** (8 g, 0.04 mol), dimethylamine hydrochloride (3.8 g, 0.046 mol), paraformaldehyde (1.5 g, 0.05 mol) and acetic acid (200 mL) was added to a flask, refluxed for 4 h. After evaporating the solvent in a rotary evaporator under reduced pressure, water (200 mL) was added to the residue. The aqueous phase was alkalized with ammonia solution, while the product was crystallized, filtered, washed with water, and dried to give 1,2,3,9-tetrahydro-9-methyl-3-dimethylaminomethyl-4H-carbazol-4-one (**5**, 9.2 g, 90%) as a light yellow solid. mp 124–128°C, Refs. [11,12] yield 67%, mp 131–132°C.

2.1.5 1,2,3,9-Tetrahydro-9-methyl-3-(4-methyl-piperazine-1-ylmethyl)-4H-carbazol-4-one (**6a**)

A mixture of **5** (12.5 g, 0.05 mol), 1-methyl-piperazine (7.5 g, 0.075 mol), methanol (100 mL) and hydrochloric acid (4 mL) was added to a flask, stirred and refluxed for 4 h. After adding activated carbon to decolour for 30 min, the reaction solution was filtered. The resulting solution was concentrated with methanol (50 mL) in a rotary evaporator under reduced pressure and cooled at room temperature to give a yellow crystallization product. The product was washed with ethyl acetate, under reflux for 20 min, filtered to give white product that was recrystallized from methanol to give 1,2,3,9-tetrahydro-9-methyl-3-(4-methyl-piperazine-1-ylmethyl)-4*H*-carbazol-4-one (**6a**, 12.4 g, 81%) as a white solid. mp 127–128°C.

^1H NMR($CDCl_3$, 300 MHz) δ: 2.14–2.16 (m, 1H, C^2H*ax*), 2.26–2.36 (m, 4H, C^2H*eq*, piperazinyl-N^4CH_3), 2.40–2.56 (m, 8H, piperazinyl-H), 2.66–2.70 (m, 2H, C^1H_2), 2.93–2.98 (m, 3H, C^3CH_2N, C^3H), 3.69 (s, 3H, N^9CH_3), 7.25–7.28 (m, 3H, $C^{5,7,8}H$), 8.23–8.25 (m, 1H, C^6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.6 (C^2), 26.9 (C^1), 29.6 (C^3), 43.9 (N^9CH_3), 45.9 (piperazinyl-N^1CH_2), 53.2 (piperazinyl-$C^{2,6}$), 55.0 (piperazinyl-N^4CH_3), 57.5 (piperazinyl-$C^{3,5}$), 109.0 (C^{4a}), 111.9 (C^8), 121.3 (C^7), 122.3 (C^5), 122.7 (C^6), 124.7 (C^{4b}), 137.4 (C^{8a}), 151.4 (C^{9a}), 194.9 (C^4); IR (KBr) ν: 3070, 2933, 2870, 1633 cm^{-1}; EI-MS (70 eV) *m*/*z*: 311 (M^+). Anal. Calcd. for $C_{19}H_{25}N_3O$: C 73.28, H 8.09, N 13.49; found C 73.08, H 8.16, N 13.57.

2.1.6 1,2,3,9-Tetrahydro-9-methyl-3-(4-ethyl-piperazine-1-ylmethyl)-4H-carbazol-4-one (**6b**)

According to the procedure reported for preparation of **6a**, 1,2,3,9-tetrahydro-9-methyl-3-(4-ethyl-piperazine-1-ylmethyl)-4*H*-carbazol-4-one (**6b**, 80%) was obtained as a white solid. mp 144.6–146°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.12 (t, J = 6.9 Hz, 3H, CCH$_3$), 2.22–2.24 (m, 1H, C^{2}H*ax*), 2.42–2.47 (m, 3H, C^{2}H*eq*, piperazinyl-N^{4}CH$_2$), 2.50–2.61 (m, 8H, piperazinyl-H), 2.69–2.74 (m, 2H, C^{1}H$_2$), 2.92–3.00 (m, 3H, C^{3}CH$_2$N, C^{3}H), 3.72 (s, 3H, N^{9}CH$_3$), 7.25–7.30 (m, 3H, C^{5,7,8}H), 8.24–8.26 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 11.9 (CH$_3$), 20.6 (C^2), 26.9 (C^1), 29.6 (C^3), 43.9 (N^{9}CH$_3$), 52.2 (piperazinyl-N^{1}CH$_2$), 52.8 (piperazinyl-N^{4}CH$_2$), 53.2 (piperazinyl-C^{2,6}), 57.6 (piperazinyl-C^{3,5}), 109.0 (C^{4a}), 112.0 (C^8), 121.3 (C^7), 122.3 (C^5), 122.7 (C^6), 124.8 (C^{4b}), 137.4 (C^{8a}), 151.4 (C^{9a}), 194.9 (C^4); IR (KBr) v: 3080, 2968, 2933, 1627 cm^{-1}; EI-MS (70 eV) m/z: 325 (M$^+$). Anal. Calcd. for $C_{20}H_{27}N_3O$: C 73.81, H 8.36, N 12.91; found C 73.72, H 8.47, N 12.87.

2.1.7 1,2,3,9-Tetrahydro-9-methyl-3-[4-(2-hydroxyethyl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (**6c**)

According to the procedure reported for preparation of **6a**, after reacting for 18 h, the product was recrystallized from mixed solvent [V(ethyl acetate):V(methanol) = 10:1] to give 1,2,3,9-tetrahydro-9-methyl-3-[4-(2-hydroxyethyl)-piperazine-1-ylmethyl]-4*H*-carbazol-4-one (**6c**, 71%) as a white solid. mp 140–141°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.11–2.13 (m, 1H, C^{2}H*ax*), 2.54–2.63 (m, 1H, C^{2}H*eq*), 3.12–3.16 (m, 2H, C^{1}H$_2$), 3.26 (bs, 1H, OH), 3.35–3.43 (m, 4H, piperazinyl^{3,5}-H), 3.74 (s, 3H, N^{9}CH$_3$), 3.89–3.95 (m, 9H, C^{3}H, C^{3}CH$_2$N, NCH$_2$, piperazinyl^{2,6}-H), 4.00–4.02 (m, 2H, OCH$_2$), 7.31–7.41 (m, 3H, C^{5,7,8}H), 8.09–8.11 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 20.3 (C^2), 26.5 (C^1), 29.1 (C^3), 39.5 (piperazinyl-N^{4}CH$_2$), 48.4 (N^{9}CH$_3$), 48.9 (piperazinyl-N^{1}CH$_2$), 54.8 (piperazinyl-C^{2,6}), 57.6 (piperazinyl-C^{3,5}), 58.0 (CH$_2$OH), 109.6 (C^{4a}), 110.0 (C^8), 119.6 (C^7), 122.6 (C^5), 123.1 (C^{4b,6}), 137.1 (C^{8a}), 154.7 (C^{9a}), 192.9 (C^4); IR (KBr) v: 3300, 3030, 2978, 2939, 1636 cm^{-1}; EI-MS (70 eV) m/z: 341 (M$^+$). Anal. Calcd. for $C_{20}H_{27}N_3O_2$: C 70.35, H 7.97, N 12.31; found C 70.48, H 7.93, N 12.18.

2.1.8 1,2,3,9-Tetrahydro-9-methyl-3-(4-phenyl-piperazine-1-ylmethyl)-4H-carbazol-4-one (**6d**)

A mixture of **5** (12.5 g, 0.05 mol), phenylpiperazine (16.2 g, 0.01 mol), H$_2$O (150 mL), hydrochloric acid (4 mL) was added to a flask, stirred and refluxed for 22 h. After cooling to room temperature, the pH of the reaction mixture was adjusted to 10 with 10% sodium hydroxide. The resulting precipitate was collected by filtration. The residue was washed with water to give a light yellow solid product. The product was washed with hot methanol, under reflux for 10 min and filtered to give white product that was recrystallized from ethyl acetate to give 1,2,3,9-Tetrahydro-9-methyl-3-(4-phenyl-piperazine-1-ylmethyl)-4*H*-carbazol-4-one (**6d**, 12.3 g, 66%) as white solid. mp 177–178°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.19–2.21 (m, 1H, C^{2}H*ax*), 2.45–2.54 (m, 1H, C^{2}H*eq*), 2.64–2.69 (m, 2H, C^{1}H$_2$), 2.77–2.80 (m, 4H, piperazinyl^{2,6}-H), 2.92–3.02 (m, 3H, C^{3}CH$_2$N, C^{3}H), 3.21–3.26 (m, 4H, piperazinyl^{3,5}-H), 3.72 (s, 3H, N^{9}CH$_3$), 6.85–6.97 (m, 3H, Ph^{2,4,6}-H), 7.26–7.31 (m, 5H, C^{5,7,8}H, Ph^{3,5}-H), 8.26–8.29 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 20.7 (C^2), 26.9 (C^1), 29.6 (C^3), 44.0 (N^{9}CH$_3$), 49.1 (piperazinyl-N^{1}CH$_2$), 53.4 (piperazinyl-C^{2,6}), 57.7 (piperazinyl-C^{3,5}), 109.1 (C^{4a}), 112.1 (C^8), 115.9 (Ph-C^{3,5}), 119.5(Ph-C^4), 121.4 (C^7), 122.4 (C^5), 122.9 (C^6), 124.8 (C^{4b}), 129.0 (Ph-C^{2,6}), 137.5 (C^{8a}), 151.2 (C^{9a}), 151.3 (Ph-C^1), 194.8 (C^4); IR (KBr) v: 3030, 2954, 2933, 1638 cm^{-1}; EI-MS (70 eV) m/z: 373 (M$^+$). Anal. Calcd. for $C_{24}H_{27}N_3O$: C 77.18, H 7.29, N 11.25; found C 77.32, H 7.17, N 11.18.

2.1.9 1,2,3,9-Tetrahydro-9-methyl-3-[4-(4-methyloxyphenyl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (**6e**)

According to the procedure reported for preparation of **6d**, after reacting for 6.5 h, the product was recrystallized from ethyl acetate to give 1,2,3,9-tetrahydro-9-methyl-3-[4-(4-methyloxyphenyl)-piperazine-1-ylmethyl]-4*H*-carbazol-4-one (**6e**, 80%) as a white solid. mp 159–160°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.14–2.16 (m, 1H, C^{2}H*ax*), 2.44–2.48 (m, 1H, C^{2}H*eq*), 2.62–2.67 (m, 2H, C^{1}H$_2$), 2.75–2.79 (m, 4H, piperazinyl^{2,6}-H), 2.92–3.02 (m, 3H, C^{3}CH^{2}N, C^{3}H), 3.06–3.14 (m, 4H, piperazinyl^{3,5}-H), 3.73 (s, 3H, N^{9}CH$_3$), 3.79 (s, 3H, OCH$_3$), 6.84–6.94 (m, 4H, Ph-H), 7.27–7.31 (m, 3H, C^{5,7,8}H), 8.26–8.28 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 19.4 (C^2), 25.6 (C^1), 28.4 (C^3), 42.7 (N^{9}CH$_3$), 49.3 (piperazinyl-N^{1}CH$_2$), 52.2 (piperazinyl-C^{2,6}), 54.2 (OCH$_3$), 56.3 (piperazinyl-C^{3,5}), 107.8 (C^{4a}), 110.8 (C^8), 113.0 (Ph-C^{3,5}), 116.7 (Ph-C^{2,6}), 120.1 (C^7), 121.5 (C^5), 121.1 (C^6), 123.5 (C^{4b}), 136.2 (C^{8a}), 144.4 (Ph-C^4), 150.2 (Ph-C^1), 152.2 (C^{9a}), 193.5 (C^4); IR (KBr) v: 3030, 2952, 2933, 2821, 1640 cm^{-1}; EI-MS (70 eV) m/z: 403 (M$^+$). Anal. Calcd. for $C_{25}H_{29}N_3O_2$: C 74.41, H 7.24, N 10.41; found C 74.20, H 7.32, N 10.50.

2.1.10 1,2,3,9-Tetrahydro-9-methyl-3-[4-(2-methyloxyphenyl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (**6f**)

According to the procedure reported for preparation of **6d**, after reacting for 6.5 h, the product was recrystallized from ethyl acetate to give 1,2,3,9-tetrahydro-9-methyl-3-[4-(2-methyloxyphenyl)-piperazine-1-ylmethyl]-4*H*-carbazol-4-one (**6f**, 76%) as a white solid. mp 170–172°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.24–2.26 (m, 1H, C^{2}H*ax*), 2.54–2.63 (m, 1H, C^{2}H*eq*), 2.68–2.72 (m, 2H, C^{1}H$_2$), 2.89–2.92 (m, 4H, piperazinyl^{2,6}-H), 3.03–3.18 (m, 3H, C^{3}CH$_2$N, C^{3}H), 3.32–3.37 (m, 4H, piperazinyl^{3,5}-H), 3.74 (s, 3H, N^{9}CH$_3$), 3.89 (s, 3H, OCH$_3$), 6.87–7.05 (m, 4H, Ph-H), 7.20–7.32 (m, 3H, C^{5,7,8}H), 8.26–8.28 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ*: 20.7 (C^2), 27.0 (C^1), 29.7 (C^3), 44.0 (N^{9}CH$_3$), 50.6 (piperazinyl-N^{1}CH$_2$), 53.3 (piperazinyl-C^{2,6}), 55.3 (OCH$_3$), 57.7 (piperazinyl-C^{3,5}), 109.0 (C^{4a}), 111.1 (C^8), 112.1 (Ph-C^3), 118.0 (Ph-C^6), 120.8 (C^7), 121.4 (C^6), 122.4 (C^5), 122.7 (Ph-C^4), 122.8 (Ph-C^5), 124.8 (C^{4b}), 141.3 (Ph-C^2), 137.4 (C^{8a}), 151.4 (Ph-C^1), 152.2 (C^{9a}), 195.0 (C^4); IR (KBr) *v*: 3030, 2952, 2934, 2819, 1643 cm^{-1}; EI-MS (70 eV) *m/z*: 403 (M$^+$). Anal. calcd. for $C_{25}H_{29}N_3O_2$: C 74.41, H 7.24, N 10.41; found C 74.34, H 7.19, N 10.52.

2.1.11 1,2,3,9-Tetrahydro-9-methyl-3-[4-(3-chlorophenyl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (**6g**)

According to the procedure reported for preparation of **6d**, after reacting for 6 h, the product was recrystallized from ethyl acetate to give 1,2,3,9-tetrahydro-9-methyl-3-[4-(2-methyloxyphenyl)-piperazine-1-ylmethyl]-4*H*-carbazol-4-one (**6g**, 78%) as a white solid. mp 170.5–173°C.

^{1}H NMR (CDCl$_3$, 300 MHz) *δ*: 2.14–2.16 (m, 1H, C^{2}H*ax*), 2.50–2.54 (m, 1H, C^{2}H*eq*), 2.61–2.68 (m, 2H, C^{1}H$_2$), 2.74–2.78 (m, 4H, piperazinyl^{2,6}-H), 2.96–3.04 (m, 3H, C^{3}CH$_2$N, C^{3}H), 3.21–3.25 (m, 4H, piperazinyl^{3,5}-H), 3.72 (s, 3H, N^{9}CH$_3$), 6.79–7.20 (m, 4H, Ph-H), 7.27–7.31 (m, 3H, C^{5,7,8}H), 8.26–8.28 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ*: 20.7 (C^2), 26.9 (C^1), 29.6 (C^3), 44.0 (N^{9}CH$_3$), 48.5 (piperazinyl-N^{1}CH$_2$), 53.2 (piperazinyl-C^{2,6}), 57.6 (piperazinyl-C^{3,5}), 109.1 (C^{4a}), 112.0 (C^8, Ph-C^5), 113.7 (Ph-C^6), 115.4 (Ph-C^4), 121.3 (C^7), 122.4 (C^6), 122.8 (C^5), 124.8 (C^{4b}), 130.0 (Ph-C^2), 134.8 (Ph-C^1), 137.4 (C^{8a}), 151.5 (Ph-C^3), 152.3 (C^{9a}), 194.7 (C^4); IR (KBr) *v*: 3030, 2960, 2934, 1634 cm^{-1}; EI-MS (70 eV) *m/z*: 407 (M$^+$). Anal. Calcd. for $C_{24}H_{26}ClN_3O$: C 70.66, H 6.42, Cl 8.69, N 10.30; found C 70.73, H 6.38, Cl 8.54, N 10.43.

2.1.12 1,2,3,9-Tetrahydro-9-methyl-3-[4-(3-trifluoromethylphenyl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (**6h**)

According to the procedure reported for preparation of **6d**, after reacting for 6 h, the product was recrystallized from ethyl acetate to 1,2,3,9-tetrahydro-9-methyl-3-[4-(3-trifluoromethylphenyl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (6h, 76%) as a white solid. mp 171–172.5°C.

^{1}H NMR (CDCl$_3$, 300 MHz) *δ*: 2.20–2.22 (m, 1H, C^{2}H*ax*), 2.50–2.54 (m, 1H, C^{2}H*eq*), 2.63–2.69 (m, 2H, C^{1}H$_2$), 2.77–2.80 (m, 4H, piperazinyl^{2,6}-H), 2.94–3.08 (m, 3H, C^{3}CH$_2$N, C^{3}H), 3.26–3.30 (m, 4H, piperazinyl^{3,5}-H), 3.72 (s, 3H, N^{9}CH$_3$), 7.07–7.39 (m, 7H, Ph-H, C^{5,7,8}H), 8.26–8.28 (m, 1H, C^{6}H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ*: 20.7 (C^2), 26.9 (C^1), 29.6 (C^3), 44.0 (N^{9}CH$_3$), 48.6 (piperazinyl-N^{1}CH$_2$), 53.2 (piperazinyl-C^{2,6}), 57.6 (piperazinyl-C^{3,5}), 109.1 (C^{4a}), 112.1 (C^8, Ph-C^5), 115.5 (Ph-C^{4,6}), 121.4 (C^7), 122.4 (C^6), 122.8 (C^5), 124.8 (C^{4b}), 130.0 (CF$_3$), 131.4 (Ph-C^2), 131.8 (Ph-C^1), 137.5 (C^{8a}), 151.4 (Ph-C^3), 151.5 (C^{9a}), 194.7 (C^4); IR (KBr) *v*: 3030, 2960, 2926, 1638 cm^{-1}; EI-MS (70 eV) *m/z*: 441 (M$^+$). Anal. Calcd. for $C_{25}H_{26}F_3N_3O$: C 68.01, H 5.94, F 12.91, N 9.52; found C 68.30, H 5.87, F 12.81, N 9.45.

2.1.13 1,2,3,9-Tetrahydro-9-methyl-3-[4-(3-pyrimidine-2-yl)-piperazine-1-ylmethyl]-4H-carbazol-4-one (**6i**)

According to the procedure reported for preparation of **6a**, after reacting for 10 h, the product was recrystallized from a mixed solvent [*V*(ethyl acetate) : *V*(methanol) = 1 : 5] to give 1,2,3,9-tetrahydro-9-methyl-3-[4-(3-pyrimidine-2-yl)- piperazine-1-ylmethyl]-4*H*-carbazol-4-one (**6i**, 70.2%) as a white solid. mp 128–130°C.

^{1}H NMR (CDCl$_3$, 300 MHz) *δ*: 2.20–2.22 (m, 1H, C^{2}H*ax*), 2.50–2.54 (m, 1H, C^{2}H*eq*), 2.64–2.71 (m, 2H, C^{1}H$_2$), 2.77–2.80 (m, 4H, piperazinyl^{2,6}-H), 2.95–3.06 (m, 3H, C^{3}CH$_2$N, C^{3}H), 3.73 (s, 3H, N^{9}CH$_3$), 3.84–3.88 (m, 4H, piperazinyl^{3,5}-H), 6.48–6.51 (m, 1H, Ar^5-H), 7.28–7.34 (m, 3H, C^{5,7,8}H), 8.24–8.26 (m, 1H, C^{6}H), 8.30–8.34 (m, 2H, Ar^{4,6}-H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ*: 20.7 (C^2), 26.9 (C^1), 29.6 (C^3), 43.6 (N^{9}CH$_3$), 43.9 (piperazinyl-N^{1}CH$_2$), 53.2 (piperazinyl-C^{2,6}), 57.7 (piperazinyl-C^{3,5}), 109.0 (C^{4a}), 110.0 (pyrimidinyl-C^5), 112.0 (C^8), 121.3 (C^7), 122.4 (C^6), 122.8 (C^5), 124.8 (C^{4b}), 137.4 (C^{8a}), 151.4 (C^{9a}), 157.6 (pyrimidinyl-C^{4,6}), 161.5 (pyrimidinyl-C^2), 194.7 (C^4); IR (KBr) *v*: 3030, 2934, 2876, 1633, 1626 cm^{-1}; EI-MS (70 eV) *m/z*: 375 (M$^+$). Anal. Calcd. for $C_{22}H_{25}N_5O$: C 70.38, H 6.71, N 18.65; found C 70.46, H 6.64, N 18.50.

2.2 Antiemetic activity

A retching model was developed as described by Bermudez [13] and Stables [14]. 132 rats were randomly divided into 22 groups in 2 lines. Each group has 6 rats. In each line, group 1 as a control group was treated with saline. Group 2 as a control group was treated with Ondansetron hydrochloride. Group 3-11 as treatment groups were treated with the new compounds. All the animals received gastric irrigation of the drugs. Line 1 was treated with a high dosage of drugs (8.0 mg/kg). Line 2 was treated with a low dosage of drugs (2.0 mg/kg). After treating for 45 minutes each group animals received intraperitoneal injection of cisplatin and were surveyed continuously for 12 h. The latent period for retches and the frequency of retches of each group were recorded and all values were expressed as means ± standard deviation ($\bar{x} \pm SD$).

Statistical comparisons were performed with a commercially available statistical package SPSS 10.0. Data were analyzed using analysis of *t* test for two comparisons. Differences were considered to be significant at $P < 0.05$.

3 Results and discussion

3.1 Chemistry

Figure 2 shows the synthetic pathway for the preparation of compounds **2**–**6**. The synthesis of the intermediate **2**–**5** was achieved with an improved strategy according to the previously reported synthetic method.

Condensation reaction of the starting material 1,3-cyclohexandione (**1**) with phenylhydrazine hydrochloride gave the substrate **2** in the presence of sodium acetic acid in diluted ethanol solution. 1,2,3,9-Tetrahydro-4*H*-carbazol-4-one (**3**) was obtained through cyclization and rearrangement reaction of compound **2** under the catalysis of $ZnCl_2$ in acetic acid. Moreover, methylation reaction by $(CH_3)_2SO_4$ and aminomethylation by Mannich reaction with acetic acid as the solvent gave the intermediate **5** as a Mannich base with good yield. The target compounds **6a**–**6i** were synthesized through nucleophilic substitution reaction of **5** with piperazine s derivatives.

Reviewing the reports of literatures, there have been two main synthetic methodologies to prepare the key substrate **5**: (a) condensation of one of the two carbonyl groups of 1,3-cyclohexandione with 2-bromoaniline, followed by cyclization of **2** [8,10,15,16]. (b) Condensation of one of the two carbonyl groups of 1,3-cyclohexandione with phenylhydrazine hydrochloride [11,12], followed by cyclization and rearrangement of **2** [17,18]. In turn, methylation and aminomethylation reaction were performed [19,20]. In the present research, the preparation of **5** was basically based on the method B with some improvements.

All the prepared compounds were proven by spectral data including IR, ^1H NMR, ^{13}C NMR and mass spectra and elemental microanalysis. The ^1H NMR spectra of all the novel compounds shows the difference between the two H protons of C^2H_2 of the 1,2,3,9-tetrahydro-4*H*-carbazol-4-one ring. All axial H*ax* show significant upfield signals (between 2.11×10^{-6} and 2.26×10^{-6}) and all equatorial H*eq* show significant downfield signals (between 2.36×10^{-6} and 2.63×10^{-6}), indicating the characteristic of ^1H NMR spectra of these new compounds. In addition, C^3H and C^2H_2 form an ABX or AMX coupling

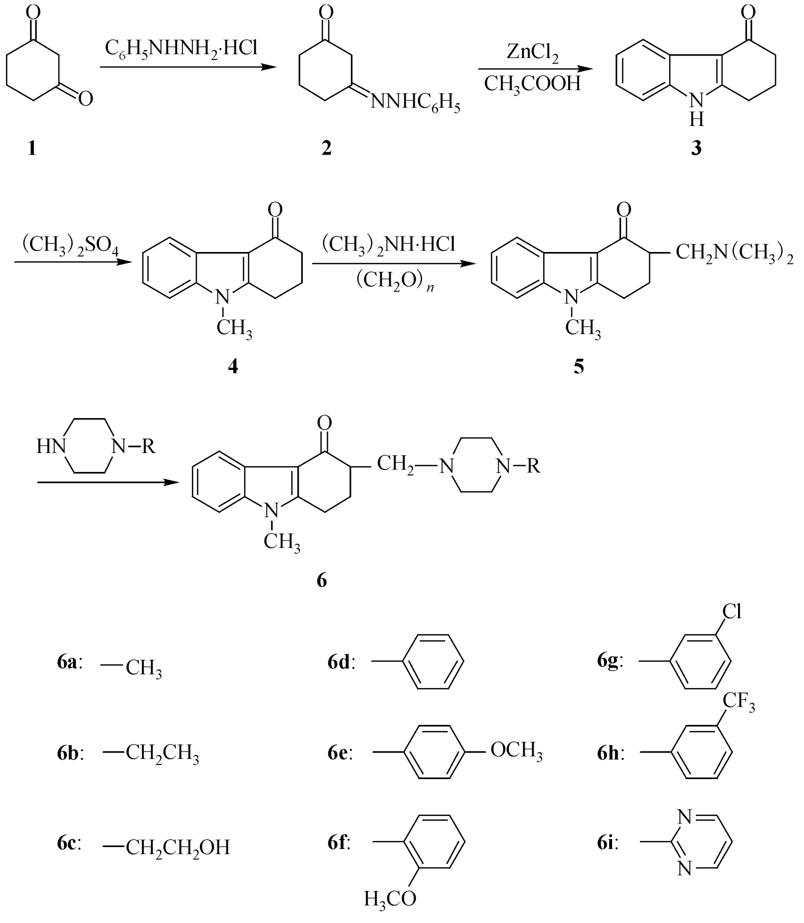

Fig. 2 Synthesis of compounds **6a**–**6i**

Table 1 The latent period to retches and the frequency of retches of groups ($\bar{x} \pm SD$, $n = 6$)

Group	8.0 mg/kg		2.0 mg/kg	
	Latent period/min	Frequency of retches	Latent period/min	Frequency of retches
Saline	75.33 ± 6.67	69.17 ± 13.44	75.33 ± 6.67	69.17 ± 13.44
Ondansetron	699.17 ± 34.72^a	0.67 ± 0.95^a	535.83 ± 105.23^a	14.83 ± 9.89^a
6a	432 ± 240	11.33 ± 11.33	156.33 ± 10.11^c	41 ± 2^c
6b	490 ± 230	10 ± 10	179.16 ± 9.44^c	35 ± 3.33^c
6c	592.5 ± 170	4.83 ± 5.52	215 ± 6.66^b	29 ± 2^c
6d	176.67 ± 6.67^c	27.33 ± 2.67^c	114.16 ± 7.77^c	45.83 ± 3.17^c
6e	309.17 ± 136.94^b	14 ± 7.67^c	155 ± 8.33^c	35.5 ± 3^c
6f	221.67 ± 9.44^c	18.33 ± 4.78^c	135 ± 6.67^c	41.67 ± 1.67^c
6g	416.67 ± 202.22^b	11 ± 7.33^b	175.83 ± 6.11^c	34.67 ± 2.67^c
6h	500.83 ± 219.17	7.5 ± 7.5	190.83 ± 4.44^b	29.33 ± 1.44^c
6i	670.83 ± 65.55	1.33 ± 1.78	529.66 ± 108.76	15 ± 11.33

$^aP < 0.01$, compared with saline group; $^bP < 0.05$, $^cP < 0.01$ compared with Ondansetron group.

system, but it wasn't easy to distinguish because these signals as they were overlapped with each other.

3.2 Antiemetic activity

The results of preliminary pharmacological test show that all compounds were more effective in a high dosage (8.0 mg/kg) than in a low dosage (2.0 mg/kg) for extending the latent period for retching and reducing the frequency of retching of groups. With a low dosage (2.0 mg/kg), only compound **6i** has an antiemetic activity comparable to that of the Ondansetron control. With a high dosage (8.0 mg/kg), compound **6a**, **6b**, **6c**, **6h** and **6i** have antiemetic activity comparable to that of the Ondansetron control (Table 1).

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