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Synthesis and dopaminergic activity of some *E*-3-(piperidin-1-yl)-1-(4-substituted phenyl)prop-2-en-1-one derivatives

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ABSTRACT

A convenient route for the synthesis of some 2-propen-1-one derivatives with *E* isomeric configuration is described. The activity of the synthesized compounds was evaluated through behavioral studies of apomorphine-induced licking in animal models. It was demonstrated that most of the synthesized compounds showed moderate activity in inhibition of lickings, among which **6a**, was the most active compound at 30 mg/kg.

1. Introduction

The role of dopaminergic system in controlling motor, cognition and motivational behaviors has been frequently explained. Schizophrenia, a psychiatric illness with the prevalence rate of 1% is identified by two major types of symptoms: positive (delusion, hallucination) and negative (abolition, anhedonia and attentional impairment).[1] The biochemical basis of schizophrenia postulates that dopaminergic activity is increased in the mesolimbic system of the brain. The activation of D1/D2 receptors in striatum is represented by an excessive and repetitive behavior called stereotypy.[2] Dopamine receptor antagonists are therefore the most important drugs used to treat the positive symptoms of the disease. Preliminary treatment of schizophrenia and psychosis has relied on neuroleptics including chloropromazine, fluphenazine and haloperidol (Fig. 1).[3] The most occurred problems caused by classic neuroleptics mainly involve movement disorders, tardive diskinesia and extrapyramidal side effects. Clozapine was the protype of new drugs which were classified as atypical antipsychotics.[1,3] The most observed side effects related to clozapine were agranulocytosis and seizures.[3] For this reasons, research for design and synthesis of new drugs with more potency and less side effects has been a challenging aim for medicinal chemists.[1,2] As a part of these studies, synthesis and antidopaminergic activity of some conformationally restricted *cis* and *trans* analogs of haloperidol has been reported (Fig. 2, structure I).[4,5] The result of activity for these compounds revealed lower affinity for *cis* derivatives to both D1 and D2 receptors.[5] In another study, synthesis and dopaminergic activity of some 1-cyclohexylmethyl-8-hydroxy-7-methoxy-tetrahydroisoquolines, (Fig. 2, II) has been described.[6] It was demonstrated that all 1-cyclohexyl methyl derivatives were able to displace [*H*]-raclopride, a selective ligand of D2-dopamine receptor, from its site in rat striatal membrane.[6] In addition dopamine reuptake inhibition activity of propiophenone derivative (structure III, Fig. 2) has been reported.[7] The structure of compound III could be divided into three fragments: (1) phenyl ring, (2) piperidine ring, (3) linker attaching phenyl to piperidine.[7] In this study by taking fragments from the structures II and III (phenyl ring from structure II and linker and piperidine ring from structure III) and restricting the configuration of linker by a double bond at *trans* position, a series of *E*-3-(piperidin-1-yl)-1-(4-methoxy and hydroxyphenyl)-2-propen-1-one derivatives were synthesized and

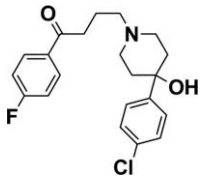

Figure 1. Haloperidol.

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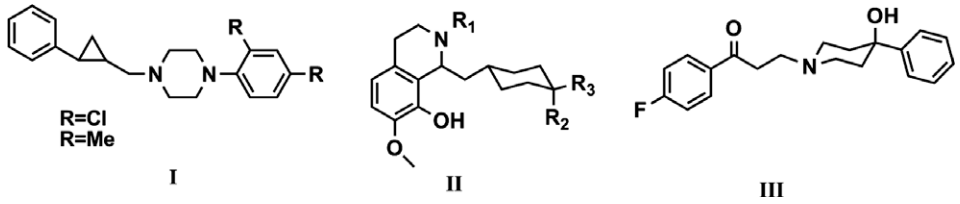


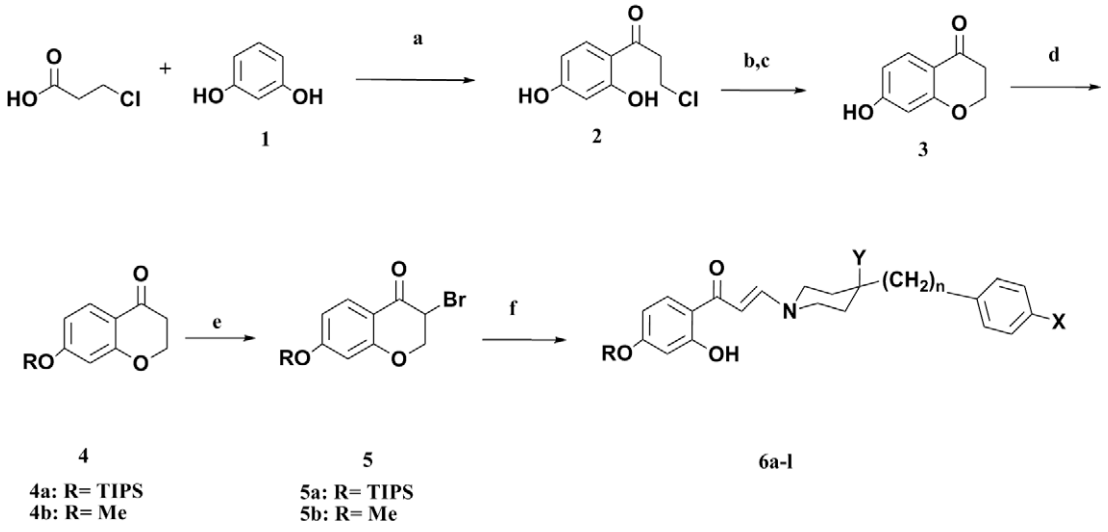
Figure 2. Structures of I, II and III.

evaluated for dopaminergic activity through apomorphine licking studies in animal model.

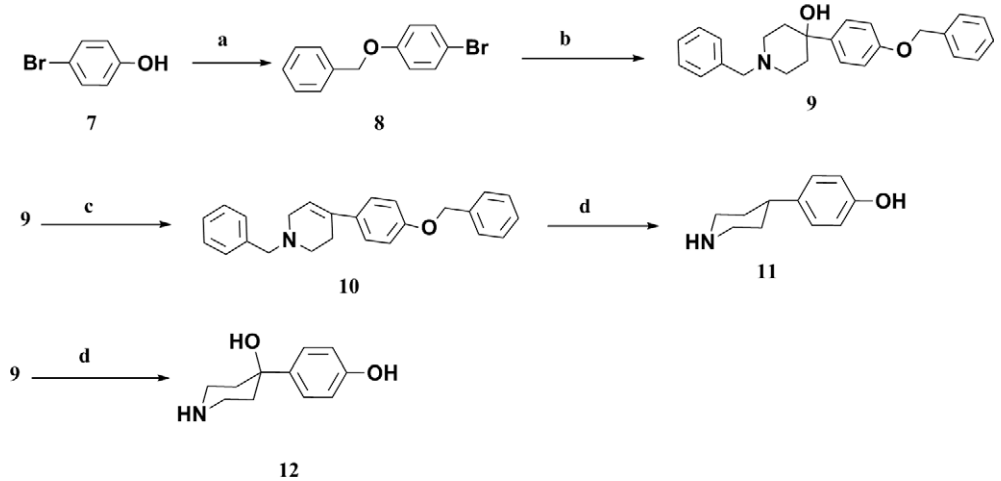
2. Results and discussion

2.1. Chemistry

Our convenient strategy for the synthesis of target compounds with *E* isomeric configuration is explained in the experimental section and depicted in Scheme 1. Reaction of resorcinol (**1**) with 3-chloropropionic acid using trifluoromethanesulfonic acid furnished 2′,4′-dihydroxy-3-chloro propiophenone (**2**). By intramolecular cyclization in the next step with NaOH, 7-hydroxy-4-chromanone (**3**) was obtained.[8] Protection of hydroxyl group in compound **3** with chlorotriisopropyl silane yielded 7-(triisopropylsilyloxy) chroman-4-one (**4a**) while methylation of (**3**) with methyl iodide afforded **4b**.[9,10] The two intermediates were then reacted with $CuBr_2$ to yield the mono brominated intermediates (**5a–b**). The target compounds were finally obtained through the addition of 4-substituted piperidines to the mono brominated intermediates, **5a–b**, in the presence of K_2CO_3. Four of the six substituted piperidnes in Scheme 1, namely 4-(4-chlorophenyl)piperidin-4-ol, 4-(4-bromophenyl)piperidin-4-ol, 4-phenylpiperidin-4-ol and 4-benzylpiperidine were commercially available. Meanwhile, the two 4-phenylpiperidine derivatives having OH at position 4 of phenyl were synthesized through the route depicted in Scheme 2.



Scheme 1. Reagents and conditions: (a) CF_3SO_3H, rt; (b) NaOH, rt; (c) HCl, rt; (d) CH_3I or chlorotrimethylsilane, rt (e) $CuBr_2$, reflux for 5 h; (f) 4-substituted piperidine, K_2CO_3.



Scheme 2. Reagents and conditions: (a) benzyl chloride, reflux; (b) *n*-BuLi, −78 °C, *n*-benzyl-4-piperidone; (c) HCl, reflux for 15 min; (d) Pd/C(10%), H_2 (50 psi), rt, overnight.

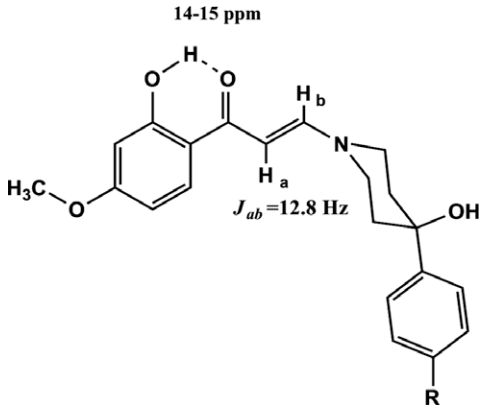


Figure 3. Preferred conformation of the target compounds (**6a–l**).

Reaction of 4-bromophenol (**7**), with benzylbromide provided 1-(benzyloxy)-4-bromobenzene (**8**). The compound **8** was then reacted with *n*-butyl lithium at -78°C followed by *n*-benzyl-4-piperidone, to yield **9**. Dehydration of **9** in acidic medium followed by hydrogenation at 49 psi in the presence of Pd/C(10%) as catalyst, yielded 4-(piperidin-4-yl)phenol (**11**). In addition, by direct hydrogenation of **9** at 49 psi 4-(4-hydroxyphenyl)piperidin-4-ol (**12**) was obtained.

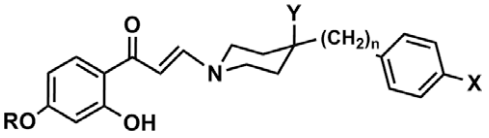
Final purification of the target compounds (**6a–l**) was performed with column chromatography using ethyl acetate–petroleum ether as the mobile phase and the purity of the synthesized compounds was rechecked by thin layer chromatography using various solvents with different polarities.

Based on ^{1}H NMR data, the coupling constant (J) of AB quartet system, relating two hydrogens at the site of double bond was 12–13 Hz, it could be therefore concluded that the configuration of double bond in final compounds (**6a–l**) is (***E***) rather than (***Z***) (Fig. 3). In addition, phenolic hydrogens adjacent to carbonyl moieties in all target compounds (**6a–l**) were observed at 14–15 ppm. The reason for deshield phenolic protons are explained by intramolecular hydrogen bond interactions between corresponding OH and adjacent carbonyl moieties (Fig. 3). A possible mechanism for reaction of piperidines with **5b** is depicted in Figure 4. It is reasonable to assume that the E_2 elimination of **5b** in basic solution affords intermediate **I**. In the next step, by Michael addition of substituted piperidines, followed by ring cleavage of the resulted intermediate **II**, the target compound **6** was formed. It should be mentioned that the N-substituted 2- and 3-alkyl-3-aminoacrylophenones has been synthesized by other routes.[11]

2.2. Biological activity

The results of behavioral dopaminergic activity for the target compounds (**6a–l**), in terms of licking count inhibition are listed in Table1. One way analysis of variances (ANOVA) followed by a post Tukey test was performed on the raw data to compare the compounds with each other and their related control groups. The

Table 1
Licking count average ± SE of the target compounds (**6a–l**) and controls



	Code	R	X	Y	*n*	Licking count ± SE
6a–f	**6a**	H	Cl	OH	0	115 ± 24.6**
	6b	H	Br	OH	0	1860 ± 318.7*
	6c	H	H	OH	0	1317 ± 135.2**
	6d	H	H	H	1	618 ± 71.72**
	6e	H	OH	H	0	664 ± 51.92**
	6f	H	OH	OH	0	1450 ± 207.4**
6g–l	**6g**	Me	Cl	OH	0	1575 ± 85.39**
	6h	Me	Br	OH	0	1140 ± 92.74**
	6i	Me	H	OH	0	1800 ± 83.67**
	6j	Me	H	H	1	520 ± 80**
	6k	Me	OH	H	0	1325 ± 154.8**
	6l	Me	OH	OH	0	2675 ± 77.73
	(+) Apomorphine (0.5 mg/kg) + Haloperidol (0.5 mg/kg)					3.667 ± 1.52**
	(−) Apomorphine (0.5 mg/kg) + Vehicle					2850 ± 183.9

* Tukey Post ANOVA test, P <0.01 with respect to negative control.
** Tukey Post ANOVA test, P <0.001 with respect to negative control.

compounds having p <0.01 and p <0.001 in respect to negative control were considered to be active and assigned with ∗ and ∗∗, respectively. Based on the statistical values, the order of activity for the group of compounds having OH at position 4 of phenyl ring was **6a > 6d, 6e > 6f, 6c > 6b**. Therefore, compound **6a** with 4-chlorophenyl substituent was the most active compound. On the other hand, the order of activity for the group of compounds with methoxy at the same position was **6j > 6h, 6k > 6g ⩾ 6i > 6l**. The most dopaminergic activity in this group was pertained to **6j** with benzyl substituent. Compound **6a** was the most active compound in both series and its activity was comparable to the positive control (haloperidol, p >0.05). The most dopaminergic activity after **6a** was observed for **6j**, **6d** and **6e**. A common feature observed in these three compounds was the absence of OH group at the 4 position of piperidine ring. In addition, the two compounds **6j** and **6d** had a benzyl substituent at position 4 of piperidine, while **6e** contained an unsubstituted phenyl at this position. Finally, it is noteworthy to mention that in most compounds when R = H, they were more active than the compounds having R = Me (**8a > 6g**, **6c > 6i**, **6e > 6k** and **6f > 6l**).

In order to obtain further information about the most active compound, **6a**, response activity calculations were repeated at 10, 30 and 50 mg/kg for this compound. The plot of activity for **6a** at three doses is shown in Figure 5. Result of this study revealed that, increasing the administered dose of **6a** from 10 to 30 mg/kg increased the activity. However, increasing the dose from 30 to 50 mg/kg did not change the dopaminergic activity significantly. Therefore, the highest activity of compound **6a** could be observed at 30 mg/kg in animal models.

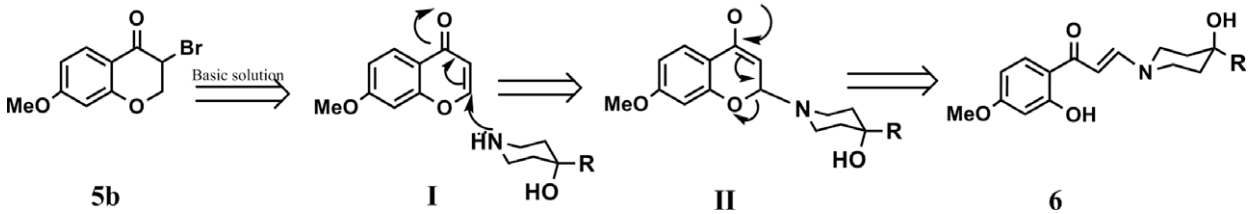


Figure 4. A possible mechanism for the reaction of substituted piperidines with monobrominated intermediate (**5b**).

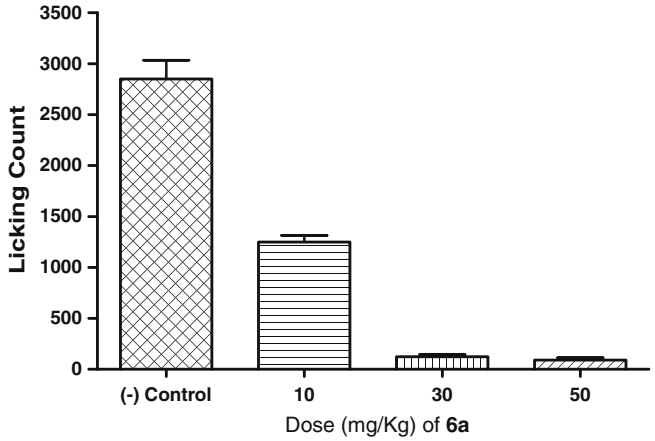


Figure 5. Dose dependent activity of **6a**.

3. Conclusion

A simple method for the synthesis of some 2-propen-1-one derivatives with *E* configuration is described. The activity of the synthesized compounds was evaluated through behavioral studies. It was shown that most synthesized compounds had moderate activity. Compound **6a** having chlorine in para position of the benzyl ring was the most active compound.

4. Experimental

4.1. Synthesis procedure

Chemical reagents and solvents used in this study were purchased from Merck AG or Aldrich Chemical. Column chromatography purifications were performed on Merck Silica Gel (70–230 mesh). All melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR Magna 550 spectrophotometer. ^{1}H NMR spectra were measured using a Bruker FT-80 or FT-500 MHz, and chemical shifts are expressed as δ (ppm) with respect to tetramethylsilane as internal standard. The mass spectra were run on a Finigan TSQ-70 spectrometer at 70 eV. Elemental microanalyses were carried out with a Perkin–Elmer 240-C apparatus and were within ±0.4% of the theoretical values for C, H, and N.

Synthesis of intermediates **2–4** and **8–12** was performed according to the procedure depicted in Schemes 1 and 2, respectively.[8–10]

4.1.1. Synthesis of 3-bromo-7-(triisopropylsilyloxy)chroman-4-one (5a)

7-(triisopropylsilyloxy)-4-chromanone (400 mg, 1.25 mmol) was treated with a heterogeneous mixture of $CuBr_2$ (900 mg, 4 mmol) in $CHCl_3$–ethyl acetate (30 mL, 1:1) and the resulted mixture was refluxed for 5 h. The mixture was filtered, washed with ethyl acetate and the solvent was evaporated. The resulted oil was purified by column chromatography using petroleum ether–ethyl acetate (90:10) as the mobile phase to afford compound **5a** (300 mg, 60% yield). ^{1}H NMR (DMSO-d_6, 80 MHz) δ: 7.79 (d, 1H, H_5, J = 8.0 Hz), 6.48 (dd, 1H, H_6, J = 2.5 Hz, J = 8.0 Hz), 6.40 (d, 1H, H_8, J = 2.5 Hz), 4.58–4.40 (m, 3H, H_2,H_3), 1.3–1 (m, 21 H, isopropyl), Anal. Calcd for $C_{18}H_{27}BrO_3Si$: C, 54.13; H, 6.81. Found: C, 54.35; H, 6.62.

4.1.2. Synthesis of 3-bromo-7-methoxy-4-chromanone (5b)

This compound was prepared according to the method described for **5a**, through the reaction of 7-methoxy-chroman-4-one (**4b**, 281.5 mg, 1.25 mmol) with $CuBr_2$ (900 mg, 4 mmol). The resulted mixture was purified by column chromatography with ethyl acetate–petroleum ether (40:60) as the mobile phase to afford **5b** (310 mg 1.2 mmol, 76% yield), mp 166–168 °C, ^{1}H NMR (DMSO-d_6, 80 MHz) δ: 7.83 (d, 1H, H_5, J = 8 Hz), 6.50 (dd, 1H, H_6, J = 2.5 Hz, J = 8 Hz), 6.46 (d, H_8, J = 2.5 Hz), 4.62–4.57 (m, 3H, H_2,H_3), 3.86 (s, 3H, OCH_3), EI-MS *m/z* (%) 258 (M^++2, 20), 256 (M^+, 21), 148 (100), 121 (58), 79 (40), 61 (60), Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.72; H. Found: C, 46.32; H, 3.41.

4.1.3. General procedure for synthesis of (*E*)-3-(4-hydroxy-4-phenyl and benzyl piperidin-1-yl)-1-(4-methoxyphenyl)-prop-2-en-1-one derivatives (6a–f)

To a solution of **5a** (398 mg, 1 mmol) in acetonitrile (10 mL), was added 4 substituted piperidine derivatives (1 mmol) and K_2CO_3 (138 mg, 1 mmol). After refluxing the mixture for 1 h, the solvent was evaporated and the crude mixture was purified by column chromatography, using petroleum ether–ethyl acetate (60:40) as the mobile phase to afford the final compounds (**6a–f**).

4.1.4. (*E*)-3-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one 6a

Compound **6a** (75% yield), mp 118–120 °C, IR ν cm^{-1}: 3405 (OH), 1613 (C=O),^{1}H NMR (DMSO-d_6, 80 MHz), δ: 14.50 (s, 1H, phenolic OH), 7.90 (d, 1H, H_a, J = 12.0 Hz), 7.75–7.2 (m, 5 H, aromatic), 6.4–6.2 (m, 2H, aromatic), 6.1 (d, 1H, H_b, J = 12.0 Hz), 3.06–1.20 (m, 8H, piperidine), EI-MS *m/z* (%) 375 (M^++2, 8), 373 (M^+, 25), 355 (M^+-H_2O, 33), 210 (100), Anal. Calcd for $C_{20}H_{20}ClNO_4$: C, 64.26; H, 5.39; N, 3.75. Found: C, 64.11; H, 5.22; N, 3.42.

4.1.5. (*E*)-3-(4-(4-Bromophenyl)-4-hydroxypiperidin-1-yl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one 6b

Compound **6b** (73% yield), mp 210–212 °C, IR ν cm^{-1}: 3373 (OH), 1615 (C=O), ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 15.00 (s, 1H, phenolic OH), 7.80 (d, 1H, H_a, J = 12.0 Hz), 7.76 (d, 1H, H_6-phenyl, J = 9.0 Hz), 7.5–7.4 (m, 4H, aromatic), 6.22 (dd, 1H, H_5-phenyl, J = 2.0 Hz, J = 9.0 Hz), 6.12 (d, 1H, H_3-phenyl, J = 2.0 Hz), 6.05 (d, 1H, H_b, J = 12.0 Hz), 2.77–2.76 (m, 4H, piperidine), 2.00 (s, 1H, OH-piperidine), 1.80–1.65 (m, 2H, piperidine), 1.5–1.48 (m, 2H, piperidine) EI-MS *m/z* (%): 419 (M^++2, 17), 417 (M^+, 18), 254 (100), Anal. Calcd for $C_{20}H_{20}BrNO_4$: C, 57.43; H, 4.82; N, 3.35. Found: C, 57.14; H, 4.61; N, 3.10.

4.1.6. (*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-hydroxy-4-phenylpiperidin-1-yl)prop-2-en-1-one 6c

Compound **6c** (34% yield) mp 115–117 °C, IR ν cm^{-1}: 3370 (OH), 1627 (C=O), ^{1}H NMR (DMSO-d_6, 80 MHz), δ: 14.00 (s, 1H, phenolic OH), 7.90 (d, 1H, H_a, J = 12.1 Hz), 7.8–7.3 (m, 6H, aromatic), 6.50–6.30 (m, 2H, H_3, H_5), 6.9 (d, 1H, H_b, J = 12.1 Hz), 4.76 (s, 1H, OH piperidine), 2.0–1.3 (m, 8H, piperidine), EI-MS *m/z* (%) 339 (M^+, 18), 176 (100), Anal. Calcd for $C_{20}H_{21}NO_4$ C, 70.78; H, 6.24; N, 4.13. Found: C, 70.95; H, 6.02; N, 3.85.

4.1.7. (*E*)-3-(4-Benzylpiperidin-1-yl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one 6d

Compound **6d** (70% yield) mp 82–84 °C, IR cm^{-1}: 3544 (OH), 1618 (C=O), ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 14.4 (s, 1H, phenolic OH), 7.89 (d, 1H, H_a, J = 12.0 Hz), 7.57 (d, 1H, H_6, J = 8.0 Hz), 7.3–7.1 (m, 5H, phenyl), 6.46 (dd, 1H, H_5-phenyl, J = 2.0 Hz, J = 8.0 Hz), 6.12 (d, 1H, H_3-phenyl, J = 2.0 Hz), 5.98 (d, 1H, H_b, J = 12.0 Hz), 2.87–2.76 (m, 2H, piperidine), 2.42 (s, 2H, CH_2, benzylic), 2.10 (s, 1H, OH-piperidine), 1.70–1.50 (m, 6H, piperidine), EI-MS *m/z* (%) 337 (M^+, 18), 174 (100) Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.96; H, 6.53; N, 3.98.

4.1.8. (*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)prop-2-en-1-one 6e

Compound **6e** (33% yield) mp 138–140 °C, IR cm^{-1}: 3503 (OH), 1615 (C=O), ^1H NMR (DMSO-d_6, 500 MHz), δ: 14.33 (s, 1H, phenolic OH), 9.00 (s, 1H, phenolic OH), 7.92 (d, 1H, H_a, J = 12.5 Hz), 7.53 (d, 1H, H_6, J = 8.5 Hz), 7.021- 6.99 (m, 4H, phenyl), 6.36 (d, 1H, H_3-phenyl, J = 2.0 Hz), 6.31 (dd, 1H, H_5-phenyl, J = 8.5 Hz, J = 2.5 Hz), 5.80 (d, 1H, H_b, J = 12.5 Hz), 3.80–3.77 (m, 2H, piperidine), 3.52–3.50 (m, 2H, piperidine), 2.95–2.83 (m, 4H, piperidine) EI-MS *m/z* (%) 339 (M^+,15), 176 (100) Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.55; H, 6.02; N, 4.27.

4.1.9. (*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-hydroxy-4-(4-hydroxyphenyl)piperidin-1-yl)prop-2-en-1-one 6f

Compound **6f** (68% yield), mp 142–144 °C, IR cm^{-1}: 3400 (OH), 1630 (C=O), ^1H NMR (DMSO-d_6, 500 MHz), δ: 14.903 (s, 1H, phenolic OH), 9.24 (s, 1H, phenolic OH), 7.90 (d, 1H, H_a, J = 12.0 Hz), 7.77 (d, 1H, J = 8.5 Hz), 7.30 (d, 2H, phenyl, J = 8.5 Hz), 6.70 (d, 2H, phenyl, J = 8.5 Hz), 6.31 (dd, 1H, H_5-phenyl, J = 8.5 Hz, J = 2.5 Hz), 6.12 (d, 1H, H_3, J = 2.5 Hz), 6.03 (d, 1H, H_b, J = 12 Hz), 3.80–3.77 (m, 2H, piperidine), 5.06 (s, 1H, OH), 3.80–3.50 (m, 4H, piperidine), 2.00–1.65 (m, 2H, piperidine) EI-MS *m/z* (%) 355 (M^+, 20), 192 (100), Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N,3.94. Found: C, 67.14; H, 5.32; N, 3.52.

4.1.10. General procedure for the synthesis of (*E*)-3-(substituted piperidin-1-yl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one derivatives (6g–l)

To a solution of **5b** (257 mg, 1 mmol) in acetonitrile (10 mL) was added 4 substituted piperidine derivatives (1 mmol) and K_2CO_3 (138 mg, 1 mmol). The reaction mixture was stirred over night. The solvent was evaporated and the crude mixture was purified by column chromatography, using petroleum ether–ethyl acetate (70:30) as the mobile phase, to yield the final compounds (**6g–l**).

4.1.11. (*E*)-3-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-1-(2-hydroxy-4-methoxyphenyl) prop-2-en-1-one 6g

Compound **6g** (56% yield) mp 166–168 °C, IR cm^{-1}: 3421 (OH), 1618 (C=O), ^1H NMR (DMSO-d_6, 80 MHz), δ: 14.59 (s, 1H, phenolic OH), 7.90 (d, 1H, H_a, J = 12.8 Hz), 7.50–7.42 (m, 7H), 5.8 (d, 1H, H_b, J = 12.8 Hz), 4.79 (s, 1H, OH-piperidine), 3.81 (s, 3H, OMe), 2.7–1.9 (m, 8H, piperidine): EI-MS *m/z* (%) 389 (M^++2, 7), 387 (M^+,18), 369 (M^+-H_2O, 15), 210 (100), 151 (35), Anal. Calcd for $C_{21}H_{22}ClNO_4$: C, 65.03; H, 5.72; N, 3.61. Found: C, 64.80; H, 5.33; N, 3.27.

4.1.12. (*E*)-3-(4-(4-Bromophenyl)-4-hydroxypiperidin-1-yl)-1-(2-hydroxy-4-methoxyphenyl) prop-2-en-1-one 6h

Compound **6h** (49% yield) mp 155–156 °C, IR ν cm^{-1}: 3395 (OH), 1608 (C=O), ^1H NMR (DMSO-d_6, 80 MHz), δ: 14.56 (s, 1H, phenolic OH), 7.91 (d, 1H, H_a, J = 12.8 Hz), 7.56–7.40 (m, 7H, aromatic), 5.9 (d, 1H, H_b, J = 12.8 Hz), 4.86 (s, 1H, OH-piperidine), 3.81 (s, 3H, OMe), 2.7–1.9 (m, 8H, piperidine), EI-MS *m/z* (%) 433 (M^++2, 14), 431 (M^+, 18), 413 (M^+-H_2O, 12), 254 (100), 149 (80), Anal. Calcd for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.64; H, 4.85; N, 2.98.

4.1.13. (*E*)-1-(2-Hydroxy-4-methoxyphenyl)-3-(4-hydroxy-4-phenylpiperidin-1-yl)prop-2-en-1-one 6i

Compound **6i** (61% yield), mp 186–188 °C, IR ν cm^{-1}: 3383 (OH), 1618 (C=O), ^1H NMR (DMSO-d_6, 80 MHz), δ: 14.62 (s, 1H, phenolic OH), 7.85 (d, 1H, H_a, J = 12.1 Hz), 7.61–7.27 (m, 6H, aromatic), 6.40–6.32 (m, 2H, aromatic), 6.67 (d, 1H, H_b, J = 12.1 Hz), 4.92 (s, 1H, OH-piperidine), 3.60 (s, 3H, OMe), 2.9–2.0 (m, 8H, piperidine), EI-MS *m/z* (%) 353 (M^+, 10), 335 (M^+-H_2O, 10), 175.9 (100), 120 (40) Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.02; H, 6.67; N, 3.72.

4.1.14. (*E*)-3-(4-Benzylpiperidin-1-yl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one 6j

Compound **6j** (58% yield), mp 122–124 °C, IR ν cm^{-1}: 3523 (OH), 1623 (C=O), ^1H NMR (DMSO-d_6, 80 MHz), δ: 14.48 (s, 1H, phenolic OH), 7.80 (d, 1H, H_a, J = 12.3 Hz), 7.57–6.5 (m, 5H, aromatic), 6.5–6.4 (m, 3H, aromatic), 5.77 (d, 1H, H_b J = 12.3 Hz) 3.80 (s, 3H, OCH_3), 3.06 (m, 4H, piperidine), 2.57 (d, 2H, CH_2-benzylic), 2.10–1.20 (m, 4H, piperidine), EI-MS *m/z* (%) 351 (M^+, 20), 333 (18), 177 (50), 151 (36), 96 (38), 91 (100), 69 (96), 55 (98) Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.93; H, 6.94; N, 3.72.

4.1.15. (*E*)-1-(2-Hydroxy-4-methoxyphenyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)prop-2-en-1-one 6k

Compound **6k** (66% yield) mp 196–198 °C, IR ν cm^{-1}: 3421 (OH), 1618 (C=O),^1H NMR (DMSO-d_6, 80 MHz), δ: 14.98 (s, 1H, phenolic OH), 9.14 (s, 1H, OH phenolic), 7.84 (d, 1H, H_a, J = 12.8 Hz), 7.07 (d, 2H, phenyl, J = 8.0 Hz), 6.7 (d, 2H, phenyl, J = 8.0 Hz), 6.56–6.43 (m, 3H, phenyl), 6.34–6.17 (d, 1H, H_b, J = 12.8 Hz), 3.79 (s, 3H, OMe) 2.1–1.6 (m, 8H, piperidine), EI-MS *m/z* (%) 353 (M^+, 10), 176 (100), 120 (40), Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.78; N, 3.65.

4.1.16. (*E*)-3-(4-Hydroxy-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one 6l

Compound **6l** (45% yield) mp 125–127 °C, ν cm^{-1}: 3435 (OH), 1640 (C=O),^1H NMR (DMSO-d_6, 80 MHz), δ 14.70 (s, 1H, phenolic OH), 8.96 (s, 1H, phenolic OH), 7.9–7.7 (m, 2H, H_a, H_5-phenyl), 7.3 (d, 2H, phenyl, J = 8.0 Hz), 6.8 (d, 2H, phenyl, J = 8.0 Hz), 6.6–6.3 (m, 2H, $H_{3,4}$-phenyl), 6.9 (d, 1H, J = 12.0 Hz), 4.91 (s, 1H, OH-piperidine), 3.60 (s, 3H, OMe), 2.5–1.8 (m, 8H, piperidine), EI-MS *m/z* (%) 369 (M^+, 16), 192 (100), Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.49; H, 6.02; N, 3.54.

4.2. Behavioral studies

Behavioral studies of the synthesized compounds have been performed based on the protocol, reported by Sharifzadeh et al.[12] The subject male Wister rats weighting 170–220 g were kept at room temperature with 12 h light/12 h dark cycle. The animals had access to food and water except during experiment. Eight animals were used for each dose of the target compounds and control groups.[12–14] The whole protocol was approved for by the ethics committee of the Faculty of Pharmacy at Tehran University of Medical Sciences.

The synthesized structures were dissolved in a vehicle composed of ethanol (5%), tween 80 (5%), propylene glycol(5%) and water (85%). As a primary screening, all target compounds were injected at 30 mg/kg. Apomorphine (0.5 mg/kg) was injected 15 min after ip injection of the synthesized compounds. Consequently, animals were individually placed in a glass cylinder and a mirror was arranged in an oblique position under the cylinder to make all observations possible. Ten minutes after administration of apomorphine the number of licks was counted by direct observation during 60 min.[12,13]

Positive control group received 0.5 mg/kg apomophine (sc), 15 min after administration of haloperidol (0.5 mg/kg, ip), meanwhile for the negative control group a 0.5 mg/kg dose of apomorphine was administered 15 min after ip injection of vehicle.

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