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2-Phenoxy-indan-1-one derivatives as acetylcholinesterase inhibitors: A study on the importance of modifications at the side chain on the activity

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ABSTRACT

As a part of our project aimed at developing new agents of potential application in AD, a new series of 2-phenoxy-indan-1-one derivatives which possess alkylamine side chain were designed, synthesized and evaluated for their inhibitory activity against AChE and BuChE. Most of the compounds were found to inhibit AChE in the nanomolar range. The optimum inhibitor **3g** exhibited 34-fold increase in AChE inhibition than donepezil and displayed neuroprotective effect against H_2O_2-induced cell death.

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia in elder, is a progressive neurodegenerative disorder characterized by loss of memory and cognition. The so-called 'cholinergic hypothesis' postulated that the cognitive decline experienced by AD patients is due to an extensive loss of cholinergic neurons.[1] To date, the enhancement of the central cholinergic function is the mainly effective approach, by means of reversible acetylcholinesterase (AChE) inhibitors, such as tacrine, donepezil, galantamine, and rivastigmine.[2]

Another theory about AD pathogenesis is 'amyloid hypothesis', which states that the production and the deposition of β-amyloid (Aβ) in the form of fibrils lead to neuronal cell death and to the clinical symptoms.[3] Since AChE is able to promote the aggregation of Aβ into amyloid fibrils through the residues located in the peripheral anionic site of the enzyme (PAS), AChE inhibitors able to interact with PAS can prevent synthesis, deposition and aggregation of toxic Aβ.[4–6] The dual-binding inhibitors target simultaneously both the catalytic and the peripheral-binding sites not only inhibited the hydrolysis of AChE toward ACh, but also prevented proaggregating activity of AChE toward Aβ. Furthermore, some clinical studies showed that patients treated with cholinesterase inhibitors did not show the widespread cortical atrophic changes associated with AD, providing empirical evidence of neuroprotection by cholinesterase inhibitors.[7–9] For these above reasons, the interest in AChE inhibitors has increased in the last few years.

In our previous work, we have designed and synthesized some hybrids of donepezil and rivastigmine, by chosen 5,6-dimethoxy-indan-1-one and *N*,*N*-dialkyl-benzylamine as the two pharmacophoric moieties.[10] Among these compounds, compound **1** demonstrated the most potent AChE inhibitory activity. The docking results showed that it could interact well with AChE along the gorge. Nevertheless, near the bottom of the gorge, the distance between the charged nitrogen of pyrrolidine in compound **1** and the pyrrole ring of Trp84 is too long (4.7 Å) to constitute close and efficient affinity. Thus we tried to make some modifications in the linker between the benzene ring and the tertiary amine and to study the effect of the changes on the binding affinity and AChE inhibitory activity (Fig. 1).

Following this strategy, the length of the linker between the benzene ring and the tertiary amine was increased up to 2–4 methylene units to identify the optimal distance (**2a**–**m**). On the other hand, a carbonyl group was introduced within the linker chain (**3a**–**n**), considering that it might have the chance to favorably interact with some of the amino acid residues of the enzyme. Moreover, the position of substituent on the benzene ring and the nature of the tertiary amino groups were changed in order to search for the correct orientation and the favorable tertiary amine group. Twenty-seven target compounds were synthesized and tested for their AChE inhibitory activities. To study further the biological profile of these compounds, their butyrylcholinesterase (BuChE) inhibitory activity and the neuroprotective effect against H_2O_2-induced cell death were also evaluated. Finally, to explore

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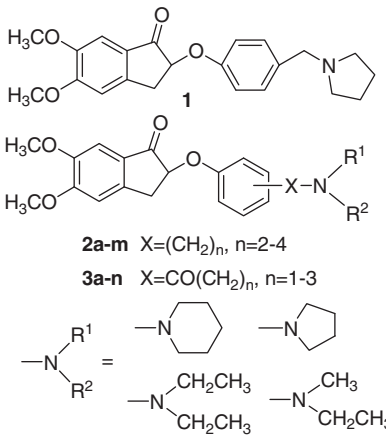


Figure 1. Chemical structure of compound **1** and 2-phenoxy-indan-1-one derivatives **2a**–**m** and **3a**–**n**.

the possible binding conformation of synthesized compounds and protein–ligand interaction mode, the docking study was performed using the Flexidock program in SYBYL software.

2. Results and discussion

2.1. Chemistry

The synthesis of target compounds **2a**–**m** and **3a**–**n** was achieved following a convergent pathway strategy summarized in Scheme 1. Treatment of 4-hydroxyalkylphenol **4a**–**c** with $SOCl_2$ in CH_2Cl_2 at room temperature for 1.5 h resulted in **5a**–**c**[11,12], which were then treated with the secondary amines to afford intermediates **6a**–**m.**[13]

For the synthesis of intermediates **9a**–**n,** different routes were followed. Reaction of 4-hydroxyacetophenone with $PyHBr_3$ led to 2-bromo-1-(4-hydroxyphenyl)ethanone **8**[14], which was then coupled with various secondary amines at low temperature to afford 2-alkylamino-1-(4-hydroxyphenyl)ethanones **9a**–**d.**[15] Intermediates **9e**–**j** could be readily prepared through Mannich reaction by treatment of hydroxyacetophenones with paraformaldehyde and secondary amines.[16] Reaction of anisole with 4-chlorobutanoyl chloride in the presence of $AlCl_3$ provided **10,** which reacted with secondary amines to achieve **11,** followed by O-demethylation with 47% HBr in acetic acid to give intermediates **9k**–**n**. Finally, intermediates **6a**–**m** and **9a**–**n** were condensed with 2-bromo-5,6-dimethoxy-indan-1-one **12**[17] in the presence of K_2CO_3 to give the corresponding target products **2a**–**m** and **3a**–**n**, respectively.

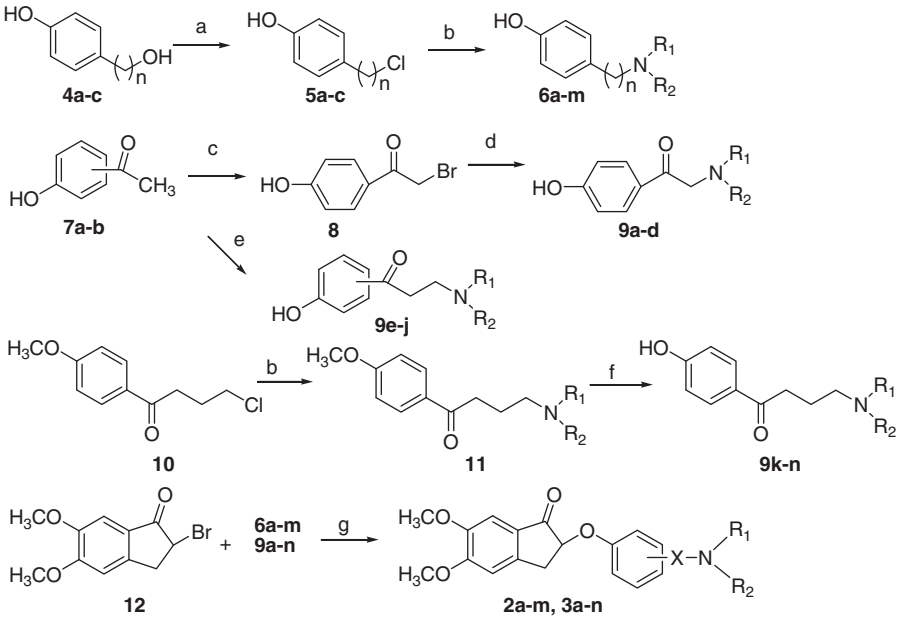
2.2. Biological activity and molecular modeling

The assay for AChE and BuChE inhibitory activity of synthesized compounds was performed according to the modified method of Ellman[18,19] using rat cortex homogenate (AChE) and rat serum (BuChE), with donepezil as the reference compound. The results are reported in Table 1.

From the IC_{50} values of compounds **2a–m**, which possess 1–4 methylene units between the benzene ring and tertiary amino, it appeared that variation of the chain length influenced AChE inhibitory activity obviously. In general, the compounds with a CH_2CH_2 (i.e. **2b** and **2c**) linker showed better inhibition than the molecules with $CH_2CH_2CH_2$ (i.e. **2g** and **2k**) or $CH_2CH_2CH_2CH_2$ (i.e. **2l** and **2m**) as the linker, which indicated that CH_2CH_2 as linker is favorable for the interaction between this series of compounds with enzyme.

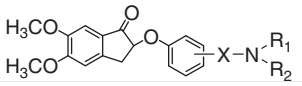
Compounds **3a–n**, which possesses carbonyl group in the linker, demonstrated similar or better inhibitory activity compared to donepezil. Generally, the compounds with a $COCH_2CH_2$ linker showed the most potent inhibitory activity in this series. Compounds **3g**[11] and **3h** possessed potent activity with IC_{50} of 0.78 nM and 1.85 nM, which were 34-fold and 14-fold more potent than donepezil, respectively. When the linker was lengthened or shortened, inhibition of AChE dropped.

Comparing series **3a–n** with **2a–m**, it appeared that the introduction of carbonyl group in the linker resulted in an obvious enhancement of AChE inhibitory activity. For example, compound



Scheme 1. Synthesis of **2a**–**m** and **3a**–**n**. Reagent and conditions: (a) $SOCl_2$, CH_2Cl_2, Et_3N; (b) CH_3CN, Et_3N, reflux 7 h for pyrrolidine or piperidine, CH_3CN, Et_3N, sealed tube, 100 °C, 5 h for diethylamine or methylethylamine; (c) $PyHBr_3$, THF, rt; (d) second amine, $NaHCO_3$, CH_3CN, 0–5 °C, 0.5 h; (e) $(CHO)_n$, EtOH, concd HCl, reflux 6 h for pyrrolidine or piperidine, $(CHO)_n$, EtOH, concd HCl, sealed tube 90 °C, 5 h for diethylamine or methylethylamine; (f) CH_3COOH, 47% HBr, reflux,11 h; (g) K_2CO_3, CH_3CN, reflux, 0.5–3 h.

Table 1
Cholinesterase inhibitory activity and selectivity of prepared compounds[a]



Compound	X	Substituted position		IC_{50} AChE (nm)	IC_{50} BuChE (nm)	Selectivity for AChE[b]
2a	CH_2CH_2	*para*	Piperidine-1-yl	50.2 ± 1.6	5114 ± 320	101.9
2b		*para*	Pyrrolidine-1-yl	37.3 ± 2.3	30,450 ± 200	816.3
2c		*para*	Diethylamino	42.1 ± 0.6	16,580 ± 400	393.8
2d		*para*	Methylethylamino	51.6 ± 2.1	22,030 ± 180	426.9
2e		*meta*	Piperidine-1-yl	1550 ± 20	7002 ± 270	4.52
2f		*meta*	Pyrrolidine-1-yl	1770 ± 130	15,380 ± 280	8.69
2g		*meta*	Diethylamino	2090 ± 21	11,100 ± 480	5.31
2h		*meta*	Methylethylamino	710 ± 18	8645 ± 350	12.2
2i	$CH_2CH_2CH_2$	*para*	Piperidine-1-yl	640 ± 51	2794 ± 310	4.36
2g		*para*	Pyrrolidine-1-yl	209 ± 4.6	2337 ± 18	11.2
2k		*para*	Diethylamino	277 ± 19	3986 ± 46	14.4
2l	$CH_2CH_2CH_2CH_2$	*para*	Pyrrolidine-1-yl	415 ± 20	3224 ± 40	7.76
2m		*para*	Diethylamino	481 ± 32	3256 ± 310	6.77
3a	$COCH_2$	*para*	Piperidine-1-yl	364 ± 4.3	1663 ± 20	4.57
3b		*para*	Pyrrolidine-1-yl	240 ± 3.2	1722 ± 460	7.2
3c		*para*	Diethylamino	280 ± 14	2428 ± 350	8.7
3d		*para*	Methylethylamino	31.6 ± 1.6	588 ± 60	18.6
3e	$COCH_2CH_2$	*para*	Piperidine-1-yl	17.3 ± 2.8	3239 ± 410	187.2
3f		*para*	Pyrrolidine-1-yl	4.16 ± 0.13	6039 ± 70	1451.6
3g		*para*	Diethylamino	0.78 ± 0.12	1520 ± 260	1948.7
3h		*para*	Methylethylamino	1.85 ± 0.32	4509 ± 200	2437
3i		*meta*	Pyrrolidine-1-yl	832 ± 20	11,110 ± 450	13.35
3j		*meta*	Diethylamino	2370 ± 240	1519 ± 35	0.64
3k	$COCH_2CH_2CH_2$	*para*	Piperidine-1-yl	529 ± 40	8973 ± 720	16.96
3l		*para*	Pyrrolidine-1-yl	62 ± 2.5	2930 ± 190	47.2
3m		*para*	Diethylamino	40.6 ± 3.6	37,650 ± 690	927.3
3n		*para*	Methylethylamino	37.6 ± 1.8	26,870 ± 430	714.6
Donepezil				26.8 ± 1.5	3260 ± 180	121

[a] Data are means ± standard deviation of three independent experiments.
[b] Selectivity for AChE is defined as IC_{50} (BuChE)/IC_{50} (AChE).

3g with $COCH_2CH_2$ as the linker showed higher potency (IC_{50} = 0.78 nM) than compound **2k** with $CH_2CH_2CH_2$ as the linker (IC_{50} = 277 nM).

On the other hand, the structure and position of alkylamine side chain on the benzene ring in the tested compounds had also effect on the inhibitory activity. Compounds with diethylamino group or methylethylamino group showed more potent inhibitory activity (i.e. **3d**, **3g, and 3h**) than those with other alkylamino groups (i.e. **3a** and **3i**). The *para*-position substituted compounds (i.e. **3f** and **3g**) were more active than the *meta*-position substituted compounds (i.e. **3i** and **3j**).

All of the compounds were less potent in inhibiting BuChE than AChE. Especially, the most potent AChE inhibitors **3g** and **3h** were 1948-fold and 2437-fold more active inhibiting AChE than BuChE, respectively, being much more selective than donepezil.

The neuroprotective effect against H_2O_2-induced cell death was determined using MTT reduction assay in PC12 cell system and donepezil was as reference compound[20] (Fig. 2). H_2O_2 (400 μM) caused a significant decrease in cell viability (about 20.4%), but the pretreatment of cells with increasing concentrations of donepezil and compound **3g** inhibited H_2O_2-induced neurotoxicity and increased the cell viability. Both compound **3g** and donepezil showed almost the same neuroprotective effects at the higher concentration (0.1 and 0.5 μM).

To explore the possible binding conformation and protein–ligand interaction mode, a molecular modeling study of the optimum compound **3g** was performed using the Tripos FlexiDock program.[21] The Flexidock simulation indicated that the obtained 20 best-scoring ligand–AChE complex models have very similar 3D structures. Thus, only the lowest energy ligand–AChE complex model was selected for further analyses on the ligand–AChE interaction.

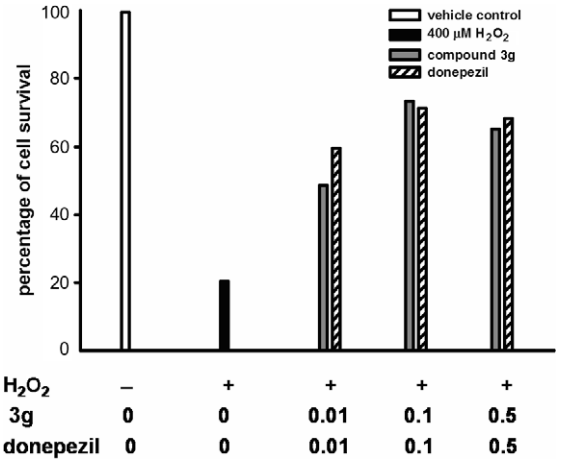


Figure 2. Neuroprotective effect of compound **3g** against H_2O_2-induced cell death in P12 cell system.

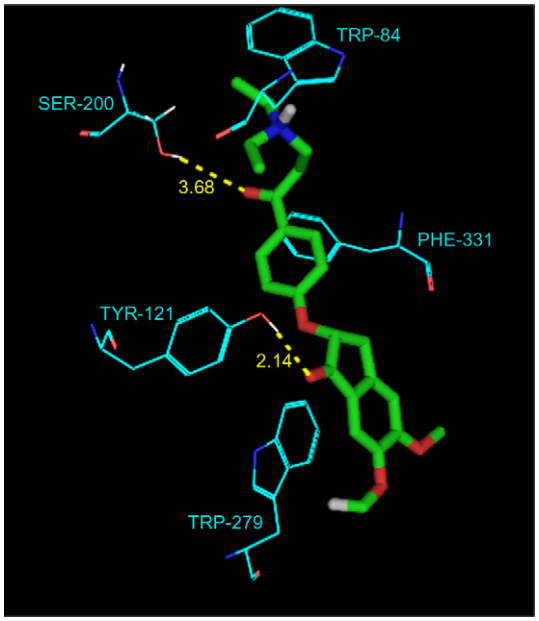


Figure 3. Interaction between ligand **3g** and AChE.

As it can be seen in Figure 3, there are some important interactions between ligand and AChE. The indanone ring occupies a position at the peripheral site and remains stacked onto the aromatic ring of Trp279 through a classical π–π stacking interaction, meanwhile, the carbonyl group of indanone moiety form a direct hydrogen-bond contact with OH group of Tyr121. Half up the gorge, the phenyl ring can establish a π–π interaction with the aromatic ring of Phe331. Noteworthy, the carbonyl group in the linker form the direct hydrogen bonds with OH group in Ser200. As expected, protonated nitrogen of the ligand is able to reach the bottom of the gorge and make a π-cation interaction with the pyrrole ring of Trp84, with a closer distance (4.1 Å) than the calculated distance between the compound **1** and AChE (4.7 Å). So, when the $COCH_2CH_2$ linker was introduced into the ligand, the compound **3g** assumed a slightly different orientation with respect to compound **1**. The carbonyl group in the linker formed a hydrogen bond and charged nitrogen established more favorable interaction with the AChE. And the subtle balance of different force makes the molecule bind well in the gorge and suggests the reason for its high inhibitory potency of AChE.

3. Conclusions

In summary, a number of 2-phenoxy-indan-1-one derivatives were designed, synthesized and tested for their biological activity, some of them exhibited more potent AChE inhibition activity and selectivity than donepezil. The preliminary structure–activity relationships and molecular modeling study provided further insight into interactions between the enzyme and its ligand. The neuroprotective effect against H_2O_2-induced cell death was revealed using MTT reduction assay. As a promising AChE inhibitor with outstanding potential, in vivo studies for **3g** is in progress.

4. Experimental

4.1. Chemistry

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. Melting points were obtained on a B-540 Buchi melting-point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Advance DMX 400 MHz spectrometer with TMS as the internal standard. Proton Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hz. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Elemental analyses were performed on a Flash EA 1112 elemental analyzer. Analytical TLC was carried out on Merck 0.2 mm precoated silica-gel (60 F-254) aluminum sheets, with visualization by irradiation with a UV lamp. Chromatographic separations were performed on silica-gel 60 (230–400 mesh).

2-Bromo-5,6-dimethoxy-indan-1-one **12** and key intermediates **6a–m** and **9a–n** were synthesized according to literature methods.

4.2. General procedure for the synthesis of 2a–m

Under N_2 atmosphere, to a solution of **6a–m** (0.32 mmol) and K_2CO_3 (0.38 mmol) in dry CH_3CN (3 mL) under reflux, was slowly added a solution of 2-bromo-5,6-dimethoxy-indan-1-one **12** (0.38 mmol) in CH_3CN (3 mL). The mixture was refluxed for 2 h. Then, it was cooled to room temperature and the solvent was removed under vacuum pressure. EtOAc (10 mL) and 2 N HCl (10 mL) was added to the residue and the aqueous solution was neutralized using 28% NH_4OH and extracted with CH_2Cl_2 (3× 10 mL). The combined organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, evaporated in vacuum. The residue was purified by a silica-gel column chromatography (PE/EtOAc/TEA = 100:100:1).

4.2.1. 5,6-Dimethoxy-2-(4-(2-(piperidin-1-yl)ethyl)phenoxy)-indan-1-one (2a)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(2-(piperidin-1-yl)ethyl)phenol (65.6 mg, 0.32 mmol) produced compound **2a** (90.4 mg, 71.5%) as white solid (mp 151–153 °C); MS (ESI): 396 $(M+1^+)^+$; ^{1}HNMR (δ, $CDCl_3$): 7.25 (s, 1H, H-7), 7.13 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.96 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.85 (s, 1H, H-4), 5.00–5.02 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.57–3.63 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.03–3.08 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.80 (t, 2H, CH_2CH_2N, J = 6 Hz), 2.54–2.67 (m, 6H, $PhCH_2CH_2$, piperidine-CH_2, H-2″ and H-6″), 1.66–1.69 (m, 4H, H-3″, H-5″), 1.49 (s, 2H, H-4″); IR (KBr), ν(cm^{-1}): 3018, 2930, 1701, 1587, 1513, 1358, 1269, 1120, 920, 861, 827, 689. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.68; H, 7.34; N, 3.58.

4.2.2. 5,6-Dimethoxy-2-(4-(2-(pyrrolidin-1-yl)ethyl)phenoxy)-indan-1-one (2b)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(2-(pyrrolidin-1-yl)ethyl)phenol (61.1 mg, 0.32 mmol) produced compound **2b** (82.6 mg, 67.8%) as white solid (mp 113–115 °C); MS (ESI): 382 $(M+1^+)^+$; ^{1}HNMR (δ, $CDCl_3$): 7.27 (s, 1H, H-7), 7.18 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 7.00 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.89 (s, 1H, H-4), 5.02–5.05 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 4.01 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.60–3.66 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.84 (t, 2H, CH_2CH_2N, J = 6 Hz), 2.74–2.78 (t, 2H, $PhCH_2CH_2$, J = 6 Hz), 2.67 (m, 4H, pyrrolidine-CH_2, H-2″, H-6″), 1.87 (m, 4H, H-3″, H-5″); IR (KBr), ν(cm^{-1}): 3008, 2936, 2786, 1711, 1605, 1504, 1461, 1234, 1081, 1012, 824. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.27; H, 7.16; N, 3.60.

4.2.3. 2-(4-(2-(Diethylamino)ethyl)phenoxy)-5,6-dimethoxy-indan-1-one (2c)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(2-(diethylamino)ethyl)phenol (61.8 mg, 0.32 mmol) produced compound **2c** (67.4 mg, 55.1%) as white solid (mp 84–86 °C); MS (ESI): 384 $(M+1^+)^+$; ^{1}HNMR (δ, $CDCl_3$): 7.24 (s,

1H, H-7), 7.12 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.96 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.85 (s, 1H, H-4), 4.99–5.03 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.57–3.63 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.04–3.09 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.72 (m, 4H, CH_2CH_2), 2.61 (q, 4H, NCH_2CH_3, J = 7.2 Hz), 1.06 (t, 6H, NCH_2CH_3, J = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): 200.0, 156.4, 156.3, 149.8, 146.1, 133.4, 129.5, 127.3, 115.6, 107.4, 104.8, 78.0, 56.2, 56.0, 54.7, 46.7, 33.7, 32.1, 11.4; IR (KBr), ν(cm^{-1}): 3075, 2964, 2803, 1710, 1589, 1512, 1468, 1011, 829. Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.71; H, 7.69; N, 3.68.

4.2.4. 2-(4-(2-(Ethyl(methyl)amino)ethyl)phenoxy)-5,6-dimethoxy-indan-1-one (2d)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(2-(ethyl(methyl)amino)ethyl)phenol (57.3 mg, 0.32 mmol) produced compound **2d** (92.1 mg, 78.3%) as white solid (mp 75–77 °C); MS (ESI): 370 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.24 (s, 1H, H-7), 7.14 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.97 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.86 (s, 1H, H-4), 5.00–5.03 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.57–3.63 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.03–3.08 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.79 (t, 2H, CH_2CH_2N, J = 6 Hz), 2.65 (t, 2H, CH_2CH_2N, J = 6 Hz), 2.57–2.62 (q, 2H, NCH_2CH_3, J = 7.6 Hz), 2.37 (s, 3H), 1.12 (t, 3H, NCH_2CH_3, J = 7.6 Hz); IR (KBr), ν(cm^{-1}): 3010, 2967, 2840, 2803, 1702, 1606, 1509, 1469, 1011, 861. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.57; H, 7.40; N, 3.68.

4.2.5. 5,6-Dimethoxy-2-(3-(2-(piperidin-1-yl)ethyl)phenoxy)-indan-1-one (2e)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(2-(piperidin-1-yl)ethyl)phenol (65.6 mg, 0.32 mmol) produced compound **2e** (89.7 mg, 71.3%) as white solid (mp 112–114 °C); MS (ESI): 396 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.20–7.25 (m, 2H, H-7, H-5′), 6.85–6.92 (m, 4H, H-4, H-2′, H-4′, H-6′), 5.02–5.05 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.60–3.65 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.04–3.09 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.81 (t, 2H, $PhCH_2CH_2N$), 2.59 (t, 2H, $PhCH_2CH_2N$), 2.515–2.521 (m, 4H, piperidine-CH_2, H-2″and H-6″), 1.63–1.68 (m, H-3″, H-5″), 1.47–1.48 (m, 2H, H-4″); IR (KBr), ν(cm^{-1}): 3015, 2956, 2872, 2780, 1705, 1586, 1503, 1450, 1012, 862. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.63; H, 7.41; N, 3.60.

4.2.6. 5,6-Dimethoxy-2-(3-(2-(pyrrolidin-1-yl)ethyl)phenoxy)-indan-1-one (2f)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(2-(pyrrolidin-1-yl)ethyl)phenol (61.1 mg, 0.32 mmol) produced compound **2f** (84.5 mg, 69.3%) as oil; MS (ESI): 382 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.20–7.24 (m, 2H, H-7, H-5′), 6.86–6.93 (m, 4H, H-4, H-2′, H-4′, H-6′), 5.02–5.05 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.60–3.66 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.01–3.06 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.88–2.90 (m, 4H, $PhCH_2CH_2N$), 2.807 (m, 4H, pyrrolidine-CH_2, H-2″, H-6″), 1.89–1.90 (m, 4H, pyrrolidine-CH_2, H-3″, H-5″); IR (KBr), ν(cm^{-1}): 3018, 2959, 2876, 2780, 1707, 1588, 1501, 1455, 1012, 862, 782. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.19; H, 7.17; N, 3.73.

4.2.7. 2-(3-(2-(Diethylamino)ethyl)phenoxy)-5,6-dimethoxy-indan-1-one (2g)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(2-(diethylamino)ethyl)phenol (61.8 mg, 0.32 mmol) produced compound 2 g (78.4 mg, 64%) as white solid (mp 59–63 °C); MS (ESI): 384 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.09–7.15 (m, 2H, H-7, H-5′), 6.75–6.80 (m, 4H, H-4, H-2′, H-4′, H-6′), 4.91–4.92 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.46–3.52 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 2.89–2.94 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.62 (m, 4H, $PhCH_2CH_2N$), 2.61 (q, 4H, NCH_2CH_3, J = 7.6 Hz), 1.06 (t, 6H, NCH_2CH_3, J = 7.6 Hz); IR (KBr), ν(cm^{-1}): 3015, 2963, 2878, 2781, 1709, 1590, 1503, 1458, 1015, 862. Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.67; H, 7.56; N, 3.69.

4.2.8. 2-(3-(2-(Ethyl(methyl)amino)ethyl)phenoxy)-5,6-dimethoxy-indan-1-one (2h)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(2-(ethyl(methyl)amino)ethyl)phenol (57.3 mg, 0.32 mmol) produced compound 2 h (67.0 mg, 56.7%) as oil. MS (ESI): 370 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.19–7.23 (m, 2H, H-7, H-5′), 6.84–6.91 (m, 4H, H-4, H-2′, H-4′, H-6′), 5.00–5.03 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.96 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.58–3.64 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.01–3.06 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.75 (t, 2H, CH_2CH_2N, J = 6 Hz), 2.60 (t, 2H, CH_2CH_2N, J = 6 Hz), 2.46 (q, 2H, NCH_2CH_3, J = 7.6 Hz), 2.30(s, 3H, NCH_3), 1.07 (t, 3H, NCH_2CH_3, J = 7.6 Hz); IR (KBr), ν(cm^{-1}): 2967, 2873, 2781, 1709, 1589, 1501, 1459, 1012, 862, 782. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.46; H, 7.48; N, 3.83.

4.2.9. 5,6-Dimethoxy-2-(4-(3-(piperidin-1-yl)propyl)phenoxy)-indan-1-one (2i)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(3-(piperidin-1-yl)propyl)phenol (70.1 mg, 0.32 mmol) produced compound **2i** (82.4 mg, 63.0%) as white solid (mp 110–112 °C);MS (ESI): 410 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.23 (s, 1H, H-7), 7.09 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.94 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.84 (s, 1H, H-4), 4.98–5.00 (dd, 1H, H-2, J = 7.6, 4.4 Hz),3.96 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.55–3.61 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.02–3.07 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.55 (t, 2H, $PhCH_2CH_2$, J = 6Hz), 2.32–2.39 (m, 6H, piperidine-CH_2, H-2″, H-6″, $CH_2CH_2CH_2N$), 1.79–1.83 (m, 2H, $PhCH_2CH_2CH_2N$), 1.57–1.62 (m, 4H, H-3″, H-5″), 1.43 (s, 2H, H-4″); IR (KBr), ν(cm^{-1}): 3005, 2935, 2830, 1710, 1605, 1512, 1452, 1010, 838. Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.45; H, 7.69; N, 3.47.

4.2.10. 5,6-Dimethoxy-2-(4-(3-(pyrrolidin-1-yl)propyl)phenoxy)-indan-1-one (2j)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(3-(pyrrolidin-1-yl)propyl)phenol (65.6 mg, 0.32 mmol) produced compound **2j** (74.6 mg, 59.0%) as white solid (mp 98–100 °C); MS (ESI): 396 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.24 (s, 1H, H-7), 7.11 (d, 2H, H-2′, H-6′, J = 8.4Hz), 6.95 (d, 2H, H-3′, H-5′, J = 8.4Hz), 6.85(s, 1H, H-4), 4.99–5.02 (dd, 1H, H-2, J = 7.6, 4.4Hz), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.56–3.62 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.04–3.09 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.59 (t, 2H, J = 6 Hz, $PhCH_2CH_2$), 2.45–2.51 (m, 6H, pyrrolidine-CH_2, H-2″, H-6″, $CH_2CH_2CH_2N$), 1.78–1.87 (m, 6H, H-3″, H-4″, $PhCH_2CH_2CH_2N$); IR (KBr), ν(cm^{-1}): 3008, 2934, 2803, 1710, 1605, 1503, 1456, 1010, 838, 774. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.56; H, 7.45; N, 3.50.

4.2.11. 2-(4-(3-(Diethylamino)propyl)phenoxy)-5,6-dimethoxy-indan-1-one (2k)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(3-(diethylamino)propyl)phenol (66.2 mg, 0.32 mmol) produced compound **2k** (72.9 mg, 57.4%) as white solid (mp 88–90 °C); MS (ESI): 398 ($M+1^+$)$^+$; ^{1}HNMR (δ, $CDCl_3$): 7.24 (s, 1H, H-7), 7.11 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.95 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.85 (s, 1H, H-4), 4.99–5.01 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.97 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.56–3.62 (dd, 1H,

H-3, J = 16.8, 7.6 Hz), 3.03–3.08 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.45 (m, 4H, PhCH_2CH$_2$CH$_2$, PhCH$_2$CH$_2$$CH_2$), 2.59 (q, 4H, N$CH_2CH_3$), 1.73–1.78 (m, 2H, PhCH$_2$$CH_2CH_2$N, J = 7.6 Hz), 0.99 (t, 6H, J = 7.6 Hz, CH$_3$); ^{13}C NMR (400 MHz, CDCl$_3$): 200.1, 156.3, 156.0, 149.8, 146.1, 135.1, 129.1, 127.2, 115.4, 107.3, 104.7, 77.9, 56.2, 56.0, 52.0, 46.6, 33.7, 32.7, 28.2, 11.2; IR (KBr), ν(cm^{-1}): 3067, 2968, 2801, 1707, 1606, 1503, 1451, 1011, 838. Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.58; H, 7.90; N, 3.59.

4.2.12. 5,6-Dimethoxy-2-(4-(4-(pyrrolidin-1-yl)butyl)phenoxy)-indan-1-one (2l)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(4-(pyrrolidin-1-yl)butyl)phenol (70.1 mg, 0.32 mmol) produced compound **2l** (81.1 mg, 62%) as white solid (mp 106–108 °C); MS (ESI): 410 (M+1$^+$)$^+$; ^{1}HNMR (δ, CDCl$_3$): 7.24 (s, 1H, H-7), 7.09 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.95 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.86 (s, 1H, H-4), 4.99–5.01 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH$_3$), 3.92 (s, 3H, OCH$_3$), 3.57–3.62 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.03–3.08 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.72 (m, 4H, pyrrolidine-CH$_2$, H-2″, H-6″), 2.58–2.63 (m, 4H, PhCH_2CH$_2$CH$_2$$CH_2$N), 1.86–1.90 (m, 4H, PhCH$_2$$CH_2$$CH_2CH_2$N), 1.64–1.66 (m, 4H, H-3″, H-4″); IR (KBr), ν(cm^{-1}): 2934, 2790, 1709, 1598, 1504, 1463, 1013, 826. Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 72.96; H, 7.76; N, 3.48.

4.2.13. 2-(4-(4-(Diethylamino)butyl)phenoxy)-5,6-dimethoxy-indan-1-one (2m)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(4-(diethylamino)butyl)phenol (70.7 mg, 0.32 mmol) produced compound **2m** (77.6 mg, 59%) as oil. MS (ESI): 412 (M+1$^+$)$^+$; ^{1}HNMR (δ, CDCl$_3$): 7.25 (s, 1H, H-7), 7.09 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.95 (d, 2H, H-3′, H-5′, J = 8.4 Hz), 6.86 (s, 1H, H-4), 5.00–5.02 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.98 (s, 3H, OCH$_3$), 3.93 (s, 3H, OCH$_3$), 3.58–3.63 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.04–3.09 (dd, 1H, H-3, J = 16.8, 4.4 Hz), 2.70–2.75 (m, 4H, NCH_2CH$_3$), 2.61–2.63 (m, 4H, PhCH_2CH$_2$CH$_2$$CH_2$N), 1.62–1.63 (m, 4H, PhCH$_2$$CH_2$$CH_2CH_2$N, J = 7.2 Hz), 1.13–1.17 (m, 6H, NCH_2CH$_3$, J = 7.2 Hz); ^{13}C NMR (400 MHz, CDCl$_3$): 200.1, 156.3, 156.0, 149.8, 146.1, 135.2, 129.1, 127.2, 115.4, 107.3, 104.7, 77.9, 56.2, 56.0, 52.2, 46.5, 34.6, 33.7, 29.3, 25.4, 10.7; IR (KBr), ν(cm^{-1}): 2930, 2862, 1707, 1604, 1506, 1468, 1011, 837. Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.83; H, 8.05; N, 3.58.

4.3. General procedure for the synthesis of 3a–n

Under N_2 atmosphere, to a solution of **9a–n** (0.32 mmol) and K_2CO_3 (0.38 mmol) in dry CH$_3$CN (3 mL), was slowly added a solution of 2-bromo-5,6-dimethoxy-indan-1-one **12** (0.38 mmol) in CH$_3$CN (3 mL). The mixture was refluxed for 0.5 h. Then, it was cooled to room temperature and the solvent was removed under vacuum pressure. The resulting residue was dissolved in methylene chloride (20 mL), washed successively with water and brine, dried over anhydrous Na_2SO_4 and evaporated to dryness, yielding syrup that was purified by silica-gel column chromatography(PE/EtOAc/TEA 100: 100: 1).

4.3.1. 5,6-Dimethoxy-2-(4-(2-(piperidin-1-yl)acetyl)phenoxy)-indan-1-one (3a)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(4-hydroxyphenyl)-2-(piperidin-1-yl)ethanone (70.1 mg, 0.32 mmol) produced compound **3a**(94.2 mg, 72.1%) as white solid (mp 58–60 °C); MS (ESI): 410 (M+1$^+$)$^+$; ^{1}HNMR (δ, CDCl$_3$): 8.03 (d, 2H, H-3′, H-5′, J = 8.8 Hz), 7.24 (s, 1H, H-7), 7.06 (d, 2H, H-2′, H-6′, J = 8.8 Hz), 6.88 (s, 1H, H-4), 5.11–5.13 (dd, 1H, H-2, J = 7.2, 3.6 Hz), 3.99 (s, 3H, OCH$_3$), 3.93 (s, 3H, OCH$_3$), 3.73 (s, 2H, COCH_2N), 3.63–3.69 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.53–2.57 (m, 4H, pyperidine-CH$_2$, H-2″, H-6″), 1.62–1.67 (m, 4H, H-3″, H-5″), 1.46–1.47 (m, 2H, H-4″); IR (KBr), ν(cm^{-1}): 2935, 2849, 1711, 1677, 1597, 1502, 1467, 1011, 837, 753. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.09; H, 6.53; N, 3.46.

4.3.2. 5,6-Dimethoxy-2-(4-(2-(pyrrolidin-1-yl)acetyl)phenoxy)-indan-1-one (3b)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(4-hydroxyphenyl)-2-(pyrrolidin-1-yl)ethanone (65.6 mg, 0.32 mmol) produced compound **3b** (80.9 mg, 64.2%) as white solid (mp 62–64 °C); MS (ESI): 396 (M+1$^+$)$^+$; ^{1}HNMR (δ, CDCl$_3$): 7.98 (d, 2H, H-3′, H-5′, J = 9.2 Hz), 7.23 (s, 1H, H-7), 7.06 (d, 2H, H-2′, H-6′, J = 9.2 Hz), 6.87 (s, 1H, H-4), 5.11–5.13 (dd, 1H, H-2, J = 7.2, 3.6 Hz), 3.99 (s, 2H, COCH_2N), 3.98 (s, 3H, OCH$_3$), 3.92 (s, 3H, OCH$_3$), 3.63–3.68 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.05–3.10 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.70–2.75 (m, 4H, NCH_2CH$_2$), 1.84–1.90 (m, 4H, NCH$_2$$CH_2$); IR (KBr), ν(cm^{-1}): 2928, 1715, 1673, 1598, 1501, 1465, 1009, 835, 751. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.47; H, 6.42; N, 3.55.

4.3.3. 2-(4-(2-(Diethylamino)acetyl)phenoxy)-5,6-dimethoxy-indan-1-one (3c)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 2-(diethylamino)-1-(4-hydroxyphenyl)ethanone (66.2 mg, 0.32 mmol) produced compound **3c** (74.2 mg, 58.4%) as white solid (mp 118–120 °C); MS (ESI): 398 (M+1$^+$)$^+$; ^{1}H NMR (δ, CDCl$_3$): 8.03 (d, 2H, H-3′, H-5′, J = 8.8 Hz), 7.22 (s, 1H, H-7), 7.06 (d, 2H, H-2′, H-6′, J = 8.8 Hz), 6.88 (s, 1H, H-4), 5.12–5.15 (dd, 1H, H-2, J = 7.2, 3.6 Hz), 3.99 (s, 3H, OCH$_3$), 3.93 (s, 3H, OCH$_3$), 3.89 (s, 2H, COCH_2N), 3.63–3.68 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.04–3.09 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.68 (q, 4H, NCH_2CH$_3$, J = 6.8 Hz), 1.07 (t, 6H, NCH$_2$$CH_3$, J = 6.8 Hz); ^{13}C NMR (400 MHz, CDCl$_3$): 199.2, 196.6, 161.8, 156.6, 150.0, 146.0, 130.5, 129.9, 127.1, 115.1, 107.4, 104.8, 77.6, 59.3, 56.3, 56.1, 47.7, 33.6, 11.7; IR (KBr), ν(cm^{-1}): 3058, 2836, 1702, 1678, 1605, 1500, 827. Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.26; H, 6.81; N, 3.59.

4.3.4. 2-(4-(2-(Ethyl(methyl)amino)acetyl)phenoxy)-5,6-dimethoxy-indan-1-one (3d)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 2-(ethyl(methyl)amino)-1-(4-hydroxyphenyl) ethanone (61.8 mg, 0.32 mmol) produced compound **3d** (77.8 mg, 63.5%) as white solid (mp 87–89 °C); MS (ESI): 384 (M+1$^+$)$^+$; ^{1}H NMR (δ, CDCl$_3$): 8.00 (d, 2H, H-3′, H-5′, J = 8.8 Hz), 7.21 (s, 1H, H-7), 7.05 (d, 2H, H-2′, H-6′, J = 8.8Hz), 6.86 (s, 1H, H-4), 5.10–5.12 (dd, 1H, H-2, J = 7.2, 3.6Hz), 3.97 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$), 3.77 (s, 2H, COCH_2N), 3.61–3.67 (dd, 1H, H-3, J = 16.8, 7.2Hz), 3.03–3.08 (dd, 1H, H-3, J = 16.8, 3.6Hz), 2.56–2.61 (q, 2H, NCH_2CH$_3$, J = 7.2Hz), 2.34 (s, 3H, NCH$_3$), 1.09 (t, 3H, NCH$_2$$CH_3$, J = 7.2Hz); IR (KBr), ν(cm^{-1}): 3072, 2966, 2935, 2836, 1700, 1675, 1601, 1502, 1011, 829. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.75; H, 6.66; N, 3.69.

4.3.5. 5,6-Dimethoxy-2-(4-(3-(piperidin-1-yl)propanoyl)phenoxy)-indan-1-one (3e)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(4-hydroxyphenyl)-3-(piperidin-1-yl)propan-1-one (74.6 mg, 0.32 mmol) produced compound **3e** (89.6 mg, 66.2%) as white solid (mp 96–98 °C); MS (ESI): 424 (M+1$^+$)$^+$; ^{1}H NMR (δ, CDCl$_3$): 7.97 (d, 2H, H-3′, H5′, J = 8Hz), 7.24 (s, 1H, H-7),

7.08 (d, 2H, H-2′, H-6′, J = 8 Hz), 6.88 (s, 1H, H-4), 5.12–5.15 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.64–3.70 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.15 (t, 2H, $COCH_2CH_2N$), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.2 Hz), 2.78 (t, 2H, $COCH_2CH_2N$), 2.46 (m, 4H, piperidine-CH_2, H-2″, H-6″), 1.58–1.63 (m, 4H, H-3″, H-5″), 1.45–1.46 (m, 2H, H-4″); IR (KBr), ν(cm^{-1}): 2934, 2840, 1711, 1676, 1598, 1502, 1467, 1011, 840, 753. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.76; H, 6.83; N, 3.51.

4.3.6. 5,6-Dimethoxy-2-(4-(3-(pyrrolidin-1-yl)propanoyl)phenoxy)-indan-1-one (3f)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(4-hydroxyphenyl)-3-(pyrrolidin-1-yl)propan-1-one (70.1 mg, 0.32 mmol) produced compound **3f** (86.4 mg, 66.0%) as white solid (mp 76–78 °C); MS (ESI): 410 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.97 (d, 2 H, H-3′, H-5′, J = 8 Hz), 7.24 (s, 1H, H-7), 7.08 (d, 2H, H-2′, H-6′, J = 8Hz), 6.88 (s, 1H, H-4), 5.13–5.15 (dd, 1H, H-2, J = 7.6, 4.4Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.64–3.70 (dd, 1H, H-3, J = 16.8, 7.6Hz), 3.25 (t, 2H, $COCH_2CH_2N$), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.2 Hz), 2.99 (t, 2H, $COCH_2CH_2N$), 2.69 (m, 4H, pyrrolidine-CH_2, H-2″, H-5″), 1.86 (m, 4H, H-3″, H-4″); IR (KBr), ν(cm^{-1}): 2961, 2835, 1709, 1674, 1598, 1502, 1461, 1011, 842. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.07; H, 6.80; N, 3.48.

4.3.7. 2-(4-(3-(Diethylamino)propanoyl)phenoxy)-5,6-dimethoxy-indan-1-one (3g)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(diethylamino)-1-(4-hydroxyphenyl)propan-1-one (70.7 mg, 0.32 mmol) produced compound **3g** (76.3 mg, 58.0%) as white solid (mp 94–96 °C); MS (ESI): 412 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.96 (d, 2H, H-3′, H-5′, J = 8.8 Hz), 7.24 (s, 1H, H-7), 7.08 (d, 2H, H-2′, H-6′, J = 8.4 Hz), 6.88 (s, 1H, H-4), 5.12–5.15 (dd, 1H, H-2, J = 7.2, 3.6 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.63–3.69 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.12 (t, 2H, $COCH_2CH_2N$), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.94 (t, 2H, $COCH_2CH_2N$), 2.60–2.65 (q, 4H, NCH_2CH_3, J = 6.8 Hz), 1.06–1.10 (t, 6H, NCH_2CH_3, J = 6.8 Hz); IR (KBr), ν(cm^{-1}): 2967, 2933, 2835, 1709, 1673, 1598, 1503, 1464, 1009, 839; ^{13}C NMR (400 MHz, $CDCl_3$): 199.1, 197.5, 161.8, 156.5, 149.9, 146.0, 130.5, 130.2, 127.0, 115.1, 107.3, 104.7, 77.5, 56.2, 56.0, 47.5, 46.6, 35.2, 33.5, 10.9; Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.78; H, 7.19; N, 3.29.

4.3.8. 2-(4-(3-(Ethyl(methyl)amino)propanoyl)phenoxy)-5,6-dimethoxy-indan-1-one (3h)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(ethyl(methyl)amino)-1-(4-hydroxyphenyl) propan-1-one (66.2 mg, 0.32 mmol) produced compound **3h** (62.2 mg, 49.2%) as oil; MS (ESI): 398 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.96 (d, 2H, H-3′, H5′, J = 8.8 Hz), 7.24 (s, 1H, H-7), 7.08 (d, 2H, H-2′, H-6′, J = 8.8 Hz), 6.88 (s, 1H, H-4), 5.12–5.15 (dd, 1H, H-2, J = 7.2, 4.0 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.64–3.70 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.12 (t, 2H, $COCH_2CH_2N$), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.82 (t, 2H, $COCH_2CH_2N$), 2.47–2.52 (q, 2H, NCH_2CH_2, J = 7.2 Hz), 2.90 (s, 3H, NCH_3), 1.07 (t, 3H, NCH_2CH_3, J = 7.2 Hz); IR (KBr), ν(cm^{-1}): 2968, 2838, 2790, 1711, 1672, 1598, 1502, 1467, 1011, 840, 753. Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.36; H, 6.81; N, 3.46.

4.3.9. 5,6-Dimethoxy-2-(3-(3-(pyrrolidin-1-yl)propanoyl)phenoxy)-indan-1-one (3i)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(3-hydroxyphenyl)-3-(pyrrolidin-1-yl)propan-1-one (70.1 mg, 0.32 mmol) produced compound **3i** (69.4 mg, 53%) as white solid (mp 76–78 °C); MS (ESI): 410 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.60–7.63 (m, 2H, H-7, H-2′), 7.38 (t, 1H, H-5′, J = 8.4 Hz), 7.24–7.28 (m, 2H, H-4′, H-6′), 6.86 (s, 1H, H-4), 5.08–5.11 (dd, 1H, H-2, J = 6.8, 3.6 Hz), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.64–3.70 (dd, 1H, H-3, J = 16.8, 6.8 Hz), 3.21 (t, 2H, $COCH_2CH_2N$, 7.6 Hz), 3.03–3.08 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.92 (t, 2H, $COCH_2CH_2N$, 7.6 Hz), 2.60 (m, 4H, pyrrolidine-CH_2, H-2″, H-5″), 1.81 (m, 4H, H-3″, H-4″); IR (KBr), ν(cm^{-1}): 2960, 2800, 1706, 1690, 1589, 1501, 1456, 1012, 753. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.23; H, 6.78; N, 3.45.

4.3.10. 2-(3-(3-(Diethylamino)propanoyl)phenoxy)-5,6-dimethoxy-indan-1-one (3j)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 3-(diethylamino)-1-(3-hydroxyphenyl)propan-1-one (70.7 mg, 0.32 mmol) produced compound **3j** (61.8 mg, 47.3%) as white solid (mp 101–103 °C); MS (ESI): 412 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.60–7.64 (m, 2H, H-7, H-2′), 7.38 (t, 1H, H-5′, J = 8.4 Hz), 7.25–7.29 (m, 2H, H-4′, H-6′), 6.87 (s, 1H, H-4), 5.09–5.12 (dd, 1H, H-2, J = 6.8, 3.6 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.65–3.71 (dd, 1H, H-3, J = 16.8, 6.8 Hz), 3.14–3.18 (t, 2H, $COCH_2CH_2N$, J = 6.8 Hz), 3.04–3.09 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.94 (t, 2H, $COCH_2CH_2N$, 7.6 Hz), 2.58 (q, 4H, NCH_2CH_3, J = 7.2 Hz), 1.05 (t, 6H, NCH_2CH_3, J = 7.2 Hz); IR (KBr), ν(cm^{-1}): 2958, 2803, 1705, 1688, 1589, 1506, 1458, 753. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.17; H, 7.16; N, 3.26.

4.3.11. 5,6-Dimethoxy-2-(4-(4-(piperidin-1-yl)butanoyl)phenoxy)-indan-1-one (3k)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(4-hydroxyphenyl)-4-(piperidin-1-yl)butan-1-one (79.0 mg, 0.32 mmol) produced compound **3k** (83.4 mg, 59.7%) as white solid (mp 52–54 °C); MS (ESI): 438 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.95 (d, 2H, H-3′, H-5′, J = 9.2 Hz), 7.24 (s, 1H, H-7), 7.06 (d, 2H, H-2′, H-6′, J = 9.2 Hz), 6.87 (s, 1H, H-4), 5.11–5.14 (dd, 1H, H-2, J = 7.6, 3.6 Hz), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.62–3.68 (dd, 1H, H-3, J = 17.2, 7.6 Hz), 3.05–3.10 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.96 (t, 2H, $COCH_2CH_2CH_2N$), 2.43–2.47 (m, 6H, piperidine-CH_2, H-2″, H-6″, $COCH_2CH_2CH_2N$), 1.96–2.04 (m, 2H, $CH_2CH_2CH_2$), 1.59–1.65 (m, 4H, H-3″, H-5″), 1.44–1.46(m, 2H, H-4″); ^{13}C NMR (400 MHz, $CDCl_3$): 199.2, 198.5, 161.7, 156.6, 150.0, 146.0, 130.8, 130.2, 127.2, 115.1, 107.4, 104.8, 77.6, 58.2, 56.3, 56.1, 54.2, 36.0, 33.6, 25.3, 24.0, 21.2; IR (KBr), ν(cm^{-1}): 3010, 2933, 2840, 1711, 1675, 1597, 1502, 1467, 1012, 835. Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.47; H, 7.14; N, 3.20. Found: C, 71.27; H, 7.19; N, 3.28.

4.3.12. 5,6-Dimethoxy-2-(4-(4-(pyrrolidin-1-yl)butanoyl)phenoxy)-indan-1-one (3l)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 1-(4-hydroxyphenyl)-4-(pyrrolidin-1-yl)butan-1-one (74.5 mg, 0.32 mmol) produced compound **3l** (52.0 mg, 38.4%) as white solid (mp 71–73 °C); MS (ESI): 424 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.96 (d, 2H, H-3′, H-5″, J = 8 Hz), 7.24 (s, 1H, H-7), 7.08 (d, 2H, H-2′, H-6′, J = 8 Hz), 6.88 (s, 1H, H-4), 5.12–5.15 (dd, 1H, H-2, J = 7.6, 4.4 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.63–3.69 (dd, 1H, H-3, J = 16.8, 7.6 Hz), 3.11–3.14 (t, 2H, $COCH_2CH_2CH_2N$), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.2 Hz), 2.97–2.99 (m, 4H, pyrrolidine-CH_2, H-2″, H-5″), 2.88 (t, 2H, $COCH_2CH_2CH_2N$), 2.12–2.19 (m, 2H, $CH_2CH_2CH_2$), 1.98–2.01 (m, 4H, NCH_2CH_2, H-3″, H-4″); IR (KBr), ν(cm^{-1}): 3071, 2940, 1714, 1603, 1504, 1010, 834, 770. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.73; H, 7.04; N, 3.17.

4.3.13. 2-(4-(4-(Diethylamino)butanoyl)phenoxy)-5,6-dimethoxy-indan-1-one (3m)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(diethylamino)-1-(4-hydroxyphenyl)butan-1-one (74.5 mg, 0.32 mmol) produced compound **3m** (63.9 mg, 47.2%) as oil; MS (ESI): 426 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.96 (d, 2H, H-3′, H-5′, J = 8.8 Hz), 7.24 (s, 1H, H-7), 7.08 (d, 2H, H-2′, H-6′, J = 9.2 Hz), 6.88 (s, 1H, H-4), 5.12–5.14 (dd, 1H, H-2, J = 6.8, 3.6 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.63–3.69 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.06–3.12 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 3.00–3.03 (t, 2H, $COCH_2CH_2CH_2N$), 2.63–2.72 (m, 6H, NCH_2CH_2, $COCH_2CH_2CH_2N$), 1.96–2.00 (m, 2H, $CH_2CH_2CH_2$), 1.10–1.14 (q, 6H, NCH_2CH_3, J = 7.2 Hz); IR (KBr), $\nu(cm^{-1})$: 2967, 2935, 1711, 1676, 1598, 1502, 1467, 1012, 835. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 69.83; H, 7.32; N, 3.16.

4.3.14. 2-(4-(4-(Ethyl(methyl)amino)butanoyl)phenoxy)-5,6-dimethoxy-indan-1-one (3n)

According to the general method, the reaction of **12** (103 mg, 0.38 mmol) with 4-(ethyl(methyl)amino)-1-(4-hydroxyphenyl) butan-1-one (70.7 mg, 0.32 mmol) produced compound **3n** (48.2 mg, 36.7%) as oil; MS (ESI): 412 $(M+1^+)^+$; ^1H NMR (δ, $CDCl_3$): 7.96 (d, 2H, H-3′, H-5′, J = 8.8 Hz), 7.24 (s, 1H, H-7), 7.08 (d, 2H, H-2′, H-6′, J = 9.2 Hz), 6.88 (s, 1H, H-4), 5.12–5.14 (dd, 1H, H-2, J = 6.8, 3.6 Hz), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.63–3.69 (dd, 1H, H-3, J = 16.8, 7.2 Hz), 3.12–3.16 (t, 2H, $COCH_2CH_2CH_2N$), 3.06–3.11 (dd, 1H, H-3, J = 16.8, 3.6 Hz), 2.82–2.86 (t, 2H, $COCH_2CH_2CH_2N$), 2.47–2.52 (q, 2H, NCH_2CH_3, J = 7.2 Hz), 2.29 (s, 3H, NCH_3), 1.96–2.00 (m, 2H, $CH_2CH_2CH_2$),1.07 (t, 3H, NCH_2CH_3, J = 7.2 Hz); IR (KBr), $\nu(cm^{-1})$: 3015, 2941, 1710, 1676, 1598, 1504, 1465, 1011, 838. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.76; H, 7.13; N, 3.26.

4.4. Biological activity and molecular modeling

4.4.1. Enzyme inhibition assays

AChE inhibition activities were measured by the spectrophotometric Ellman's method using rat cortex homogenate and rat serum as the resource of AChE and BuChE, respectively. The brain homogenate was preincubated with tetraisoprpyl pyrophosphoramido (isoOMPA) (0.04 mmol/L), a selective inhibitor of BuChE. For assay of AChE or BuChE activity, a reaction mixture containing acetylthiocholine iodide or butyrylthiocholine iodide, sodium phosphate buffer (pH 7.4), homogenate or serum, different concentration of the tested compounds was incubated at 37 °C for 15 min. The reaction was terminated by adding 3% sodium lauryl sulphate, then 0.2% 5,5′-dithio-bis (2-nitrobenzoic acid) to produce the yellow anion of 5-thio-2-nitro-benzoic acid. The values of IC_{50} were calculated by UV spectroscopy, from the absorbance changes at 450 nm.

4.4.2. Determination of cell viability

Undifferentiated PC12 cells were plated at a density of 5000 cells/well on 96-well plates, and cultured (37 °C, 5% CO_2). The cells were allowed to attach 1 day prior to the addition of NGF in complete medium. Compound **3g** (final concentration 0.01, 0.1, 0.5 μM) was added into wells 3 days after NGF incubation. 2 h later, cells were exposed to hydrogen dioxide (final concentration 400 μM) and plates were assayed 12 h later. Twenty microliters of stock 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT, Sigma) solution was added to each well (0.25 mg/mL) for another 4 h incubation. Afterwards, DMSO was added to each well and optical density (OD) was read at 570 nm by Thermo Multiskan Spectrum (Thermo Electron Corporation). The viability of untreated control cells was defined as 100%.[22,23]

4.4.3. Molecular modeling of compound 3g

Molecular modeling studies were performed using a flexible docking method with the Tripos FlexiDock program. The X-ray crystal structure of *Torpedo californica* AChE complexed with donepezil (PDB file identificator 1EVE)[24] was retrieved from the Protein Data Bank (PDB). A CB2-binding pocket was defined to cover all residues within 4 Å of the ligand in the initial AChE–ligand complex. All of the single bonds of residue side chains inside the defined AChE-binding pocket were regarded as rotatable or flexible bonds, and the ligand was allowed to rotate on all single bonds and move flexibly within the tentative-binding pocket. The atomic charges were recalculated using the Kollman all-atom approach for the protein and the Gasteiger–Hückel approach for the ligand. The binding interaction energy was calculated to include van der Waals, electrostatic, and torsional energy terms defined in the Tripos force field. The structure optimization was performed for 200,000 generations using a genetic algorithm and the 20 best-scoring ligand–protein complexes were kept for further analyses.

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