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Substituted propanolamines and alkylamines derived from fluoxetine as potent appetite suppressants☆

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Abstract—A series of propanolamine and alkylamine analogues of fluoxetine (**7**–**26**, **28**–**31**) were synthesized and assessed for their anorexigenic and antidepressant activities. Effect of various substituents at C-4 aryl position of fluoxetine has also been studied. Most of the propanolamine analogues (**7**–**13**, **16**–**26**) displayed significant anorexigenic activity but interestingly they were devoid of antidepressant activity whereas anorexigenic as well as antidepressant activity was retained in the alkylamine series (**28-31**). Compounds **10** and **26** emerged as the most active compound and anorexigenic activity was better (83.67% and 82.45%) compared to fluoxetine (81.25%).

1. Introduction

The last 25 years have seen a great increase in the incidence of obesity, both in the developed as well as in developing countries.[1,2] Despite the seeming inexorable progression of this disease, there have been limited advances in the pharmacotherapy of this condition. Obesity is a complicating factor in diabetes, cardiovascular disease and other disorders.[3] In the United States, it is estimated that over one third of the population is overweight.[4,5] These factors have led to a heavy demand for treatments resulting in long-term weight loss. Stimulant drugs such as amphetamine, fenfluramine, phentermine and ephedrine (Fig. 1) have been used to treat obesity, however, adverse effects and addiction have limited their use.[6,7]

In recent decades, the importance of serotonergic neurotransmission[8,9] in the control of appetite has become evident. Because of the role that serotonergic modulation can play in the regulation of food consumption, selective serotonin reuptake inhibitors (SSRIs) have been evaluated as antiobesity agents (Fig. 2). Fluoxetine,[10,11] a selective serotonin reuptake inhibitor,

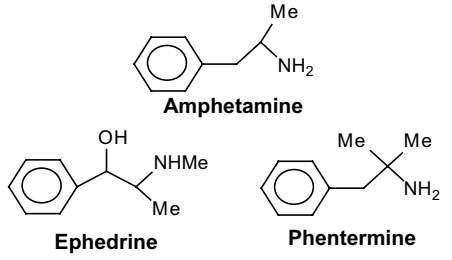

Figure 1. Representative stimulant drugs that have been marketed as anorectic agents.

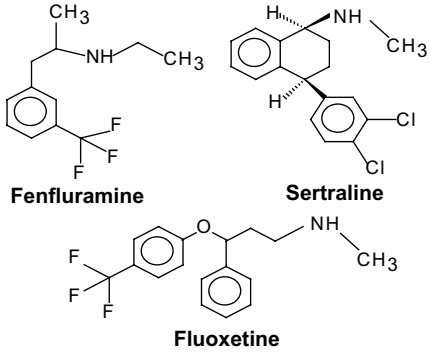

Figure 2. Chemical structures of serotonergic antiobesity agents.

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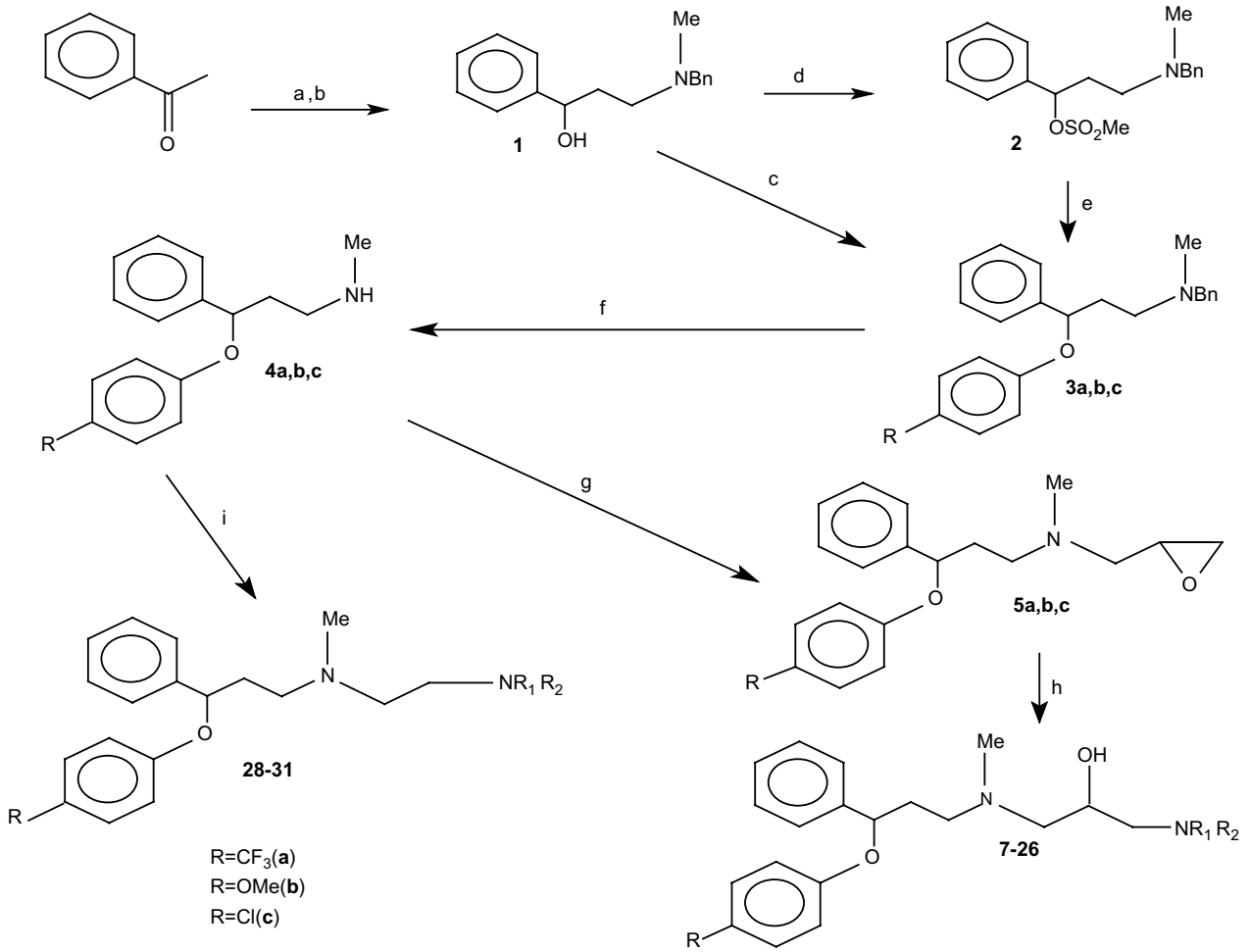
provided an important lead to develop SSRIs. The massive use of this drug as antidepressant and its adverse effects of appetite suppression[12,13] and concurrent loss of body weight indicated its use for the treatment of obesity.[14] Recent researches, more specifically implicate the 5-HT_{2C} receptor subtype as playing the key role in regulation of appetite.[15,16] Fluoxetine, the most potent anorexigenic of the SSRIs, is known to be the only member of this group with direct 5-HT_{2C} agonist activity in addition to its 5-HT reuptake blocking properties.[17] This prompted us to synthesize fluoxetine analogues that are devoid of antidepressant effect. We have previously demonstrated that introduction of aryloxypropanolyl substructure in fluoxetine resulted in appreciable loss of antidepressant effect.[18] Efforts to develop the SAR of this class of compounds have focussed on the substitution of NH and C-4 aryl functionalities of fluoxetine. It is interesting to note that linear propanolamine and alkylamine substructures in the NH portion caused a modest reduction in the antidepressant effect with the retention of anorexigenic effect. Thus we present herein the synthesis, pharmacological evaluation and SAR studies of derivatives **7**–**26**, **28**–**31** which are propanolamine and alkylamine analogues of fluoxetine.

2. Chemistry

The synthetic strategies adopted to obtain the target compounds (**7**–**26**, **28**–**31**) are depicted in Scheme 1. The key intermediate fluoxetine *N*-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine (**4a**, R = CF_3) was synthesized by reported method.[19,20] Mannich reaction of acetophenone and benzylmethylamine furnished the benzylmethylaminopropiophenone which on sodium borohydride reduction gave the hydroxy intermediate (**1**). Condensation of the hydroxy intermediate with *p*-chlorobenzotrifluoride gave **3a**[20] (R = CF_3), which on debenzylation gave the required intermediate **4a** (R = CF_3). The intermediates *N*-methyl-3-phenyl-3-(4-substituted phenoxy)propanamine (**4b** and **4c**) were prepared by treating the hydroxy compound (**1**) with methanesulfonylchloride to furnish the corresponding *O*-mesylate derivative (**2**) which on condensation with sodium salt of substituted phenol followed by debenzylation gave the required intermediate **4b** (R = OCH_3) and **4c** (R = Cl).[21] The key intermediates **4a**, **4b** and **4c** were alkylated with epichlorohydrin using K_2CO_3 at low temperature (0–4 °C) to furnish the corresponding epoxypropanes (**5a**, **5b** and **5c**). The ring opening of



Scheme 1. Synthesis of **7**–**26**, **28**–**31**. Reagents and conditions: (a) Bn·MeNH·HCl, $(CH_2O)_n$, propanol; (b) $NaBH_4$/MeOH; (c) NaH, *p*-chlorobenzotrifluoride, DMAC; (d) $MeSO_2Cl$, K_2CO_3, dry acetone; (e) 4-methoxyphenol/4-chlorophenol, NaOH, EtOH; (f) $ClCOOCH_3$, KOH, $NH_2NH_2{\cdot}H_2O$, *n*-propanol; (g) epichlorohydrin, K_2CO_3, absolute EtOH; (h) primary and secondary amines (**6a**–**l**), absolute EtOH; (i) chloroethylamines (**27a**–**d**), K_2CO_3, absolute EtOH.

epoxides **5a**, **5b** and **5c** with various primary and secondary amines (**6a**–**l**) in ethanol gave the desired propanolamines **7**–**26** (Scheme 1). The compound **28**–**31** were prepared by condensing fluoxetine (**4a**) with corresponding 2-chloroethylamines (**27a**–**d**) in presence of K_2CO_3.

3. Results and discussion

All the synthesized compounds (**7**–**26**, **28**–**31**) were screened for their effect on the gross behavior, anorexigenic and antidepressant activities by standard methods.[22] The results were compared to those of fluoxetine (Table 1). The tested compounds did not cause any marked changes in the gross behavior, whereas fluoxetine showed sign of stimulation. In antidepressant test, all the propanolamine analogues (**8**, **10**–**14**, **16**–**26**) except **7**, **9** and **15** were inactive where as the alkylamine analogues (**28**–**31**) showed varied activity (Table 1). Fluoxetine, the standard drug had shown 100% reversal of reserpine induced ptosis, sedation and crouching. All the propanolamine and alkylamine analogues of fluoxetine except **14** and **15** were found to have significant anorexigenic activity ($P \leqslant 0.05$) with significant decrease in the milk intake (22.45–95.42%) in comparison to the control group (Fig. 3). The most anorexigenic (95.42%) compound **31** also displayed significant antidepressant activity. Compound **10** and **26** emerged as the most active compound with 83.67% and 82.45% anorexigenic activity, respectively, which is better than the standard compound fluoxetine (81.25%). These compounds were devoid of unwanted antidepressant effects.

The above results indicate that the replacement of H of NHMe of fluoxetine by propanolamine and alkylamine moieties retained the anorexigenic activity and almost all compounds (except **14** and **15**) exhibited significant anorexigenic activity. Introduction of a propanolamine substructure (**7**–**26**) resulted in a dramatic loss of antidepressant effect in most of the compounds where as the antidepressant activity was maintained in the

Table 1. Pharmacological data of fluoxetine analogues (**7**–**26**, **28**–**31**) at 75 μmol/kg i.p.

S. No.	Compd No.	R	NR_1R_2	Anorexigenic activity		Antidepressant activity[a]	
				Milk intake in 15 min	M ± SEM of milk intake	Ptosis (% incidence)	Sedation and crouching (median score)
	Control			2.45	0.49 ± 0.01	0	0
1	**7**	CF_3	Pyrrolidino	0.95	0.19 ± 0.32*	40[b]	2[b]
2	**8**	CF_3	4-Phenylpiperazino	1.0	0.2 ± 0.05*	100	4
3	**9**	CF_3	Benzylmethylamino	0.75	0.15 ± 0.04*	40[b]	2[b]
4	**10**	CF_3	4-(2-Pyridyl)piperazino	0.4	0.08 ± 0.04*	100	4
5	**11**	CF_3	4-[(4-Fluoro)phenyl]piperazino	1.9	0.38 ± 0.04*	100	4
	Control			2.4	0.48 ± 0.02	0	0
6	**12**	CF_3	4-[(3-Chloro)phenyl]piperazino	0.95	0.19 ± 0.05*	100	4
7	**13**	CF_3	4-[(4-Methyl)phenyl]piperazino	1.1	0.22 ± 0.04*	100	4
8	**14**	CF_3	4-(3-α,α,α-Trifluorotolyl)piperazino	1.5	0.30 ± 0.07	100	4
9	**15**	CF_3	4-Methylpiperazino	1.9	0.38 ± 0.08	20[b]	1[b]
10	**16**	CF_3	2-Phenethylamino	0.95	0.19 ± 0.04*	100	4
	Control			2.4	0.48 ± 0.01	0	0
11	**17**	CF_3	Cyclohexylamino	1.65	0.33 ± 0.05*	100	4
12	**18**	CF_3	Morpholino	0.82	0.16 ± 0.02*	100	4
13	**19**	OMe	4-Phenylpiperazino	0.53	0.11 ± 0.04*	100	4
14	**20**	OMe	4-(2-Pyridyl)piperazino	0.85	0.17 ± 0.05*	100	4
15	**21**	OMe	4-[(3-Chloro)phenyl]piperazino	0.51	0.10 ± 0.01*	100	4
	Control			2.45	0.49 ± 0.01	0	0
16	**22**	Cl	4-Phenylpiperazino	0.58	0.12 ± 0.03*	100	4
17	**23**	Cl	4-(2-Pyridyl)piperazino	1.04	0.21 ± 0.06*	100	4
18	**24**	Cl	4-[(3-Chloro)phenyl]piperazino	0.57	0.11 ± 0.06*	100	4
19	**25**	Cl	Pyrrolidino	0.89	0.18 ± 0.05*	100	4
20	**26**	Cl	Morpholino	0.43	0.09 ± 0.02*	100	4
	Control			2.4	0.48 ± 0.01	0	0
21	**28**	CF_3	Pyrrolidino	0.77	0.15 ± 0.04*	60[b]	2[b]
22	**29**	CF_3	Morpholino	0.75	0.15 ± 0.03*	0[b]	0[b]
23	**30**	CF_3	Piperidino	0.75	0.15 ± 0.04*	40[b]	2[b]
24	**31**	CF_3	Dimethylamino	0.11	0.02 ± 0.01*	40[b]	2[b]
25	**Fluoxetine**			0.45	0.09 ± 0.02*	0[b]	0[b]
26	**Reserpine**			—	—	100	4

Control: saline treated mice.

[a] The antidepressant activity of the fluoxetine and the compounds (**7**–**26**, **28**–**31**) was evaluated after 3 h of reserpine treatment.

[b] Significant antidepressant activity.

* Significant anorexigenic activity ($P \leqslant 0.05$).

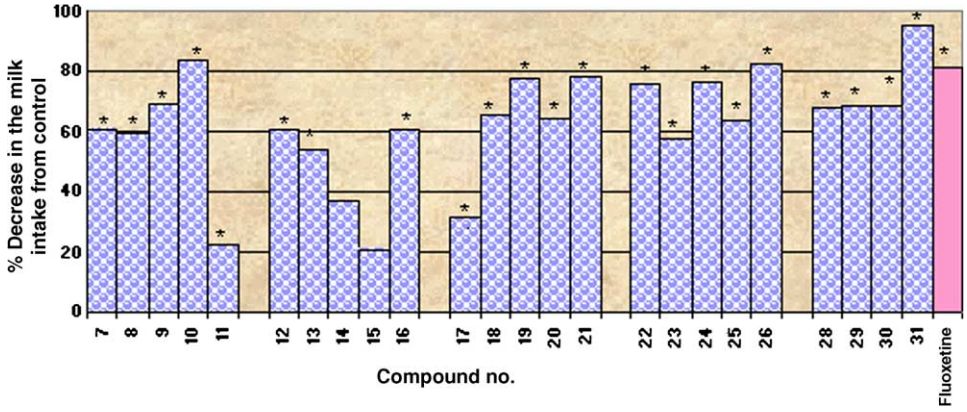


Figure 3. Percentage decrease in the milk intake of the tested compounds and the standard Fluoxetine based on control milk intake (100%). *Significant differences against the control group ($P \leqslant 0.05$).

compounds substituted with alkylamine moiety (**28**–**31**). From the SAR studies it appears that the propanolamine series has an edge over alkylamines in exhibiting better biological activity profile. However, the replacement of 4-CF_3 by 4-OMe (**19**–**21**) and 4-Cl (**22**–**26**) in the aromatic ring of propanolamine derivatives resulted in the enhancement of anorexigenic activity with optimum activity in compounds containing OCH_3 group in decreasing order by Cl and CF_3 (except compound **10**). Only the compound **10** behaved differently and was more active than its Cl (**23**) and OCH_3 analogues (**20**).

4. Conclusion

In summary we have carried out the synthesis of propanolamine and alkylamine derivatives of fluoxetine and assessed their anorexigenic and antidepressant activities and compared with that of fluoxetine. The data suggest that (1) introduction of diversity at NH side chain as illustrated by the introduction of propanolamine and alkylamine play a crucial role in determining their enhanced anorexigenic and decreased antidepressant activity (2) the introduction of substituents different from trifluoromethyl in the aryl ring (**19**–**26**) led to a substantial increase of anorexigenic activity with the maximum potency for OMe group followed in decreasing order by Cl and CF_3.

The data from biological evaluation suggest that fluoxetine propanolamines may be very promising candidate for further development as an anorexigenic agent. To acquire more information about structural requirements for enhancing anorexigenic and minimizing antidepressant effect, the synthesis of more new fluoxetine analogues with different substituents at other position is needed.

5. Experimental

5.1. Chemistry

Melting points were determined in open capillaries in an electrically heated block and are uncorrected. IR spectra of all the compounds were recorded on Perkin–Elmer AC-1 spectrophotometer. ^{1}H NMR spectra were recorded on Brucker WM 200 MHz spectrometer in deuterated solvents with TMS as internal reference. Mass spectra were recorded on Jeol JMS-D 300 spectrometer (70 eV). Microanalyses were determined on Carlo Erba EA-1108 element analyzer within ±0.4% of the theoretical value. Thin layer chromatography was performed on 7.5 × 3.0 cm. precoated silica gel plastic plates (Aldrich). For column chromatography, basic alumina from Acme's Synthetic Chemicals and silica gel of 60–120 mesh from Qualigen Fine Chemicals were used.

5.1.1. *N*-Methyl-3-phenyl-3-(4-trifluoromethylphenoxy)-propanamine (4a). *N*-Methyl-*N*-benzylmethyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine (**3a**) was prepared starting from acetophenone by known methods reported in the literature.[20] For debenzylation, a mixture of intermediate compound **3a** (5.9 g, 14 mmol) and methylchloroformate (2.7 g, 28 mmol) in benzene (30 mL) was refluxed for 12 h, cooled to room temperature. Reaction discontinued, sodium bicarbonate (5%, 10 mL) was added and benzene layer was separated and concentrated to an oil. A solution of this oil in propanol (30 mL), potassium hydroxide pellets (1.68 g, 30 mmol) and hydrazine hydrate (2.8 g, 56 mmol) was refluxed under stirring for 5 h, cooled and filtered. Filtrate was concentrated, water (30 mL) was added to it and extracted with ethyl acetate (30 mL × 3). Combined ethyl acetate extracts dried (anhyd. Na_2SO_4) and concentrated to give **4a** as an oil. Yield 65%; MS (FAB) *m*/*z*: 310 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02–2.21 (m, 2H, NCH_2–CH_2), 2.41 (s, 3H, NMe), 2.69–2.76 (t, 2H, J = 6.6 Hz, NCH_2), 5.26–5.32 (m, 1H, OCH), 6.87–6.92 (d, 2H, J = 8.6 Hz, ArH *ortho* to O), 7.25–7.34 (m, 5H, ArH), 7.40–7.44 (d, 2H, J = 8.6 Hz, ArH *ortho* to CF_3); IR (Neat): 2959, 2733, 2447, 1615, 1329, 1245, 1165, 1109, 843 cm^{-1}.

5.1.2. *N*-Methyl-3-phenyl-3-(4-methoxyphenoxy)propanamine (4b). *N*-Methyl-*N*-benzylmethyl-3-phenyl-3-(4-methoxyphenoxy)propanamine (**3b**) was prepared starting from acetophenone by known methods reported in the literature.[21] Debenzylation of **3b** was carried out in the same manner as in the case of **3a** and **4b** was

obtained as an oil. Yield 56%; MS (FAB) *m/z*: 272 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.14 (m, 2H, NCH_2–CH_2), 2.41 (s, 3H, NMe), 2.71–2.77 (m, 2H, NCH_2), 3.70 (s, 3H, OMe), 5.08–5.14 (m, 1H, OCH), 6.68–6.79 (m, 4H, ArH containing OMe group), 7.23–7.33 (m, 5H, ArH); IR (Neat): 3425, 2144, 1642, 1506, 1221, 769 cm^{-1}.

5.1.3. *N*-Methyl-3-phenyl-3-(4-chlorophenoxy)propanamine (4c). It was prepared in the same manner as **4b** using 4-chlorophenol instead of 4-methoxyphenol. Yield 58%; MS (FAB) *m/z*: 276 ($[M+1]^+$, 90%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99–2.18 (m, 2H, NCH_2–CH_2), 2.40 (s, 3H, NMe), 2.68–2.75 (t, 2H, J = 6.7 Hz, NCH_2), 5.15–5.21 (m, 1H, OCH), 6.71–6.78 (m, 2H, ArH *ortho* to O), 7.07–7.13 (m, 2H, ArH *ortho* to Cl), 7.24–7.33 (d, 5H, ArH); IR (Neat): 3781, 3454, 2364, 1637, 1489, 1236, 770 cm^{-1}.

5.1.4. General procedure for the preparation of oxiranylmethyl-[3-phenyl-3-(4-substituted phenoxy)propyl]-amine (5a, b, c). A mixture of *N*-Methyl-3-phenyl-3-(4-substituted phenoxy)propanamine (**4a**, **b**, **c**) (20 mmol), K_2CO_3 (30 mmol) and epichlorohydrin (40 mmol) was stirred in absolute alcohol (25 mL) at 0–4 °C for 17 h. After completion of reaction, the solid was filtered and the filtrate was concentrated to give an oily residue. The oily residue was treated with distilled water (25 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with water (10 mL × 2), dried over sodium sulfate and concentrated to give an oil which was chromatographed on a silica gel column to get the desired oxirane (**5a**, **b**, **c**) in good yield.

5.1.4.1. Oxiranylmethyl-[3-phenyl-3-(4-trifluoromethylphenoxy)propyl]amine (5a). Yield 70%; MS (FAB) *m/z*: 366 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.26 (m, 2H, $MeNCH_2$–CH_2), 2.29–2.36 (m, 4H, NMe, NCH_2 adjacent to epoxide ring), 2.44–2.47 (m, 1H, NCH_2 adjacent to epoxide ring), 2.54–2.73 (m, 4H, MeNCH_2, epoxide CH_2), 2.99 (m, 1H, epoxide CH), 5.28–5.34 (m, 1H, Ar–C*H*–O), 6.88–6.92 (d, 2H, J = 8.53 Hz, ArH *ortho* to O), 7.26–7.35 (m, 5H, ArH), 7.40–7.44 (d, 2H, J = 8.7 Hz, ArH *ortho* to CF_3); IR (Neat): 3420, 3250, 2932, 2835, 2364, 1508, 1347, 1221 cm^{-1}.

5.1.4.2. [3-(4-Methoxyphenoxy)-3-phenyl-propyl]-oxiranylmethylamine (5b). Yield 74%; MS (FAB) *m/z*: 328 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10–2.11 (m, 2H, $MeNCH_2$–CH_2), 2.28–2.33 (m, 4H, NMe, NCH_2 adjacent to epoxide ring), 2.43–2.49 (m, 1H, NCH_2 adjacent to epoxide ring), 2.57–2.65 (m, 4H, MeNCH_2 epoxide CH_2), 2.90 (m, 1H, epoxide CH), 5.06 (m, 1H, Ar–C*H*–O), 6.68–6.77 (m, 4H, ArH containing OMe group), 7.26–7.34 (m, 5H, ArH); IR (Neat): 3310, 2951, 2836, 1626, 1505, 1455, 1224, 1038, 757 cm^{-1}.

5.1.4.3. [3-(4-Chlorophenoxy)-3-phenyl-propyl]-oxiranylmethylamine (5c). Yield 80%; MS (FAB) *m/z*: 332 ($[M+1]^+$, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.9–2.1 (m, 2H, $MeNCH_2$–CH_2), 2.21–2.29 (m, 4H, NMe, NCH_2 adjacent to epoxide ring), 2.36–2.40 (m, 1H, NCH_2 adjacent to epoxide ring), 2.52–2.66 (m, 4H, MeNCH_2 epoxide CH_2), 3.33–3.36 (m, 1H, epoxide CH), 5.15 (m, 1H, Ar–C*H*–O), 6.67–6.72 (m, 2H, ArH *ortho* to O), 7.01–7.06 (m, 2H, ArH *ortho* to Cl), 7.17–7.28 (m, 5H, ArH); IR (Neat): 3435, 2958, 2854, 1635, 1596, 1489, 1456, 1238, 1092, 824 cm^{-1}.

5.1.5. General procedure for the preparation of propanolamine derivatives (7–26). A mixture of **5(a/b/c)** (1 mmol) and appropriate primary or secondary amines (**6a–l**) (1 mmol) in absolute alcohol (15 mL) was refluxed for 6–8 h. The solvent was distilled off to afford the crude product as an oil, which was purified on alumina column using ethyl acetate–hexane (25–30%) as an eluant.

5.1.5.1. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-pyrrolidino-propan-2-ol (7). With pyrrolidine (**6a**). Yield 56%; MS (FAB) *m/z*: 437 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75–1.78 (m, 4H, pyrrolidinyl CH_2), 2.00–2.17 (m, 2H, MeN–CH_2–CH_2), 2.29 (s, 3H, NMe), 2.32–2.66 (m, 10H, NCH_2), 3.74–3.77 (m, 1H, OH–C*H*), 5.23–5.32 (m, 1H, Ar–C*H*–O), 6.87–6.92 (d, 2H, J = 8.54 Hz, ArH *ortho* to O), 7.26–7.34 (m, 5H, ArH), 7.42 (d, 2H, J = 8.55 Hz, ArH *ortho* to CF_3); IR (Neat): 3431, 2961, 2803, 1615, 1326, 1252, 1116 cm^{-1}. Anal. Calcd for $C_{24}H_{31}F_3N_2O_2{\cdot}2HCl{\cdot}2.1H_2O$: C, 52.67; H, 6.80; N, 5.12. Found: C, 53.03; H, 6.91; N, 4.72.

5.1.5.2. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-(4-phenylpiperazino)-propan-2-ol (8). With 1-phenylpiperazine (**6b**). Yield 70%; MS (FAB) *m/z*: 528 ($[M+1]^+$, 80%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.97–2.15 (m, 2H, $MeNCH_2$–CH_2), 2.23 (s, 3H, NMe), 2.28–2.61 (m, 10H, NCH_2), 3.03–3.12 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.75 (m, 1H, OH–C*H*), 5.20–5.22 (m, 1H, Ar–C*H*–O), 6.75–6.85 (m, 5H, ArH *ortho* to O and ArH *ortho* and *para* to N), 7.15–7.25 (m, 7H, ArH), 7.33–7.38 (d, 2H, J = 8.58 Hz, ArH *ortho* to CF_3); IR (Neat): 3428, 2929, 2369, 1607, 1326, 1249, 1115 cm^{-1}. Anal. Calcd for $C_{30}H_{36}F_3N_3O_2{\cdot}3HCl{\cdot}1.8H_2O$: C, 53.82; H, 6.37; N, 6.28. Found: C, 53.71; H, 6.70; N, 5.93.

5.1.5.3. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-(*N*-methyl-*N*-benzylamino)-propan-2-ol (9). With benzylmethylamine (**6c**). Yield 58%; MS (FAB) *m/z*: 487 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99–2.03 (m, 2H, $MeNCH_2$–CH_2), 2.18 (s, 3H, NMe), 2.27 (m, 3H, *Me*N–CH_2–Ph), 2.31–2.59 (m, 6H, NCH_2), 3.48–3.60 (m, 2H, Ph–CH_2), 3.77–3.79 (m, 1H, OH–C*H*), 5.23–5.29 (m, 1H, Ar–C*H*–O), 6.87–6.91 (d, 2H, J = 8.62 Hz, ArH *ortho* to O), 7.26–7.34 (m, 10H, ArH), 7.39–7.43 (d, 2H, J = 8.65 Hz, ArH *ortho* to CF_3); IR (Neat): 3411, 2957, 2652, 1615, 1327, 1116, 763 cm^{-1}. Anal. Calcd for $C_{28}H_{33}F_3N_2O_2{\cdot}2HCl{\cdot}1.5H_2O$: C, 61.09; H, 6.91; N, 5.09. Found: C, 60.77; H, 6.77; N, 4.74.

5.1.5.4. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-[4-(2-pyridyl)piperazino]propan-2-ol (10). With 1-(2-pyridyl)piperazine (**6d**). Yield 71%; MS (FAB) *m/z*: 529 ($[M+1]^+$, 80%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.28–2.31 (m, 2H, $MeNCH_2$–CH_2), 2.57 (s, 3H, NMe), 2.62–2.98 (m, 10H, NCH_2), 3.57–3.62 (m, 4H, piperazinyl H's adjacent to pyridyl ring), 4.15 (m, 1H, OH–C*H*), 5.35–5.39 (m, 1H, Ar–C*H*–O), 6.62 (m, 2H, ArH), 6.89–6.92 (d, 2H, *J* = 8.1 Hz, ArH), 7.29–7.39 (m, 4H, ArH), 7.42–7.51 (m, 4H, ArH), 8.18–8.19 (m, 1H, ArH); IR (Neat): 3421, 1636, 1326, 1114, 762 cm^{-1}. Anal. Calcd for $C_{29}H_{35}F_3N_4O_2{\cdot}3HCl{\cdot}1.2H_2O$: C, 52.79; H, 6.13; N, 8.49. Found: C, 52.43; H, 5.77; N, 8.19.

5.1.5.5. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-[4-(4-fluorophenyl)piperazino]propan-2-ol (11). With 1-[(4-fluoro)phenyl]piperazine (**6e**). Yield 80%; MS (FAB) *m/z*: 546 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02–2.24 (m, 2H, $MeNCH_2$–CH_2), 2.37–2.50 (m, 7H, NMe, NCH_2), 2.58–2.77 (m, 6H, NCH_2), 3.08–3.14 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.87–3.89 (m, 1H, OH–C*H*), 5.30–5.31 (m, 1H, Ar–C*H*–O), 6.83–6.99 (m, 6H, ArH *ortho* to O, ArH containing F atom), 7.28–7.35 (m, 5H, ArH), 7.41–7.44 (d, 2H, *J* = 8.2 Hz, ArH *ortho* to CF_3); IR (Neat): 3429, 3020, 2964, 1721, 1216, 761 cm^{-1}. Anal. Calcd for $C_{30}H_{35}F_4N_3O_2{\cdot}3HCl{\cdot}0.75H_2O$: C, 53.89; H, 5.91; N, 6.29. Found: C, 53.62; H, 6.11; N, 6.18.

5.1.5.6. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-[4-(3-chlorophenyl)piperazino]propan-2-ol (12). With 1-[(3-chloro)phenyl]piperazine (**6f**). Yield 57%; MS (FAB) *m/z*: 561 (M^+, 95%), 562 ($[M+2]^+$, 35%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03–2.17 (m, 2H, $MeNCH_2$–CH_2), 2.31–2.38 (m, 7H, NMe, NCH_2), 2.53–2.62 (m, 6H, NCH_2), 3.14–3.19 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.8 (m, 1H, OH–C*H*), 5.35 (m, 1H, Ar–C*H*–O), 6.79–6.92 (m, 5H, ArH *ortho* to O, ArH *ortho para* to Cl), 7.26–7.45 (m, 8H, ArH); IR (Neat): 3432, 2958, 2830, 1723, 1595, 1454, 1326, 1250, 1117, 759 cm^{-1}. Anal. Calcd for $C_{30}H_{35}ClF_3N_3O_2{\cdot}3HCl{\cdot}0.5H_2O$: C, 52.94; H, 5.74; N, 6.18. Found: C, 52.64; H, 6.00; N, 6.56.

5.1.5.7. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-[4-(4-methylphenyl)piperazino]propan-2-ol (13). With 1-[(4-methyl)-phenyl]piperazine (**6g**). Yield 75%; MS (FAB) m/z: 541 (M^+, 100%); ^{1}H NMR (200MHz, $CDCl_3$): δ 2.15–2.21 (m, 2H, $MeNCH_2$–C H_2), 2.26 (s, 3H, NMe), 2.33–2.43 (m, 7H, ArCH_3, NCH_2), 2.55–2.71 (m, 6H, NCH_2), 3.10–3.15 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.9 (m, 1H, OH–C*H*), 5.27–5.29 (m, 1H, Ar–C*H*–O), 6.81–6.85 (d, 2H, J = 8.15Hz, ArH *ortho* to N), 6.88–6.92 (d, 2H, J = 8.6Hz, ArH *ortho* to O), 7.05–7.09 (d, 2H, J = 8.16Hz, ArH *ortho* to CH_3), 7.25–7.35 (m, 5H, ArH), 7.40–7.44 (d, 2H, J = 8.57Hz, ArH *ortho* to CF_3); IR (Neat): 3404, 2947, 2823, 1615, 1516, 1455, 1327, 1249, 1117, 758 cm^{-1}. Anal. Calcd for $C_{31}H_{38}F_3N_3O_2{\cdot}3HCl{\cdot}1.25H_2O$: C, 55.27; H, 6.46; N, 6.24. Found: C, 54.99; H, 6.78; N, 6.37.

5.1.5.8. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-[4-α,α,α-trifluorotolyl-piperazino]propan-2-ol (14). With 1-(3-α,α,α-trifluorotolyl)piperazine (**6h**). Yield 80%; MS (FAB) *m/z*: 596 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99–2.10 (m, 2H, $MeNCH_2$–CH_2), 2.22–2.38 (m, 7H, NMe, NCH_2), 2.43–2.63 (m, 6H, NCH_2), 3.11–3.16 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.85 (m, 1H, OH–C*H*), 5.18–5.25 (m, 1H, Ar–C*H*–O), 6.81–6.85 (d, 2H, *J* = 8.5 Hz, ArH *ortho* to O), 6.95–7.02 (m, 3H, ArH *ortho* and *para* to N), 7.19–7.27 (m, 6H, ArH), 7.33–7.38 (d, 2H, *J* = 8.68 Hz, ArH *ortho* to CF_3); IR (Neat): 3413, 2932, 2832, 1613, 1452, 1324, 1250, 1163, 1119, 758 cm^{-1}. Anal. Calcd for $C_{31}H_{35}F_6N_3O_2{\cdot}3HCl{\cdot}1.25H_2O$: C, 50.36; H, 5.66; N, 5.69. Found: C, 50.02; H, 5.77; N, 5.86.

5.1.5.9. 1-[*N*-Methyl-N-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-[4-methylpiperazino]-propan-2-ol (15). With 2-methylpiperazine (**6i**). Yield 64%; MS (FAB) *m/z*: 465 ($[M+1]^+$, 80%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7 (m, 2H, $MeNCH_2$–CH_2), 2.16 (m, 3H, NMe), 2.43–2.54 (m, 7H, piperazinyl NMe, NCH_2), 2.63–2.80 (m, 10H, NCH_2), 3.9 (m, 1H, OH–C*H*), 5.29–5.33 (m, 1H, Ar–C*H*–O), 6.87–6.91 (d, 2H, *J* = 8.54 Hz, ArH *ortho* to O), 7.32–7.33 (m, 5H, ArH), 7.40–7.44 (d, 2H, *J* = 8.66 Hz, ArH *ortho* to CF_3); IR (Neat): 3411, 2965, 2718, 2365, 1619, 1328, 1248, 1116 cm^{-1}. Anal. Calcd for $C_{25}H_{34}F_3N_3O_2{\cdot}3HCl{\cdot}1.75H_2O$: C, 49.50; H, 6.68; N, 6.93. Found: C, 49.13; H, 6.92; N, 7.09.

5.1.5.10. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-(2-phenethylamino)propan-2-ol (16). With 2-phenylethylamine (**6j**). Yield 65%; MS (FAB) *m/z*: 487 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.01–2.21 (m, 2H, $MeNCH_2$–CH_2), 2.26–2.41 (m, 4H, NMe, NCH_2), 2.47–2.69 (m, 4H, NCH_2), 2.75–2.82 (m, 4H, ArCH_2, NCH_2), 3.69–3.73 (m, 1H, OH–C*H*), 5.19–5.27 (m, 1H, Ar–C*H*–O), 6.86–6.90 (d, 2H, *J* = 8.56 Hz, ArH *ortho* to O), 7.17–7.32 (m, 5H, ArH), 7.39–7.44 (d, 2H, *J* = 8.66 Hz, ArH *ortho* to CF_3); IR (Neat): 3425, 2960, 1616, 1456, 1327, 1246, 1116, 759 cm^{-1}. Anal. Calcd for $C_{28}H_{33}F_3N_2O_2{\cdot}2HCl{\cdot}0.8H_2O$: C, 58.59; H, 6.38; N, 4.88. Found: C, 58.29; H, 6.61; N, 4.67.

5.1.5.11. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-cyclohexylaminopropan-2-ol (17). With cyclohexylamine (**6k**). Yield 56%; MS (FAB) *m/z*: 465 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19–1.25 (m, 6H, cyclohexyl H's), 1.72 (m, 2H, cyclohexyl H's), 1.90–2.14 (m, 4H, cyclohexyl H's, $MeNCH_2$–CH_2), 2.28 (s, 3H, NMe), 2.33–2.64 (m, 6H, NCH_2), 2.79 (m, 1H, NH–C*H*), 3.87–3.91 (m, 1H, OH–C*H*), 5.22–5.28 (m, 1H, Ar–C*H*–O), 6.87–6.91 (d, 2H, *J* = 8.61 Hz, ArH *ortho* to O), 7.30–7.34 (m, 5H, ArH), 7.40–7.44 (d, 2H, *J* = 8.65 Hz, ArH *ortho* to CF_3); IR (Neat): 3415, 2940, 2817, 2365, 1595, 1349 cm^{-1}. Anal. Calcd for $C_{26}H_{35}F_3N_2O_2{\cdot}2HCl{\cdot}0.5H_2O$: C, 57.14; H, 6.96; N, 5.13. Found: C, 57.30; H, 7.28; N, 5.38.

5.1.5.12. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)propyl)amino]-3-morpholinopropan-2-ol (18). With morpholine (**6l**). Yield 64%; MS (FAB) *m/z*: 452 (M^+, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99–2.17 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.27–2.61 (m, 13H, NMe, NCH_2), 3.66–3.71 (m, 5H, OH–C*H*, OCH_2), 5.26–5.32 (m, 1H, Ar–C*H*–O), 6.87–6.91 (d, 2H, J = 8.62 Hz, ArH *ortho* to O), 7.28–7.34 (m, 5H, ArH), 7.39–7.44 (d, 2H, J = 8.67 Hz, ArH *ortho* to CF_3); IR (Neat): 3417, 2926, 2856, 1617, 1326, 1253, 1114, 760 cm^{-1}. Anal. Calcd for $C_{24}H_{31}F_3N_2O_3$·2HCl·0.6H_2O: C, 62.23; H, 6.96; N, 6.05. Found: C, 61.91; H, 6.64; N, 5.69.

5.1.5.13. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-methoxyphenoxy)propyl)amino]-3-(4-phenylpiperazino)-propan-2-ol (19). With 1-phenylpiperazine (**6b**). Yield 56%; MS (FAB) *m/z*: 490 ($[M+1]^+$, 65%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.97–2.16 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.30–2.38 (s, 7H, NMe, NCH_2), 2.58–2.71 (m, 6H, NCH_2), 3.17 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.68 (s, 3H, OMe), 3.79–3.81 (m, 1H, OH–C*H*), 5.09–5.11 (m, 1H, Ar–C*H*–O), 6.68–6.78 (m, 4H, ArH containing OMe group), 6.85–6.94 (m, 3H, ArH *ortho* and *para* to N), 7.22–7.33 (m, 7H, ArH); IR (Neat): 2947, 2830, 2364, 1670, 1505, 1227, 757 cm^{-1}. Anal. Calcd for $C_{30}H_{39}N_3O_3$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.84; H, 8.29; N, 8.74.

5.1.5.14. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-methoxyphenoxy)propyl)amino]-3-[4-(2-pyridyl)piperazino-propan-2-ol (20). With 1-(2-pyridyl)piperazine (**6d**). Yield 55%; MS (FAB) *m/z*: 491 ($[M+1]^+$, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.27–2.38 (m, 7H, NMe, NCH_2), 2.53–2.66 (m, 4H, NCH_2), 2.66–3.00 (m, 2H, NCH_2), 3.47–3.54 (m, 4H, piperazinyl H's adjacent to pyridyl ring), 3.69 (s, 3H, OMe), 3.75 (m, 1H, OH–C*H*), 5.1 (m, 1H, Ar–C*H*–O), 6.58–6.67 (m, 2H, ArH), 6.72–6.76 (m, 4H, ArH), 7.27–7.33 (m, 4H, ArH), 7.42–7.47 (m, 2H, ArH), 8.17–8.19 (m, 1H, ArH); IR (Neat): 3416, 2928, 2843, 1596, 1504, 1483, 1438, 1229, 1037, 772 cm^{-1}. Anal. Calcd for $C_{29}H_{38}N_4O_3$·0.5H_2O: C, 71.02; H, 7.82; N, 11.22. Found: C, 71.17; H, 7.52; N, 10.93.

5.1.5.15. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-methoxyphenoxy)propyl)amino]-3-[4-(3-chlorophenyl)piperazino]propan-2-ol (21). With 1-[(3-chloro)phenyl]piperazine (**6f**). Yield 59%; MS (FAB) *m/z*: 525 ($[M+1]^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.29–2.39 (m, 7H, NMe, NCH_2), 2.55–2.65 (m, 6H, NCH_2), 3.14–3.19 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.69 (s, 3H, OMe), 3.85 (m, 1H, OH–C*H*), 5.29 (m, 1H, Ar–C*H*–O), 6.68–6.87 (m, 8H, ArH containing OMe, ArH containing Cl), 7.11–7.34 (m, 5H, ArH); IR (Neat): 3658, 3425, 2945, 2832, 2365, 1665, 1594, 1224, 768 cm^{-1}. Anal. Calcd for $C_{30}H_{38}ClN_3O_3$·3HCl: C, 56.87; H, 6.48; N, 6.64. Found: C, 57.06; H, 6.68; N, 6.64.

5.1.5.16. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-chlorophenoxy)propyl)amino]-3-(4-phenylpiperazino)-propan-2-ol (22). With 1-phenylpiperazine (**6b**). Yield 80%; MS (FAB) *m/z*: 493 (M^+, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.17 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.27–2.41 (m, 7H, NMe, NCH_2), 2.51–2.68 (m, 6H, NCH_2), 3.15–3.20 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.9 (m, 1H, OH–C*H*), 5.17 (m, 1H, Ar–C*H*–O), 6.74–6.78 (d, 2H, J = 8.84 Hz, ArH), 6.81–6.94 (m, 3H, ArH), 7.09–7.13 (d, 2H, J = 8.92 Hz, ArH *ortho* to Cl), 7.22–7.33 (m, 7H, ArH); IR (Neat): 3438, 2824, 2364, 1637, 1491, 1236, 757 cm^{-1}. Anal. Calcd for $C_{29}H_{36}ClN_3O_2$·3HCl·1.5H_2O: C, 55.24; H, 6.67; N, 6.67. Found: C, 55.46; H, 7.05; N, 6.48.

5.1.5.17. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-chlorophenoxy)propyl)amino]-3-[4-(2-pyridyl)piperazino]propan-2-ol (23). With 1-(2-pyridyl)piperazine (**6d**). Yield 55%; MS (FAB) *m/z*: 494 (M^+, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.96–2.00 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.30–2.41 (m, 7H, NMe, NCH_2), 2.49–2.68 (m, 6H, NCH_2), 3.46–3.55 (m, 4H, piperazinyl H's adjacent to pyridyl ring), 3.9 (m, 1H, OH–C*H*), 5.2 (m, 1H, Ar–C*H*–O), 6.59–6.66 (m, 2H, ArH), 6.73–6.78 (d, 2H, J = 8.8 Hz, ArH *ortho* to O), 7.08–7.13 (d, 2H, J = 8.8 Hz, ArH *ortho* to Cl), 7.28–7.33 (m, 5H, ArH), 7.44–7.48 (m, 1H, ArH), 8.17–8.20 (m, 1H, ArH); IR (Neat): 3632, 3413, 2943, 2834, 2363, 1594, 1486, 1439, 1240, 769 cm^{-1}. Anal. Calcd for $C_{28}H_{35}ClN_4O_2$·4HCl: C, 52.46; H, 6.09; N, 8.74. Found: C, 52.59; H, 6.48; N, 8.73.

5.1.5.18. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-chlorophenoxy)propyl)amino]-3-[4-(3-chlorophenyl)piperazino]propan-2-ol (24). With 1-[(3-chloro)phenyl]piperazine (**6f**). Yield 66%; MS (FAB) *m/z*: 528 (M^+, 40%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99–2.16 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.29–2.41 (m, 7H, NMe, NCH_2), 2.50–2.65 (m, 6H, NCH_2), 3.10–3.19 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.9 (m, 1H, OH–C*H*), 5.15–5.19 (m, 1H, Ar–C*H*–O), 6.74–6.86 (m, 5H, ArH), 7.09–7.15 (m, 2H, ArH), 7.19–7.33 (m, 6H, ArH); IR (Neat): 3430, 2943, 2826, 2364, 1594, 1488, 1238, 1095 cm^{-1}. Anal. Calcd for $C_{29}H_{35}Cl_2N_3O_2$·3HCl: C, 54.59; H, 5.96; N, 6.59. Found: C, 54.80; H, 6.32; N, 6.20.

5.1.5.19. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-chlorophenoxy)propyl)amino]-3-pyrrolidino-propan-2-ol (25). With pyrrolidine (**6a**). Yield 75%; MS (FAB) *m/z*: 403 (M^+, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73–1.76 (m, 4H, pyrrolidinyl CH_2), 2.00 (m, 2H, MeN–CH_2–C*H*$_2$), 2.27–2.37 (s, 5H, NMe, NCH_2), 2.44–2.60 (m, 8H, NCH_2), 3.9 (m, 1H, OH–C*H*), 5.2 (m, 1H, Ar–C*H*–O), 6.73–6.77 (m, 2H, J = 8.9 Hz, ArH *ortho* to O), 7.08–7.12 (d, 2H, J = 8.9 Hz, ArH *ortho* to Cl), 7.28–7.33 (m, 5H, ArH); IR (Neat): 3453, 2959, 2365, 1646, 1489, 1238, 701 cm^{-1}. Anal. Calcd for $C_{23}H_{31}ClN_2O_2$·2HCl·0.5H_2O: C, 56.97; H, 7.02; N, 5.78. Found: C, 56.86; H, 7.23; N, 5.49.

5.1.5.20. 1-[*N*-Methyl-*N*-(3-phenyl-3-(4-chlorophenoxy)propyl)amino]-3-morpholinopropan-2-ol (26). With morpholine (**6l**). Yield 56%; MS (FAB) *m/z*: 418 (M^+, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (m, 2H, $MeNCH_2$–C*H*$_2$), 2.26–2.58 (m, 13H, NMe, NCH_2), 3.64–3.71 (m, 5H, OCH_2, OH–C*H*), 5.15–5.18 (m, 1H,

Ar–C*H*–O), 6.73–6.77 (d, 2H, $J = 8.94$ Hz, ArH *ortho* to O), 7.08–7.12 (d, 2H, $J = 8.94$ Hz, ArH *ortho* to Cl), 7.24–7.33 (m, 5H, ArH); IR (Neat): 3439, 1638, 1490, 1217, 761 cm^{-1}. Anal. Calcd for $C_{23}H_{31}ClN_2O_3 \cdot 2HCl \cdot H_2O$: C, 54.17; H, 6.87; N, 5.49. Found: C, 54.34; H, 7.19; N, 5.59.

5.1.6. General procedure for the preparation of compounds 28–31. A mixture of fluoxetine (**4a**) (1 mmol), chloroethylamino compound (**27a–d**) (2 mmol) and K_2CO_3 (1.5 mmol) in acetonitrile (15 mL) was refluxed at 100–110 °C for 8 h. The inorganic solid was filtered. Concentration of the filtrate afforded the crude product which was purified on alumina column using ethyl acetate–hexane (25–30%) as an eluant to give **28–31** as an oil.

5.1.6.1. [3-Phenyl-3-(4-α,α,α-trifluoromethylphenoxy)-propyl]-(2-pyrrolidin-1-yl-ethyl)-amine(28). With 1-(2-Chloroethyl)pyrrolidine hydrochloride (**27a**). Yield 69%; MS (FAB) *m/z*: 407 ($[M+1]^+$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.89–1.93 (m, 4H, pyrrolidinyl CH_2), 2.04–2.10 (m, 2H, $MeNCH_2$–C*H*$_2$–CH), 2.31 (s, 3H, NMe), 2.31–3.03 (m, 10H, NCH_2), 5.4 (m, 1H, O–CH), 6.92–6.96 (d, 2H, $J = 8.48$ Hz, ArH *ortho* to O), 7.28–7.36 (m, 5H, ArH), 7.41–7.45 (d, 2H, $J = 8.72$ Hz, ArH *ortho* to CF_3); IR (Neat): 2927, 2797, 1615, 1458, 1326, 1252, 1118, 1066, 756 cm^{-1}. Anal. Calcd for $C_{23}H_{29}F_3N_2O \cdot 2HCl$: C, 57.62; H, 6.47; N, 5.85. Found: C, 57.23; H, 6.57; N, 5.48.

5.1.6.2. (2-Morpholin-4-yl-ethyl)-[3-phenyl-3-(4-α,α,α-trifluoromethyl phenoxy)-propyl]-amine (29). With 4-(2-Chloroethyl)morpholine hydrochloride (**27b**). Yield 52%; MS (FAB) *m/z*: 423 ($[M+1]^+$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.98–2.17 (m, 2H, $MeNCH_2$–C*H*$_2$–CH), 2.26 (s, 3H, NMe), 2.37–2.60 (m, 10H, NCH_2), 3.66–3.68 (t, 4H, $J = 4.7$ Hz, CH_2–O–CH_2), 5.25–5.32 (m, 1H, O–CH), 6.87–6.92 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to O), 7.27–7.34 (m, 5H, ArH), 7.40–7.44 (d, 2H, $J = 8.64$ Hz, ArH *ortho* to CF_3); IR (Neat): 3435, 2937, 2864, 2542, 2422, 2365, 1612, 1456, 1328, 1114, 700 cm^{-1}. Anal. Calcd for $C_{23}H_{29}F_3N_2O_2 \cdot 2HCl \cdot 0.75H_2O$: C, 54.28; H, 6.39; N, 5.51. Found: C, 54.05; H, 6.72; N, 5.12.

5.1.6.3. [3-Phenyl-3-(4-α,α,α-trifluoromethylphenoxy)-propyl]-(2-piperidin-1-yl-ethyl)-amine (30). With 1-(2-Chloroethyl)piperidine hydrochloride (**27a**). Yield 41%; MS (FAB) *m/z*: 421 ($[M+1]^+$, 86%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.42–1.44 (m, 2H, piperidinyl CH_2), 1.63–1.65 (m, 4H, piperidinyl CH_2), 1.98–2.04 (m, 2H, $MeNCH_2$–C*H*$_2$–CH), 2.28 (s, 3H, NMe), 2.43–2.69 (m, 10H, NCH_2), 5.27–5.34 (m, 1H, O–CH), 6.88–6.92 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to O), 7.28–7.35 (m, 5H, ArH), 7.40–7.45 (d, 2H, $J = 8.6$ Hz, ArH *ortho* to CF_3); IR (Neat): 3434, 2941, 2456, 2367, 1609, 1329, 1115, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{31}F_3N_2O \cdot 2HCl$: C, 58.42; H, 6.69; N, 5.68. Found: C, 58.06; H, 6.86; N, 5.33.

5.1.6.4. *N*,*N*-Dimethyl-*N*′-[3-phenyl-3-(4-α,α,α-trifluoromethylphenoxy)-propyl]-ethane-1,2-diamine (31). With (2-Dimethylamino)ethylchloride hydrochloride (**27d**). Yield 56%; MS (FAB) *m/z*: 381 ($[M+1]^+$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 2.20–2.31 (m, 11H, *Me* NCH_2 C*H*$_2$–CH, *Me* N–*Me*), 2.47–2.60 (m, 6H, NCH_2), 5.33–5.37 (m, 1H, O–CH), 6.88–6.92 (d, 2H, $J = 8.5$ Hz, ArH *ortho* to O), 7.26–7.34 (m, 5H, ArH), 7.40–7.44 (d, 2H, $J = 8.7$ Hz, ArH *ortho* to CF_3); IR (Neat): 3776, 3446, 2933, 2856, 2366, 1618, 1460, 1326, 1251, 1116, 764 cm^{-1}. Anal. Calcd For $C_{21}H_{27}F_3N_2O \cdot 2HCl$: C, 55.63; H, 5.96; N, 6.18. Found: C, 55.17; H, 5.89; N, 6.56.

5.2. Pharmacology

The pharmacological activity of the compounds reported here was examined at 75 mol/kg doses in a group of five Swiss mice (weighing 16–20 g) of either sex. Each mouse was individually caged and pretreated with graded doses of the compound. The compounds were administered intraperitoneally either as aqueous solution or suspension in gum acacia. For gross behavior observation, the mice were examined continuously for 3 h after i.p. administration of compounds, then every 30 min for next 3 h and finally after 24 h. CNS stimulation was judged by increased spontaneous motor activity (SMA), pilorection, exopthalamous, clonic or tonic convulsions. Reduced SMA, sedation, ptosis, crouching and catalepsy assessed CNS depression. Autonomic effects—pilorection, urination, defecation, salivation and lachrymation were also observed. For anorexigenic activity, mice were deprived of food for 24 h before the administration of compounds. After 1 h of i.p. administration of compounds, each mouse in a group of five was offered 0.5 mL of the milk (sweetened and reconstituted as 25% aqueous suspension from powdered milk manufactured by Nestle) for 15 min. The milk intake of the control group and the treated group were noted and the significance of difference between them was determined by unpaired student's *t* test (two tailed *P* value) with Welch correction wherever required. The results were compared to those of fluoxetine (Table 1, Fig. 3). For antidepressant testing, groups of five mice each were administered 2.5 mg/kg. i.p. dose of reserpine. After 3 h, in an attempt to look for reversal of reserpine induced effect, for example, reduced locomotor activity, ptosis, sedation and crouching, each mouse was administered 75 μmol/kg. i.p. dose of the compound. Antidepressant activity of the compounds was evaluated using Chi Square test with Yate's correction (one sided *P* value) (for ptosis) and nonparametric statistical analysis by Mann Whitney 'U' test (for sedation and crouching) and compared with the antidepressant activity of the standard drug fluoxetine (Table 1).

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