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Bioorganic & Medicinal Chemistry 14 (2006) 2535–2544
Bioorganic & Medicinal Chemistry

Synthesis and appetite suppressant activity of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalenes as conformationally rigid analogues of fluoxetine☆

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Received 20 October 2005; revised 14 November 2005; accepted 15 November 2005
Available online 5 December 2005

Abstract—Several 1-aryloxy-2-substituted aminomethyltetrahydronaphthalenes (**7**–**21**) as conformationally rigid analogues of fluoxetine were synthesized and evaluated for their anorexigenic and antidepressant activities. For SAR studies the related acyclic analogues (**22**–**27**) were also prepared. Out of the 21 synthesized compounds, 10 compounds (**9**, **10**, **11**, **15**, **16**, **18**, **21**, **22**, **23** and **27**) exhibited significant anorexigenic activity (at 75 μmol/kg). Interestingly, all the compounds (**7**–**20**, **22**–**26**) were devoid of antidepressant effect, except for compounds **21** and **27** in which the antidepressant activity was retained. Compound **16** emerged as the most active compound of the series with better anorexigenic activity (97.92%) compared to fluoxetine (76.25%) and even with a clinically used drug sibutramine, thus providing a new structural lead for appetite suppressants.

1. Introduction

Despite a rising worldwide epidemic of obesity[1–3] there are currently only a very small number of anti-obesity drugs available to manage the problem.[4] Some of these drugs may assist weight loss by modifying the functioning of the appetite system as measured by subjective changes in feelings of hunger and fullness (indices of satiety). Such drugs can be considered as appetite suppressants[5] with clinical potential as anti-obesity agents. Centrally acting appetite suppressant drugs (Fig. 1) used in the treatment of obesity fall into two broad pharmacological categories:[6] those, which act via catecholamine[7] pathways, and those, which act via serotonin[8] pathways. Of the former group, amphetamine and phenmetrazine are no longer recommended because of their stimulant properties and addictive potential.[9,10] The remaining drugs[11] in this class include diethylpropion, phentermine, mazindol and phenylpropanolamine, all have been shown to reduce appetite and lower food intake. They all have some sympathomimetic and stimulant properties. Anorectic drugs, which promote serotonin neurotransmission[8,12], have no such stimulant or sympathomimetic properties. They are fenfluramine, together with its dextrorotatory stereoisomers dexfenfluramine and fluoxetine.[13,14] They reduce appetite and food intake, and are effective in the treatment of obesity but their use has been limited by side effects. This necessitates the development of more effective drugs.

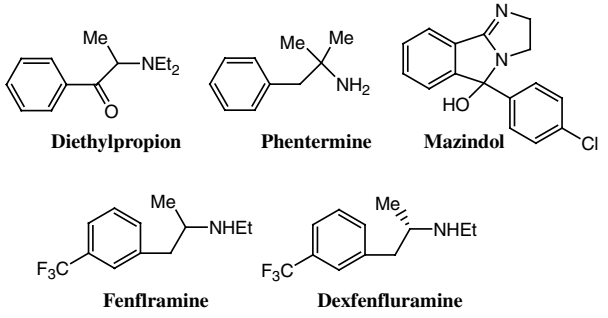

Figure 1. Centrally acting appetite suppressant drugs.

The above report and our interest in fluoxetine analogues[15–17] have induced us to investigate how the anorectic and antidepressant activities of fluoxetine would be influenced by restricting the free movement of

Keywords: Fluoxetine; Appetite suppressant; Antidepressant; Rigid analogue.
☆ CDRI Communication No. 6856.
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doi:10.1016/j.bmc.2005.11.032

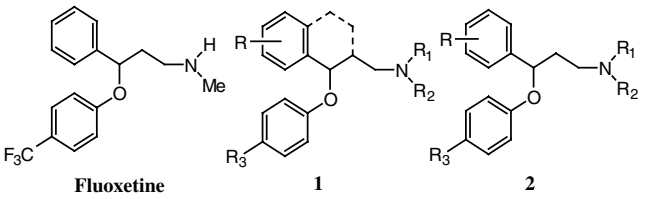
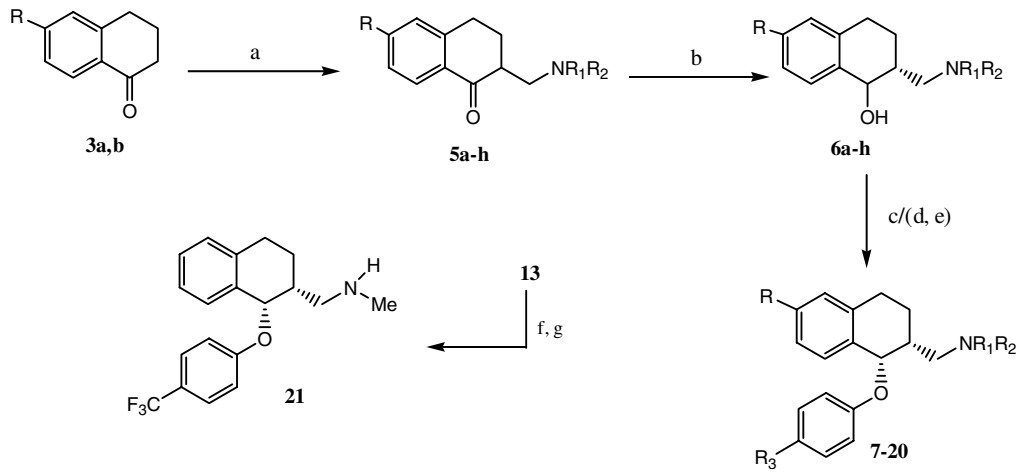


Figure 2.

propylamine chain. It has been carried out by linking the C-2 carbon atom of propylamine chain and C-2 of the phenyl ring through a two carbon spacer. Thus, we herein report the synthesis, pharmacological evaluation and SAR studies of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalene derivatives (**1**) as conformationally rigid analogues of fluoxetine (Fig. 2). The impact of the rigidity of the structure has been evaluated with respect to the anorexigenic and antidepressant effects and compared with that of the parent compound fluoxetine. In an attempt to explore the SAR of these rigid analogues (**1**), we also prepared related acyclic derivatives (**2**) (Fig. 2) and evaluated them for both anorexigenic and antidepressant effects.

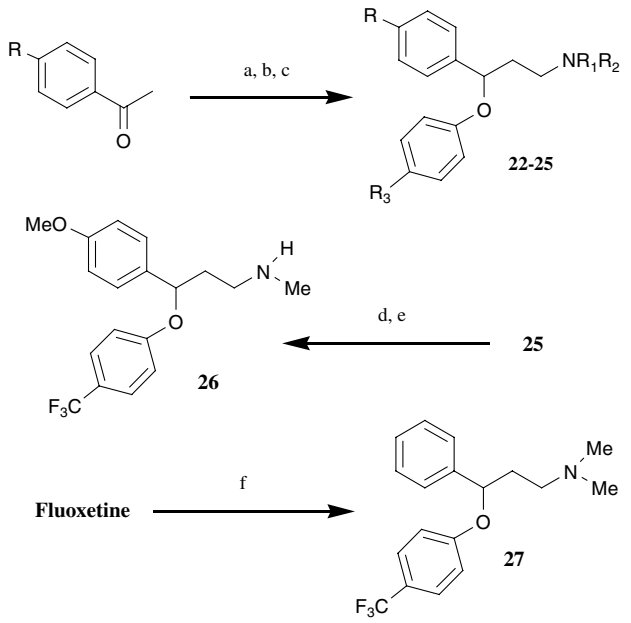
2. Chemistry

The synthetic route for 1-aryloxy-2-substituted aminomethyltetrahydronaphthalenes (**7**–**21**) is depicted in Scheme 1. Substituted aminomethyl-3,4-dihydro-2*H*-naphthalen-1-one (**5a**–**5h**) was prepared from 1-tetralone (**3a**)/6-methoxy-1-tetralone (**3b**) by Mannich reaction using different secondary amines (**4a**–**4e**) which on sodium borohydride reduction gave the hydroxy intermediate (**6a**–**6h**) in a substantially pure *trans* isomeric form. Condensation of the hydroxy intermediate (**6a**–**6h**) with (i) 4-fluorobenzotrifluoride/4-fluoroacetophenone in the presence of sodium hydride in dimethylacetamide or with (ii) methanesulfonyl chloride followed by condensation with the sodium salts of phenol/4-methoxyphenol furnished the desired ethers (**7**–**20**) with *cis* stereoselectivity. The reaction typically proceeded with inversion of stereochemistry, thus the *trans* hydroxy compounds (**6a**–**6h**) yielded predominantly the *cis* phenoxy ethers of formula (**7**–**20**). The *cis* stereochemistry with respect to phenoxy and methylamine moieties of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalenes (**7**–**20**) was established on the basis of ^{1}H NMR spectra.[18] 3-Aryl-3-aryloxypropanamines (**22**–**25**) were synthesized from acetophenone/4-methoxyacetophenone and different secondary amines (**4d**, **4e**) by the method reported earlier (Scheme 2).[19] Debenzylation of **13** and **25** with methyl chloroformate and hydrazinehydrate gave **21** and **26**, respectively (Schemes 1 and 2).[16] Fluoxetine was treated with formaldehyde followed by sodium borohydride to give *N*,*N*-dimethyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine **27** (Scheme 2).



Compd.No.	NR_1R_2	R	R_3	Compd.No.	NR_1R_2	R	R_3
7	4-[(4-methyl)phenyl]piperazino	H	CF_3	**14**	benzylmethylamino	H	$COCH_3$
8	4-[(4-methyl)phenyl]piperazino	H	$COCH_3$	**15**	dibenzylamino	H	$COCH_3$
9	4-(3-α,α,α-trifluorotolyl)piperazino	H	CF_3	**16**	4-[(4-methyl)phenyl]piperazino	OMe	$COCH_3$
10	4-(3-α,α,α-trifluorotolyl)piperazino	H	$COCH_3$	**17**	dimethylamino	OMe	$COCH_3$
11	dimethylamino	H	CF_3	**18**	benzylmethylamino	OMe	$COCH_3$
12	dimethylamino	H	$COCH_3$	**19**	dimethylamino	H	OMe
13	benzylmethylamino	H	CF_3	**20**	dimethylamino	H	H

Scheme 1. Reagents and conditions: (a) HNR_1R_2 (**4a**–**4e**), $(HCHO)_3$, isopropanol, 95 °C; (b) $NaBH_4$, MeOH, rt; (c) NaH, 4-fluorobenzotrifluoride/4-fluoroacetophenone, dry DMAC; (d) CH_3SO_2Cl, K_2CO_3, dry acetone, 0–4 °C; (e) NaOH, phenol/4-methoxyphenol, EtOH, rt; (f) ClCOOMe, dry benzene, reflux; (g) NH_2–$NH_2{\cdot}H_2O$, KOH, *n*-propanol, reflux.



Compd. no.	NR_1R_2	R	R_3
22	Dibenzylamino	H	$COCH_3$
23	Dibenzylamino	H	CF_3
24	Benzylmethylamino	H	CF_3
25	Benzylmethylamino	OMe	CF_3

Scheme 2. Reagents and conditions: (a) HNR_1R_2 (**4d**, **4e**), $(HCHO)_3$, *n*-propanol, reflux; (b) $NaBH_4$, MeOH, rt; (c) NaH, 4-fluorobenzotrifluoride/4-fluoroacetophenone, dry DMAC; (d) ClCOOMe, dry benzene, reflux; (e) NH_2–$NH_2{\cdot}H_2O$, KOH, *n*-propanol, reflux; (f) HCHO, MeOH, $NaBH_4$, rt.

3. Results and discussion

The synthesized compounds (**7**–**27**) were assessed for gross behavioural, anorexigenic and antidepressant effects by standard methods.[15] The results are summarized in Table 1 and compared with the activity of the parent compound fluoxetine. The tested compounds did not show any significant effect on the gross behaviour, except for **21** which showed mild stimulation (increased locomotor activity) similar to that of fluoxetine.

First, we focused our attention mainly on compound **21** the fluoxetine-like structure for a direct comparison of its antidepressant and anorexigenic activities with that of the lead fluoxetine. The results indicated that the conformationally restricted rigid analogue **21** at 75 μmol/kg dose exhibited significant anorexigenic activity (66%) with signs of stimulation. The stimulant activity may be attributed to the propylamino chain in rigid frame. However, at half dose (37.5 μmol/kg), compound **21** showed the dose-dependent activity pattern; it showed antidepressant activity with insignificant anorexigenic and stimulant effects; **21** was found to be better than fluoxetine (at 37.5 μmol/kg) in exhibiting antidepressant activity.

The substitution of hydrogen of the NH of **21** by benzyl group resulted in complete loss of antidepressant effect with the retention of weak anorexigenic activity (10.42%) in compound **13**, suggesting that the secondary amino group may be responsible for the antidepressant effect. We therefore attempted to minimize the antidepressant effect and to improve the anorexigenic activity of **21** by replacing the secondary amino groups with various amino substructures (**7**–**20**). Interestingly, all the rigid analogues (**7**–**20**) were devoid of antidepressant activity. Among the 14 synthesized N-substituted rigid analogues, compound nos. **9**, **10**, **11**, **15**, **16** and **18** showed significant anorexigenic activity ($P \leqslant 0.05$) with a significant decrease in milk intake (28.57–97.92%) in comparison to the control group (Fig. 3). Compound **16** emerged as the most potent appetite suppressant with 97.92% anorexigenic activity, which was better than that of the parent compound fluoxetine (76.25%). The anorexigenic activity of the test compound **16** was also found to be superior compared to the clinically used drug sibutramine (80%).

SAR studies revealed that among the five groups substituted at NH, 4-(3-trifluorotolyl)piperazino group was found to be the most effective in exhibiting a better appetite suppressant activity profile followed by dimethyl amino, dibenzyl amino, 4-(4-methylphenyl)piperazino and benzylmethyl amino in decreasing order. Introduction of substituents different from trifluoromethyl in the aryloxy ring of the rigid analogue led to a substantial decrease of anorexigenic activity with the maximum potency for CF_3 following the decreasing order by $COCH_3$ > H > OMe. Only compound numbers **9** and **10** behaved differently in which acetyl analogue **10** was more active than its CF_3 analogue **9**. Introduction of methoxy functionality at the 6-position of the tetrahydronaphthalene ring in compounds **16**, **17** and **18** resulted in the enhancement of the percentage anorexia than their unsubstituted counterparts **8**, **12** and **14**, respectively.

Similarly, among the acyclic fluoxetine analogues in which the secondary amino group was replaced by dibenzyl (**22** and **23**), benzylmethyl (**24**) and dimethyl (**27**) amino substructures showed significant anorexia (except for **24**) whereas the antidepressant activity was either decreased (**27**), insignificant (**24**) or completely lost (**22** and **23**). Surprisingly, contrary to rigid analogues (**16**–**18**), the introduction of methoxyl group at 4-position of the aryl ring in acyclic analogues (**25** and **26**) resulted in the reduction of both anorexigenic as well as antidepressant activities.

4. Conclusion

The current study was performed to evaluate a new series of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalenes as conformationally rigid analogues of fluoxetine for appetite suppressant and antidepressant activities. The following conclusions can be drawn from the SARs of this series of compounds—(1) compound **21**, the fluoxetine-like structure (with free NH), can be presented as selective antidepressant as it showed better activity than fluoxetine at lower doses (37.5 μmol/kg ip);

Table 1. Pharmacological data of fluoxetine analogues (**7**–**27**) at 75 μmol/kg ip in a Swiss albino mice model

Compound	Anorexigenic activity		Antidepressant activity[e]	
	Means ± SEM of milk intake (mL)	% decrease in milk intake (anorexia)	Ptosis (% incidence)	Sedation and crouching (median score)
Control	0.49 ± 0.01		0	0
7	0.33 ± 0.06	31.68	100	4
8	0.34 ± 0.06	30.04	100	4
9	0.27 ± 0.08[b]	44.44	100	4
10	0.22 ± 0.05[b]	54.73	100	4
11	0.23 ± 0.07[b]	52.67	100	4
Control	0.48 ± 0.01		0	0
12	0.34 ± 0.09	29.17	100	4
13	0.43 ± 0.03	10.42	100	4
14	0.47 ± 0.02	2.08	100	4
15	0.24 ± 0.08[b]	50.42	100	4
16	0.01 ± 0.01[b]	97.92	100	4
Control	0.49 ± 0.01		0	0
17	0.34 ± 0.07	30.61	100	4
18	0.35 ± 0.04[b]	28.57	100	4
19	0.38 ± 0.09	22.45	100	4
20	0.37 ± 0.07	24.49	100	4
21	0.17 ± 0.05[b]	66.90	0[d]	0[d]
21[a]	0.43 ± 0.05	12.24	20[c]	1[c]
Control	0.48 ± 0.01		0	0
22	0.29 ± 0.04[b]	38.54	100	4
23	0.29 ± 0.03[b]	40.40	100	4
24	0.43 ± 0.04	11.43	80	4
25	0.47 ± 0.01	2.08	100	4
26	0.49 ± 0.01	2.08	80	4
27	0.16 ± 0.01[b]	67.50	40[c]	2[c]
Fluoxetine	0.11 ± 0.06[b]	76.25	0[c]	0[c]
Fluoxetine[a]	0.46 ± 0.04	4.17	40[c]	2[c]
Sibutramine	0.09 ± 0.05[b]	80	—	—
Reserpine control			100	4

(—) not tested. Control: saline treated mice.
[a] Dose: 37.5 μmol/kg.
[b] Significant anorexigenic activity ($P \leqslant 0.05$).
[c] Significant antidepressant activity.
[d] Stimulant action (increased locomotor activity).
[e] The antidepressant activity of Fluoxetine and the compounds was evaluated after 3 h of reserpine treatment.

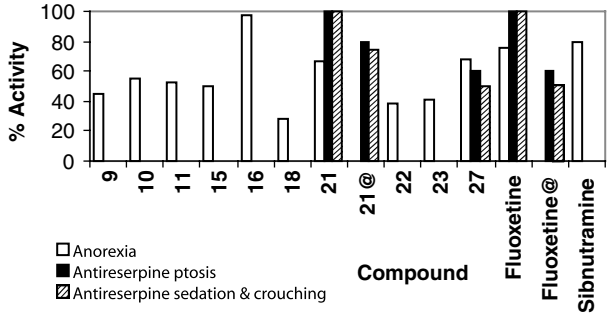


Figure 3. Comparative activity profile of the compounds at 75 μmol/kg dose showing significant ($P \leqslant 0.05$) anorexigenic and/or antidepressant (antireserpine) activities in terms of % decrease from the saline and reserpine treated control, respectively; @at 37.5 μmol/kg dose.

(2) the substitution of NH by different amino substructures (**7**–**20**, **22**–**27**) can lead to the development of potent appetite suppressants as out of 21 synthesized compounds ten exhibited significant anorexigenic activity; (3) different substituents introduced in the aryl and aryloxy rings played an important role in influencing the activity pattern; the methoxy substitution in the aryl ring of rigid analogues enhanced the anorexigenic activity, whereas in the acyclic analogues both the activities were reduced; however, substitutions in the aryloxy ring followed the same pattern in both rigid as well as acyclic analogues with the maximum potency for the CF_3 substitution.

In conclusion, we have identified a novel lead compound **16** exhibiting better anorexigenic activity compared to that of fluoxetine as well as sibutramine. The results of the present study encourage further research in this series of compounds in order to find the selective and more potent appetite suppressant.

5. Experimental

5.1. Chemistry

Melting points were determined in open capillaries with an electrically heated block and are uncorrected.

IR spectra of all the compounds were recorded on a Perkin-Elmer AC–1 spectrophotometer. ^{1}H NMR spectra were recorded on a 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 a 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. General procedure for the preparation of Mannich bases (5a–5h). A mixtute of 1-tetralone (**3a**)/6-methoxy-1-tetralone (**3b**) (11 mmol), hydrochloride salt of secondary amines (**4a**–**4e**) (10 mmol) and 1/5th of paraformaldehyde (20 mmol) in isopropanol (15 mL) was stirred and concd HCl was added dropwise to adjust the pH of the solution to 4. The reaction mixture was then heated in an oil bath at 90–95 °C for 30 min with stirring. Other four portions of the paraformaldehyde were added at 15 min interval. The reaction mixture was further refluxed for 4 h. The solvent was distilled off. The residue obtained was washed with hexane (2× 5 mL), added sodium bicarbonate solution to make the pH alkaline and extracted with dichloromethane (3× 15 mL). Combined organic extracts were dried over Na_2SO_4 and distilled to afford the Mannich bases (**5a**–**5h**) in good yield.

5.1.1.1. 2-[1-(4-Methylphenyl)-piperazinyl]-methyl-3,4-dihydro-2*H*-naphthalen-1- one (5a). With 1-tetralone (**3a**) and 1-(4-methylphenyl)piperazine.dihydrochloride (**4a**). Yield 77%; Mp 171–175 °C; MS (FAB) *m*/*z*: 335 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02 (m, 1H, H-3), 2.26 (s, 3H, Ar–CH_3), 2.4 (m, 1H, H-3), 2.54–2.75 (m, 6H, N–CH_2), 2.93–3.04 (m, 3H, H-4, CO–CH), 3.12–3.17 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 6.82–6.86 (d, 2H, J = 8.54 Hz, ArH *ortho* to N), 7.05–7.09 (d, 2H, J = 8.46 Hz, ArH *ortho* to CH_3), 7.23–7.33 (m, 2H, H-5, H-7), 7.43–7.51 (m, 1H, H-6), 8.01–8.04 (d, 1H, J = 6.84 Hz, H-8); IR (KBr): 3418, 2980, 2917, 2364, 1684, 1601, 1451, 1231, 740 cm^{-1}.

5.1.1.2. 2-[1-(3-Trifluoromethylphenyl)-piperazinyl] methyl-3,4-dihydro-2*H*-naphthalen-1-one (5b). With 1-tetralone (**3a**) and 1-(3-trifluoromethylphenyl)piperazine. dihydrochloride (**4b**). Yield 70%; MS (FAB) *m*/*z*: 390 ((M+2)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.020 (m, 1H, H-3), 2.4 (m, 1H, H-3), 2.53–2.74 (m, 5H, N–CH_2), 2.90–3.03 (m, 4H, H-2, H-4, N–CH_2), 3.19–3.24 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 6.99–7.05 (m, 3H, ArH *ortho* and *para* to N), 7.17–7.47 (m, 4H, ArH), 7.97–8.01 (d, 1H, J = 7.8 Hz, H-8); IR (Neat): 3432, 2937, 2363, 1681, 1596, 1452, 1353, 1118, 692 cm^{-1}.

5.1.1.3. 2-Dimethylaminomethyl-3,4-dihydro-2*H*-naphthalen-1-one (5c). With 1-tetralone (**3a**) and dimethyl ammonium chloride (**4c**). Yield 72%; MS (FAB) *m*/*z*: 204 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (m, 1H, H-3), 2.20–2.35 (m, 7H, H-3, N(Me)$_2$), 2.5–2.76 (m, 3H, CO–CH–CH_2–N), 2.97–3.04 (m, 2H, H-4), 7.22–7.29 (m, 2H, H-5, H-7), 7.46 (m, 1H, H-6), 7.99–8.03 (d, 1H, J = 7.84 Hz, H-8); IR (Neat): 3423, 2936, 2705, 2043, 1680, 1598, 1455, 1231, 746 cm^{-1}.

5.1.1.4. 2-Benzylmethylaminomethyl-3,4-dihydro-2*H*-naphthalen-1-one (5d). With 1-tetralone (**3a**) and benzylmethylammonium chloride (**4d**). Yield 85%; MS (FAB) *m*/*z*: 280 ((M+1)$^+$, 65%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85–1.92 (m, 1H, H-3), 2.15–2.47 (m, 7H, H-3, *Me*–N–CH_2–C*H*), 2.76–2.84 (m, 2H, H-4), 3.00–3.03 (m, 1H, Ar–CH_2–N), 3.17–3.20 (m, 1H, Ar–CH_2–N), 7.07–7.12 (m, 3H, ArH), 7.25–7.35 (m, 4H, ArH), 7.45–7.53 (m, 1H, H-6), 8.01–8.05 (d, 1H, J = 7.81 Hz, H-8); IR (Neat): 3338, 3024, 2939, 2844, 2791, 1680, 1454, 1221, 757 cm^{-1}.

5.1.1.5. 2-Dibenzylaminomethyl-3,4-dihydro-2*H*-naphthalen-1-one (5e). With 1-tetralone (**3a**) and dibenzylammonium chloride (**4e**). Yield 83%; MS (FAB) *m*/*z*: 356 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54–1.61 (m, 1H, H-3), 2.1 (m, 2H, H-3, N–CH_2–CH), 2.36–2.43 (m, 1H, N–CH_2–CH), 2.61–2.72 (m, 3H, H-4, H-2), 3.06–3.12 (m, 2H, Ar–CH_2–N), 4.01–4.08 (m, 1H, Ar–CH_2–N), 4.21–4.26 (m, 1H, Ar–CH_2–N), 6.94–7.29 (m, 13H, ArH), 7.50–7.54 (d, 1H, J = 7.36 Hz, ArH); IR (Neat): 3433, 2923, 2789, 2737, 2595, 2435, 1675, 1573, 1455, 1424, 743 cm^{-1}.

5.1.1.6. 6-Methoxy-2-[1-(4-methylphenyl)-piperazinyl]-methyl-3,4-dihydro-2*H*-naphthalen-1-one (5f). With 6-methoxy-1-tetralone (**3b**) and 1-(4-methylphenyl) piperazine.dihydrochloride (**4a**). Yield 68%; Mp 165–169 °C; MS (FAB) *m*/*z*: 365 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (m, 1H, H-3), 2.27–2.36 (m, 4H, Ar–CH_3, H-3), 2.53–2.78 (m, 6H, NCH_2), 2.94–3.00 (m, 3H, H-2, H-4), 3.13–3.15 (m, 4H, piperazinyl NH_2 adjacent to phenyl ring), 3.85 (s, 3H, OMe), 6.70 (s, 1H, H-5), 6.80–6.87 (m, 3H, ArH *ortho* to N, H-7), 7.05–7.09 (d, 2H, J = 8.42 Hz, ArH *ortho* to CH_3), 7.98–8.02 (d, 1H, J = 8.78 Hz, H-8); IR (KBr): 3360, 2916, 2707, 2477, 2365, 1675, 1603, 1453, 1276, 1248, 1023, 817 cm^{-1}.

5.1.1.7. 6-Methoxy-2-dimethylaminomethyl-3,4-dihydro-2*H*-naphthalen-1-one (5g). With 6-methoxy-1-tetralone (**3b**) and dimethylammonium chloride (**4c**). Yield 69%; MS (FAB) *m*/*z*: 234 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (m, 1H, H-3), 2.66–3.14 (m, 12H, H-3, CO–CH–CH_2–N(Me)$_2$, H-4), 3.86 (s, 3H, OMe), 6.70 (s, 1H, H-5), 6.80–6.89 (m, 1H, H-7), 7.94–7.98 (d, 1H, J = 8.72 Hz, H-8); IR (Neat): 3433, 3018, 2937, 2675, 1665, 1602, 1255, 1237, 1019 cm^{-1}.

5.1.1.8. 6-Methoxy-2-benzylmethylaminomethyl-3,4-dihydro-2*H*-naphthalen-1-one (5h). With 6-methoxy-1-tetralone (**3b**) and benzylmethylammonium chloride (**4d**). Yield 89%; MS (FAB) *m*/*z*: 310 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 (m, 1H, H-3), 2.23 (s, 3H, N-Me), 2.44 (m, 1H, H-3), 2.58–2.68 (m, 2H, N–CH_2–CH), 2.81–2.93 (m, 3H, H-4, CO–C*H*),

3.37–3.43 (m, 1H, Ar–CH_2–N), 3.62–3.76 (m, 1H, Ar–CH_2–N), 3.83 (s, 3H, OMe), 6.65 (s, 1H, H-5), 6.76–6.82 (m, 1H, H-7), 7.21–7.31 (m, 5H, ArH), 7.94–7.99 (d, 1H, J = 8.71 Hz, H-8); IR (Neat): 3424, 2944, 2840, 2708, 1667, 1598, 1458, 1252, 1026, 751 cm^{-1}.

5.1.2. General procedure for the preparation of 2-substituted aminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (6a–6h). Sodium borohydride (30 mmol) was added in portions to a stirred and cooled solution of Mannich bases (**5a**–**5h**) (10 mmol) in methanol (25 mL) over a period of 30 min. The reaction mixture was further stirred at room temperature for 4 h. Methanol was distilled under reduced pressure. The residue was triturated with water (25 mL) and extracted with dichloromethane (3× 15 mL). The combined organic layer was dried over sodium sulfate and concentrated to give the hydroxy compounds (**6a**–**6h**) in excellent yield.

5.1.2.1. 2-[1-(4-Methylphenyl)-piperazinyl]-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (6a). Yield 98%; Mp 170–175 °C; MS (FAB) *m*/*z*: 336 (M^+, 90%), 337 $(M+1)^+$, 80%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47–1.50 (m, 1H, H-2), 1.68–1.70 (m, 1H, H-3), 2.00–2.07 (m, 1H, H-3), 2.26 (s, 3H, Ar–CH_3), 2.58–2.67 (m, 4H, NCH_2), 2.88–2.98 (m, 4H, H-4, N–CH_2), 3.16–3.21 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 4.67–4.71 (d, 1H, J = 9.25 Hz, OH–C*H*), 6.81–6.85 (d, 2H, J = 8.45 Hz, ArH *ortho* to N), 7.05–7.22 (m, 5H, ArH), 7.57–7.60 (d, 1H, J = 7.26 Hz, ArH); IR (KBr): 3364, 3226, 2928, 2812, 1611, 1516, 1446, 1244, 808 cm^{-1}.

5.1.2.2. 2-[1-(3-Trifluoromethylphenyl)-piperazinyl]-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (6b). Yield 97%; MS (FAB) *m*/*z*: 391 ($(M+1)^+$, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43–1.57 (m, 2H, H-2, H-3), 2.02–2.06 (m, 1H, H-3), 2.64–2.76 (m, 4H, NCH_2), 2.88–2.94 (m, 4H, H-4, N–CH_2), 3.29 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 4.69–4.73 (d, 1H, J = 9.09 Hz, OH–C*H*), 7.10–7.39 (m, 7H, ArH), 7.57–7.61 (d, 1H, J = 6.72 Hz, ArH); IR (Neat): 3223, 2921, 2877, 2824, 2364, 1611, 1498, 1450, 1361, 1311, 1250, 1163, 1105, 950, 742 cm^{-1}.

5.1.2.3. 2-Dimethylaminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (6c). Yield 97%; MS (FAB) *m*/*z*: 206 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (m, 1H, H-2), 1.7 (m, 1H, H-3), 2.00 (m, 1H, H-3), 2.19–2.43 (m, 7H, CH_2-N-(*Me*)$_2$), 2.55–2.61 (m, 1H, N–CH_2), 2.84–2.86 (m, 2H, H-4), 4.62–4.67 (d, 1H, J = 9.58 Hz, OH–C*H*), 7.08–7.22 (m, 3H, ArH), 7.57–7.61 (d, 1H, J = 7.05 Hz, ArH); IR (Neat): 3259, 2924, 2827, 2788, 1605, 1466, 1382, 1259, 1042, 743 cm^{-1}.

5.1.2.4. 2-Benzylmethylaminomethyl-1,2,3,4-tetrahydro naphthalen-1-ol (6d). Yield 94%; MS (FAB) *m*/*z*: 282 (M^+, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (m, 1H, H-2), 1.65 (m, 1H, H-3), 1.99 (m, 1H, H-3), 2.22–2.51 (m, 4H, CH–CH_2–N–CH_3), 2.79–3.04 (m, 3H, H-4, CH–CH_2–N), 3.40–3.46 (m, 1H, N–CH_2–Ph), 3.74–3.80 (m, 1H, N–CH_2–Ph), 4.57–4.61 (d, 2H, J = 9.03 Hz, OH–C*H*), 7.07–7.39 (m, 8H, ArH), 7.64–7.98 (d, 1H, J = 7.36 Hz, ArH); IR (Neat): 3250, 2924, 2846, 2801, 1680, 1456, 1039, 742 cm^{-1}.

5.1.2.5. 2-Dibenzylaminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (6e). Yield 96%; MS (FAB) *m*/*z*: 358 (M^+, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2 (m, 1H, H-2), 1.65 (m, 1H, H-3), 2.15–2.16 (m, 1H, H-3), 2.44 (m, 1H, CH–CH_2–N), 2.67–3.19 (m, 4H, H-4, CH–CH_2–N), 3.78–3.90 (m, 3H, N–CH_2–Ph), 4.08–4.14 (m, 1H, N–CH_2–Ph), 4.25–4.29 (d, 1H, J = 8 Hz, OH–C*H*), 7.04–7.34 (m, 13H, ArH), 7.6 (m, 1H, ArH); IR (Neat): 3259, 3025, 2930, 2814, 2364, 1454, 1217, 1039, 757 cm^{-1}.

5.1.2.6. 6-Methoxy-2-[1-(4-methylphenyl)-piperazinyl]-methyl-1,2,3,4- tetrahydronaphthalen-1-ol (6f). Yield 97%; Mp 50–55 °C. MS (FAB) *m*/*z*: 367 $(M+1)^+$, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (m, 1H, H-2), 1.67–1.73 (m, 1H, H-3), 2.27 (s, 3H, Ar–CH_3), 2.56–2.68 (m, 4H, NCH_2), 2.81–2.97 (m, 4H, H-4, N–CH_2), 3.16–3.19 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 3.78 (s, 3H, OMe), 4.64–4.68 (d, 1H, J = 9.20 Hz, OH–C*H*), 6.59–6.60 (d, 1H, J = 2.4 Hz, H-5), 6.76–6.85 (m, 3H, ArH *ortho* to N, H-7), 7.05–7.09 (d, 2H, J = 8.39 Hz, ArH *ortho* to CH_3), 7.47–7.52 (d, 1H, J = 8.49 Hz, H-8); IR (KBr): 3266, 2928, 2822, 2364, 1615, 1517, 1248, 1052, 802 cm^{-1}.

5.1.2.7. 6-Methoxy-2-dimethylaminomethyl-1,2,3,4-tetra hydronaphthalen-1-ol (6g). Yield 97%; MS (FAB) *m*/*z*: 236 ($(M+1)^+$, 82%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (m, 1H, H-2), 1.68 (m, 1H, H-3), 1.9 (m, 1H, H-3), 2.27–2.41 (m, 7H, CH_2-N-(*Me*)$_2$), 2.54–2.81 (m, 3H, N–CH_2, H-4), 3.77 (s, 3H, OMe), 4.58–4.63 (d, 1H, J = 9.188 Hz, OH–C*H*), 6.59 (s, 1H, H-5), 6.80–6.81 (m, 1H, H-7), 7.48–7.52 (d, 1H, J = 8.55 Hz, H-8); IR (Neat): 3206, 2997, 2929, 2831, 2792, 1501, 1466, 1254, 1219, 1037, 757 cm^{-1}.

5.1.2.8. 6-Methoxy-2-benzylmethylaminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (6h). Yield 95%; MS (FAB) *m*/*z*: 312 ($(M+1)^+$, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35–1.42 (m, 1H, H-2), 1.63–1.69 (m, 1H, H-3), 1.96–2.03 (m, 1H, H-3), 2.28 (s, 3H, N–Me), 2.41–2.49 (m, 1H, N–CH_2– CH), 2.66–2.89 (m, 3H, N–CH_2, H-4), 3.39–3.45 (d, 1H, J = 12.9 Hz, Ar–CH_2–N), 3.73–3.77 (m, OMe, Ar–CH_2–N), 4.52–4.57 (d, 1H, J = 9.18 Hz, OH–C*H*), 6.58 (s, 1H, H-5), 6.76–6.80 (d, 1H, J = 8.6 Hz, H-7), 7.33 (m, 5H, ArH), 7.50–7.54 (d, 1H, J = 8.56 Hz, H-8); IR (Neat): 3222, 3065, 3008, 2931, 2838, 2804, 1611, 1500, 1464, 1217, 757 cm^{-1}.

5.1.3. General procedure for the preparation of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalene derivatives (7–18). A solution of 2-substituted aminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (**6a**–**6h**) (5 mmol) in dry dimethyl acetamide (DMAC) (2 mL) was added dropwise to stirred and cooled (0–4 °C) suspension of sodium hydride (50%, 15 mmol) in dry (DMAC) (3 mL). It was further stirred with cooling for 30 min after which the reaction mixture was allowed to attain the rt and heated at 80–90 °C for 2 h. The reaction

mixture was cooled to rt and 4-fluorobenzotrifluoride/4-fluoroacetophenone (7.5 mmol) was added dropwise with stirring. The dark coloured reaction mixture was heated at 100–110 °C for 3–4 h. The reaction was discontinued, treated with water (15 mL) and extracted with ethyl acetate (3× 10 mL). The combined organic layer was washed with water (6× 10 mL), dried over sodium sulfate and concentrated to give the crude product, which was chromatographed on a silica gel column using ethyl acetate–hexane (10–18%) as an eluent to get the desired ethers (**7**–**18**) in good yield and converted into the oxalate salt in dry methanol.

5.1.3.1. 1-(4-Methylphenyl)-4-[1-(4-trifluoromethyl phenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]-piperazine dioxalate (7). With **6a** and 4-fluorobenzotrifluoride. Yield 83%; Mp 185–190 °C; MS (FAB) *m/z*: 481 ($(M+1)^+$, 90%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59–1.64 (m, 1H, H-3), 2.20–2.48 (m, 9H, Ar–CH_3, NCH_2, H-3, H-2), 2.59–2.77 (m, 4H, NCH_2, H-4), 3.11 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 5.35 (s, 1H, O–CH), 6.77–6.81 (d, 2H, J = 8.06 Hz, ArH *ortho* to N), 7.00–7.04 (d, 2H, J = 7.74 Hz, ArH *ortho* to O), 7.14–7.18 (m, 6H, ArH), 7.44–7.48 (d, 2H, J = 8.16 Hz, ArH *ortho* to CF_3); IR (KBr): 3448, 3028, 2923, 2502, 2364, 1733, 1618, 1516, 1329, 1166, 707 cm^{-1}. Anal. Calcd for $C_{29}H_{31}F_3N_2O{\cdot}2H_2C_2O_4{\cdot}0.75H_2O$: C, 58.79; H, 5.42; N, 4.16. Found: C, 58.98; H, 5.40; N, 4.12.

5.1.3.2. 1-(4-Methylphenyl)-4-[1-(4-acetylphenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]piperazine dioxalate (8). With **6a** and 4-fluoroacetophenone. Yield 60%; Mp 142–144 °C; MS (FAB) *m/z*: 454 ($(M+1)^+$, 90%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69 (m, 1H, H-3), 2.17–2.35 (m, 4H, Ar–CH_3, H-3), 2.39–2.56 (m, 8H, NCH_2, H-2, $COCH_3$), 2.66–2.82 (m, 4H, NCH_2, H-4), 3.19 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 5.48 (s, 1H, O–CH), 6.85–6.89 (d, 2H, J = 8.03 Hz, ArH *ortho* to N), 7.07–7.31 (m, 8H, ArH), 7.91–7.95 (d, 2H, J = 7.58 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 3038, 2925, 2692, 1734, 1614, 1325, 1243, 1114, 842 cm^{-1}. Anal. Calcd for $C_{30}H_{34}N_2O_2{\cdot}2H_2C_2O_4{\cdot}0.5H_2O$: C, 63.45; H, 6.07; N, 4.35. Found: C, 63.07; H, 5.68; N, 4.39.

5.1.3.3. 1-(3-Trifluoromethylphenyl)-4-[1-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]piperazine dioxalate (9). With **6b** and 4-fluorobenzotrifluoride. Yield 66%; Mp 135–140 °C; MS (FAB) *m/z*: 534 (M^+, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–1.74 (m, 1H, H-3), 2.17–2.82 (m, 10H, H-3, H-2, NCH_2, H-4), 3.27 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 5.42 (s, 1H, O–CH), 7.12–7.36 (m, 10H, ArH), 7.53–7.57 (d, 2H, J = 8.07 Hz, ArH); IR (KBr): 3754, 3449, 2951, 2819, 2363, 1601, 1352, 1115 cm^{-1}. Anal. Calcd for $C_{29}H_{28}F_6N_2O{\cdot}2H_2C_2O_4$: C, 55.46; H, 4.48; N, 3.92. Found: C, 55.80; H, 4.84; N, 4.05.

5.1.3.4. 1-(3-Trifluoromethylphenyl)-4-[1-(4-acetyl phenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl] piperazine dioxalate (10). With **6b** and 4-fluoroacetophenone. Yield 58%; Mp 130–135 °C; MS (FAB) *m/z*: 509 ($(M+1)^+$, 75%), 508 (M^+, 78%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67–1.74 (m, 1H, H-3), 2.35–3.06 (m, 13H, H-3, H-2, NCH_2, H-4, $COCH_3$), 3.28 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 5.47 (s, 1H, O–CH), 7.06–7.36 (m, 10H, ArH), 7.92–7.96 (d, 2H, J = 8.78 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 2930, 2823, 1675, 1598, 1452, 1314, 1245, 1122, 752 cm^{-1}. Anal. Calcd for $C_{30}H_{31}F_3N_2O_2{\cdot}2H_2C_2O_4{\cdot}2H_2O$: C, 56.35; H, 5.39; N, 3.87. Found: C, 56.19; H, 5.10; N, 3.51.

5.1.3.5. Dimethyl-[1-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]-amine oxalate (11). With **6c** and 4-fluorobenzotrifluoride. Yield 77%; Mp 195–200 °C; MS (FAB) *m/z*: 350 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7 (m, 1H, H-3), 2.23–2.35 (m, 10H, H-3, H-2, NCH_2, N–$(Me)_2$), 2.78–2.80 (m, 2H, H-4), 5.32–5.33 (d, 1H, J = 2.49 Hz, O–CH), 7.11–7.18 (m, 6H, ArH), 7.53–7.58 (d, 2H, J = 8.49 Hz, ArH *ortho* to CF_3); IR (KBr): 3021, 2927, 2708, 1737, 1659, 1614, 1325, 1216, 763 cm^{-1}. Anal. Calcd for $C_{20}H_{22}F_3NO$. $H_2C_2O_4$: C, 60.14; H, 5.47; N, 3.19. Found: C, 59.77; H, 5.38; N, 2.97.

5.1.3.6. Dimethyl-[1-(4-acetylphenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]-amine oxalate (12). With **6c** and 4-fluoroacetophenone. Yield 65%; Mp 88–90 °C; MS (FAB) *m/z*: 324 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69–1.73 (m, 1H, H-3), 2.31–2.40 (m, 10H, H-3, H-2, NCH_2, N–$(Me)_2$), 2.57 (s, 3H, $COCH_3$), 2.84 (m, 2H, H-4), 5.38 (s, 1H, O–CH), 7.09–7.26 (m, 6H, ArH), 7.93–7.97 (d, 2H, J = 8.65 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 2932, 2374, 1598, 1353, 1241, 768 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_2{\cdot}H_2C_2O_4{\cdot}0.75H_2O$: C, 64.71; H, 6.68; N, 3.28. Found: C, 64.41; H, 6.61; N, 2.89.

5.1.3.7. Benzylmethyl-[1-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydronaphthalen- 2-yl-methyl]-amine oxalate (13). With **6d** and 4-fluorobenzotrifluoride. Yield 67%; Mp 110–115 °C; MS (FAB) *m/z*: 425 (M^+, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64–1.68 (m, 1H, H-3), 2.23–2.47 (m, 7H, H-3, H-2, NCH_2, N–Me), 2.60–2.77 (m, 2H, H-4), 3.41–3.56 (m, 2H, Ar–CH_2–N), 5.34 (s, 1H, O–CH), 7.13–7.41 (m, 11H, ArH), 7.50–7.54 (d, 2H, J = 8.22 Hz, ArH *ortho* to CF_3); IR (KBr): 3759, 3622, 3436, 1326, 1218, 1164, 767 cm^{-1}. Anal. Calcd for $C_{26}H_{26}F_3NO$. $H_2C_2O_4{\cdot}0.5H_2O$: C, 64.12; H, 5.53; N, 2.67. Found: C, 64.21; H, 5.21; N, 2.38.

5.1.3.8. Benzylmethyl-[1-(4-acetylphenoxy)-1,2,3,4-tetra hydronaphthalen-2-yl-methyl]-amine oxalate (14). With **6d** and 4-fluoroacetophenone. Yield 76%; Mp 100–104 °C; MS (FAB) *m/z*: 400 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.61–1.70 (m, 1H, H-3), 2.17–2.35 (m, 5H, N–Me, H-3, H-2), 2.39–2.55 (m, 5H, $COCH_3$, NCH_2), 2.69–2.80 (m, 2H, H-4), 3.41–3.50 (m, 2H, Ar–CH_2–N), 5.39 (s, 1H, O–CH), 6.63–6.67 (d, 1H, J = 8.92 Hz, ArH), 7.10–7.33 (m, 9H, ArH), 7.85–7.93 (m, 3H, ArH); IR (KBr): 3025, 2932, 2796, 1675, 1598, 1505, 1361, 1277, 1172, 749 cm^{-1}. Anal. Calcd for $C_{27}H_{29}NO_2{\cdot}H_2C_2O_4{\cdot}0.5H_2O$: C, 69.88; H, 6.43; N, 2.81. Found: C, 70.01; H, 6.81; N, 2.78.

5.1.3.9. Dibenzyl-[1-(4-acetylphenoxy)-1,2,3,4-tetrahydro naphthalen-2-yl-methyl]-amine oxalate (15). With **6e** and 4-fluoroacetophenone. Yield 50%; oil; MS (FAB) *m/z*: 476 (M^+, 25%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.6 (m, 1H, H-3), 2.09–2.28 (m, 2H, H-3, H-2), 2.39–2.48 (m, 5H, $COCH_3$, NCH_2), 2.65 (m, 2H, H-4), 3.40–3.64 (m, 2H, Ar–CH_2–N), 5.09–5.11 (d, 1H, J = 2.84 Hz, O–CH), 6.87–7.06 (m, 4H, ArH), 7.11–7.20 (m, 12H, ArH), 7.76–7.80 (d, 2H, J = 8.76 Hz, ArH *ortho* to $COCH_3$); IR (Neat): 3468, 3020, 2401, 1677, 1598, 1216, 770 cm^{-1}. Anal. Calcd for $C_{33}H_{33}NO_2 \cdot H_2C_2O_4 \cdot 1.5H_2O$: C, 70.95; H, 6.42; N, 2.36. Found: C, 70.59; H, 6.53; N, 2.48

5.1.3.10. 1-(4-Methylphenyl)-4-[6-methoxy-1-(4-acetyl phenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]-piperazine dioxalate (16). With **6f** and 4-fluoroacetophenone. Yield 91%; Mp 165–170 °C; MS (FAB) *m/z*: 484 (M^+, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (m, 1H, H-3), 2.17–2.77 (m, 16H, H-2, H-3, H-4, NCH_2, Ar–CH_3, $COCH_3$), 3.19 (m, 4H, piperazinyl NCH_2 adjacent to phenyl ring), 3.80 (s, 3H, OMe), 5.44 (s, 1H, O–CH), 6.69–6.89 (m, 4H, ArH), 7.07–7.19 (m, 5H, ArH), 7.90–7.94 (d, 2H, J = 8.2 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 3433, 3018, 2936, 1672, 1598, 1505, 1218, 1171, 765 cm^{-1}. Anal. Calcd for $C_{31}H_{36}N_2O_3 \cdot 2H_2C_2O_4 \cdot 2H_2O$: C, 60.00; H, 6.29; N, 4.00. Found: C, 59.69; H, 5.90; N, 4.16.

5.1.3.11. Dimethyl-[6-methoxy-1-(4-acetylphenoxy)-1,2,3,4-tetrahydronaphthalen-2- yl-methyl]-amine oxalate (17). With **6g** and 4-fluoroacetophenone. Yield 52%; Mp 90–95 °C; MS (FAB) *m/z*: 354 ($(M+1)^+$, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7 (m, 1H, H-3), 2.07–2.34 (m, 10H, H-3, H-2, CH_2–N–$(Me)_2$), 2.56 (s, 3H, $COCH_3$), 2.75–2.77 (m, 2H, H-4), 3.79 (s, 3H, OMe), 5.33–5.35 (d, 1H, J = 2.48 Hz, O–CH), 6.68–6.78 (m, 2H, ArH), 7.07–7.12 (d, 2H, J = 8.87 Hz, ArH), 7.17–7.21 (d, 1H, J = 8.42 Hz, ArH), 7.92–7.97 (d, 2H, J = 8.85 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 3011, 2937, 1673, 1599, 1506, 1246, 1169, 761 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_3 \cdot H_2C_2O_4 \cdot 1.5H_2O$: C, 61.28; H, 6.81; N, 2.98. Found: C, 61.41; H, 7.19; N, 2.61.

5.1.3.12. Benzyl-[6-methoxy-1-(4-acetylphenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]-methylamine oxalate (18). With **6h** and 4-fluoroacetophenone. Yield 58%; Mp 75–80 °C; MS (FAB) *m/z*: 430 ($(M+1)^+$, 20%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60 (m, 1H, H-3), 2.13–2.45 (m, 7H, H-2, H-3, CH–CH_2–NMe), 2.55 (s, 3H, $COCH_3$), 2.60–2.77 (m, 2H, H-4), 3.47–3.50 (m, 2H, Ar–CH_2–N), 3.78 (s, 3H, OMe), 5.36 (s, 1H, O–CH), 6.64–6.75 (m, 2H, ArH), 7.09–7.37 (m, 8H, ArH), 7.88–7.93 (d, 2H, J = 8.7 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 3164, 2372, 1658, 1401, 1279, 1229, 1112 cm^{-1}. Anal. Calcd for $C_{28}H_{31}NO_3 \cdot H_2C_2O_4 \cdot 1H_2O$: C, 67.04; H, 6.52; N, 2.61. Found: C, 66.94; H, 6.36; N, 2.57.

5.1.4. General procedure for the preparation of 19 and 20. To a precooled (0–4 °C) suspension of **6c** (10 mmol) and anhyd. K_2CO_3 (25 mmol) in dry acetone (25 mL) was added methanesulfonyl chloride (25 mmol) dropwise under stirring over a period of 15 min. The reaction mixture was further stirred for 2 h at 0–4 °C. After completion of reaction, the solid was filtered and the filtrate was concentrated to give the mesylate residue. The sodium salt of 4-methoxy phenol/phenol was prepared by adding the corresponding phenol (11 mmol) to a solution of sodium hydroxide (12 mmol) in ethanol (20 mL) The solution of mesylate in alcohol (5 mL) was then added dropwise to the sodium salt. The reaction mixture was further stirred for 12 h at room temperature. Then solvent was distilled off, treated with brine (20 mL), extracted with chloroform (3× 15 mL) and dried (anhyd Na_2SO_4). The solvent was then removed under reduced pressure to give the crude, which was chromatographed on silica gel using ethyl acetate–hexane (10–15%) as an eluent to afford **19** and **20** as an oil which were converted into oxalate salt in dry methanol.

5.1.4.1. Dimethyl-[1-(4-methoxyphenoxy)-1,2,3,4-tetra hydronaphthalen-2-yl-methyl]-amine oxalate (19). Yield 50%; Mp 140–142 °C; MS (FAB) *m/z*: 312 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69–1.75 (m, 1H, H-3), 2.30–2.44 (m, 10H, H-3, H-2, CH_2–N–$(Me)_2$), 2.87 (m, 2H, H-4), 3.8 (s, 3H, OMe), 5.11 (s, 1H, O–CH), 6.83–6.88 (d, 2H, J = 8.84 Hz, ArH *ortho* to O), 6.97–7.01 (d, 2H, J = 8.92 Hz, ArH *ortho* to O), 7.18–7.37 (m, 4H, ArH); IR (KBr): 3410, 2935, 2859, 2771, 1668, 1504, 1458, 1220, 1036, 748 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_2 \cdot H_2C_2O_4$: C, 65.84; H, 6.73; N, 3.49. Found: C, 65.52; H, 6.38; N, 3.28.

5.1.4.2. Dimethyl-[1-phenoxy-1,2,3,4-tetrahydronaph thalen-2-yl-methyl]-amine oxalate (20). Yield 52%; Mp 168–170 °C; MS (FAB) *m/z*: 282 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7 (m, 1H, H-3), 2.18–2.29 (m, 10H, H-3, H-2, CH_2–N–$(Me)_2$), 2.78–2.80 (m, 2H, H-4), 5.21–5.22 (d, 1H, J = 3.86 Hz, O–CH), 6.95–7.34 (m, 9H, ArH); IR (KBr): 3403, 2932, 2362, 2339, 1657, 1588, 1219, 771 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO \cdot H_2C_2O_4$: C, 67.92; H, 6.74; N, 3.77. Found: C, 68.13; H, 6.60; N, 4.11.

5.1.5. Methyl-[1-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl]-amine oxalate (21). It was prepared by known methods reported in the literature starting from **13**.[16] Yield 73%; Mp 225–227 °C; MS (FAB) *m/z*: 336 ($(M+1)^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76 (m, 1H, H-3), 2.17–2.41 (m, 5H, H-3, H-2, N-Me), 2.54–2.74 (m, 2H, NCH_2), 2.80–2.88 (m, 2H, H-4), 5.39–5.42 (d, 1H, J = 5.26 Hz, O–CH), 7.11–7.28 (m, 6H, ArH), 7.54–7.58 (d, 2H, J = 8.58 Hz, ArH *ortho* to CF_3); IR (KBr): 3323, 2931, 2852, 2798, 1675, 1613, 1516, 1326, 1249, 1162, 1114, 749 cm^{-1}. Anal. Calcd for $C_{19}H_{20}F_3NO \cdot H_2C_2O_4 \cdot 0.25H_2O$: C, 58.67; H, 5.24; N, 3.26. Found: C, 58.79; H, 5.09; N, 3.59.

5.1.6. *N*,*N*-Dibenzyl-3-phenyl-3-(4-acetylphenoxy) propanamine hydrochloride (22). It was prepared by known methods reported in the literature using acetophenone, dibenzylammonium chloride (**4e**) and 4-fluoroacetophenone.[19] Yield 60%; Mp 55 °C; MS (FAB) *m/z*: 450

((M+1)$^+$, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (m, 2H, CH–CH_2), 2.4–2.5 (m, 4H, $COCH_3$, CH–CH_2–CH_2), 2.7 (m, 1H, CH–CH_2–CH_2), 3.44–3.70 (m, 4H, Ar–CH_2–N), 5.24–5.31 (m, 1H, O–CH), 6.67–6.72 (d, 2H, J = 8.86 Hz, ArH *ortho* to $COCH_3$), 7.10–7.34 (m, 15H, ArH), 7.74–7.78 (d, 2H, J = 8.86 Hz, ArH *ortho* to $COCH_3$); IR (KBr): 3447, 3028, 2927, 2082, 2363, 1675, 1599, 1249, 749 cm^{-1}. Anal. Calcd for $C_{31}H_{31}NO_2$·HCl·1.5H_2O: C, 72.59; H, 6.83; N, 2.73. Found: C, 72.83; H, 6.89; N, 3.11.

5.1.7. *N*,*N*-Dibenzyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine hydrochloride (23). It was prepared by known methods reported in the literature using acetophenone, dibenzylammonium chloride (**4e**) and 4-chlorobenzotrifluoride.[19] Yield 70%; Mp 162–166 °C; MS (FAB) *m*/*z*: 475 (M$^+$, 70%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.1 (m, 2H, CH–CH_2), 2.5 (m, 1H, CH–CH_2–CH_2), 2.7 (m, 1H, CH–CH_2–CH_2), 3.43–3.70 (m, 4H, Ar–CH_2–N), 5.25 (m, 1H, O–CH), 6.70–6.74 (d, 2H, J = 8.54 Hz, ArH *ortho* to O), 7.16–7.40 (m, 17H, ArH), IR (KBr): 3029, 2930, 2803, 1614, 1452, 1326, 1252, 1117, 755 cm^{-1}. Anal. Calcd for $C_{30}H_{28}F_3NO$·HCl·H_2O: C, 67.99; H, 5.85; N, 2.64. Found: C, 67.67; H, 5.90; N, 2.41.

5.1.8. *N*-Benzyl-*N*-methyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine hydrochloride (24). It was prepared by known methods reported in the literature using acetophenone, benzylmethylammonium chloride (**4d**) and 4-chlorobenzotrifluoride.[19] Yield 77%; Mp 145–147 °C; MS (FAB) *m*/*z*: 400 ((M+1)$^+$, 30%), 399 (M$^+$, 100%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01–2.06 (m, 1H, CH–CH_2), 2.18–2.29 (m, 4H, N–Me, CH–CH_2), 2.45–2.51 (m, 1H, CH–CH_2–CH_2), 2.60–2.67 (m, 1H, CH–CH_2–CH_2), 3.44–3.57 (m, 2H, Ar–CH_2–N), 5.33–5.37 (m, 1H, O–CH), 6.87–6.90 (d, 2H, J = 8.7 Hz, ArH *ortho* to O), 7.23–7.36 (m, 10H, ArH), 7.42–7.45 (d, 2H, J = 8.7 Hz, ArH *ortho* to CF_3); IR (KBr): 3440, 2937, 2619, 1614, 1517, 1461 cm^{-1}.

5.1.9. *N*-Benzyl-*N*-methyl-3-(4-methoxyphenyl)-3-(4-trifluoromethylphenoxy)propanamine hydrochloride (25). It was prepared by known methods reported in the literature using 4-methoxy acetophenone, benzylmethylammonium chloride (**4d**) and 4-chlorobenzotrifluoride.[19] Yield 72%; MS (FAB) *m*/*z*: 268 ((M-(O–Ar–CF_3))$^+$, 50%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89–2.00 (m, 1H, CH–CH_2), 2.09–2.19 (m, 4H, N-Me, CH–CH_2), 2.33–2.39 (m, 1H, CH–CH_2–CH_2), 2.49–2.56 (m, 1H, CH–CH_2–CH_2), 3.43–3.45 (m, 2H, Ar–CH_2–N), 3.74 (s, 3H, OMe), 5.21–5.28 (m, 1H, O–CH), 6.74–6.82 (m, 4H, ArH *ortho* to O), 7.13–7.23 (m, 7H, ArH), 7.36–7.41 (d, 2H, J = 8.61 Hz, ArH *ortho* to CF_3); IR (Neat): 3417, 3020, 2958, 2363, 1614, 1514, 1326, 1249, 1217, 761 cm^{-1}. Anal. Calcd for $C_{25}H_{26}F_3NO_2$·HCl·0.5H_2O: C, 63.22; H, 5.90; N, 2.95. Found: C, 62.96; H, 6.28; N, 3.10.

5.1.10. *N*-Methyl-3-(4-methoxyphenyl)-3-(4-trifluoromethylphenoxy)propanamine hydrochloride (26). It was prepared by known methods in the literature starting from **25**.[16] Yield 67%; MS (FAB) *m*/*z*: 340 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99–2.07 (m, 1H, NCH_2–CH_2), 2.12–2.21 (m, 1H, NCH_2–CH_2), 2.44 (s, 3H, NMe), 2.72–2.77 (t, 2H, J = 6.28 Hz, NCH_2), 3.77 (s, 3H, OMe), 5.22–5.30 (m, 1H, OCH), 6.81–6.89 (m, 4H, ArH *ortho* to O), 7.19–7.25 (m, 2H, ArH), 7.39–7.44 (d, 2H, J = 8.64 Hz, ArH *ortho* to CF_3); IR (Neat): 3427, 2955, 2840, 2481, 1613, 1514, 1327, 1249, 1143, 1033, 836 cm^{-1}. Anal. Calcd for $C_{18}H_{20}F_3NO_2$·HCl·0.5H_2O: C, 56.18; H, 5.72; N, 3.64. Found: C, 55.95; H, 6.03; N, 3.38.

5.1.11. *N*-Methyl-3-phenyl-3-(4-trifluoromethylphenoxy)-propanamine hydrochloride (fluoxetine). It was prepared by known methods reported in the literature.[16]

5.1.12. *N*,*N*-Dimethyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine hydrochloride (27). A mixture of fluoxetine (618 mg, 2 mmol) and formaldehyde solution (40%, 2.1 mL) in dry methanol (5 mL) was allowed to stir for 1 h , which was followed by the addition of sodium borohydride (200 mg) in portions. The reaction mixture was further stirred for overnight. The solvent was distilled off under reduced pressure. The residue obtained was treated with water (15 mL), extracted with dichloromethane (3× 10 mL) and chromatographed on silica gel column using methanol:chloroform (2:98) as an eluant to afford **27** as an oil, which was converted into hydrochloride salt using methanolic hydrochloric acid. Yield 85%; MS (FAB) *m*/*z*: 324 ((M+1)$^+$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (m, 2H, CH-CH_2), 2.23 (s, 6H, N(Me)$_2$), 2.38–2.42 (m, 2H, CH–CH_2–CH_2), 5.3 (m, 1H, CH), 6.86–6.90 (d, 2H, J = 8.6 Hz, ArH *ortho* to O), 7.25–7.33 (m, 5H, ArH), 7.39–7.43 (d, 2H, J = 8.6 Hz, ArH *ortho* to CF_3); IR (Neat): 2949, 2819, 2771, 1615, 1516, 1327, 1251, 1066, 836, 702 cm^{-1}. Anal. Calcd for $C_{18}H_{20}F_3NO$·HCl·1.75H_2O: C, 55.24; H, 6.27; N, 3.58. Found: C, 55.58; H, 6.54; N, 3.26.

5.2. Pharmacology

All the synthesized compounds were tested for anorexigenic and antidepressant activities by standard methods.[15] The present study was carried out in a group of five Swiss albino mice (weighing 16–20 g) of either sex. Each mouse was individually caged and the compounds were administered intraperitoneally at 75 μmol/kg dose (as oxalate or hydrochloride salt) either as aqueous solution or suspension in gum acacia. After ip administration of the compounds, the animals were observed for gross behaviour. The mice were examined continuously for 3 h after ip 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 fasted for 24 h and pretreated with 75 μmol/kg dose of the compound intraperitoneally. After 1 h, each mouse was exposed to 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 was 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 (Table 1 and Fig. 3). For antidepressant testing, groups of five mice each were administered 2.5 mg/kg ip 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. ip dose of the compound. Antidepressant activity of the compounds was analysed by chi-square test with Yate's correction (one sided *P* value) for ptosis and Mann Whitney '*U*' test for sedation and crouching. Anorexigenic and antidepressant activities of the synthesized compounds were compared with that of the standard drug fluoxetine (Table 1).

Acknowledgments

S.S. thanks the Council of Scientific and Industrial Research (India) for the award of Senior Research Fellowship. The authors are thankful to Mr. Anoop K. Srivastava for providing technical assistance.

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