Med Chem Res 13:8/9 (2004) 631–642

MEDICINAL CHEMISTRY RESEARCH

SYNTHESIS, ANOREXIGENIC ACTIVITY AND QSAR OF SUBSTITUTED ARYLOXYPROPANOLAMINES†

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Abstract. Substituted aryloxypropanolamines (**6-20**) were synthesized and evaluated for their anorexigenic activity. Among them 4-cyanoaryloxy (**7**), 2-methylaryloxy (**9**), 2-methoxyl aryloxy (**10**), 4–acetamidoaryloxy (**15**), 4-bromoaryloxy (**16**) and 4-ethylaminoaryloxy (**20**) exhibited potent anorexigenic activity. According to QSAR studies, the electronic parameter 'σ' plays an important role in describing the variance in activity.

Introduction

The obesity is a chronic and stigmatized disorder in both children and adults, it is widely prevalent in the developed as well as in the developing countries throughout the world.[1,2] It is responsible for various adverse effects on health, being associated with an increase in morbidity and mortality from non-insulin dependent diabetes mellitus (NIDDM), hypertension, hypercholesterolemia, sleep apnea and other medical conditions.[3] Currently available therapies[4,5] for the treatment of obesity are effective only when they are being used and the ability to achieve long-term weight loss by behavioral modification (diet and exercise) is limited. These realizations have resulted in intensified effort to develop new pharmacological approaches for the treatment of obesity.

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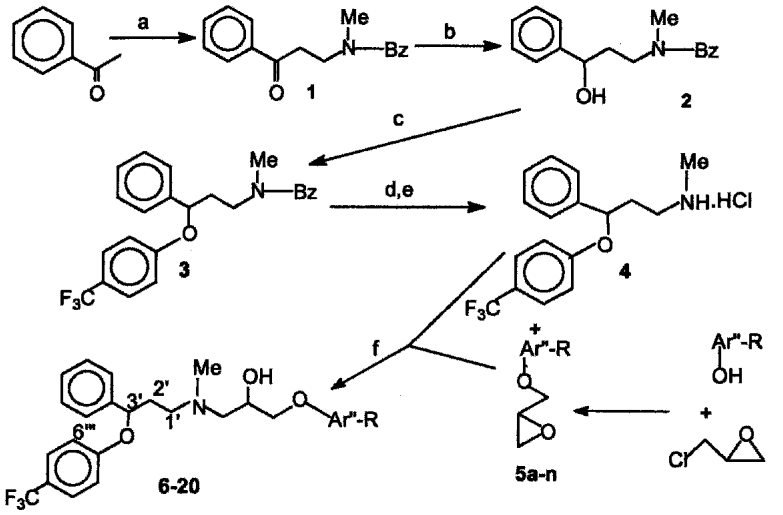
The three types of drugs[6] for the treatment of obesity are: (i) 'drugs' which can reduce the amount of fat absorbed in the gut; (ii) 'thermogenic' drugs, which increase the amount of fat that is metabolized in the body; and (iii) 'satiety' drugs or 'appetite suppressants', which reduce the appetite. Orlistat[7] and Sibutramine[8] are the only two drugs that are currently available for the long term treatment of obesity. Sibutramine suppresses appetite by altering norepenephrine and 5HT metabolism in the brain where as the other drug, Orlistat, reduces fat absorption by inhibiting gastric, pancreatic and other gastrointestinal lipases. Both of these drugs are of limited efficacy. Therefore there is a need of drug with better efficacy and potency.

Selective optimization of side activities (SOSA)[9] has been reported to be an approach for new lead. In view of the anorectic side effects[10,11] of Fluoxetine,[12,13] an antidepressant drug (a selective serotonin reuptake inhibitor), it appeared of interest to substitute the secondary NH group by other substructures so as to optimize the anorexigenic side effect and minimize the antidepressant effect. These studies involving the synthesis of substituted aryloxy propanolamines, their pharmacological evaluation and QSAR analysis are reported in this paper.

Chemistry

The synthetic route for substituted aryloxypropanolamines (**6-20**) is outlined in **scheme 1**.

Scheme 1



	Ar"R		Ar"R		Ar"R
6.	2-Naphthyl	**11.**	C_6H_4-4-COC_2H_5	**16.**	C_6H_4-4-Br
7.	C_6H_4-4-CN	**12.**	C_6H_4-4-CF_3	**17.**	C_6H_4-4-OCH_3
8.	C_6H_5	**13.**	C_6H_4-4-$COCH_3$	**18.**	C_6H_4-4-CHO
9.	C_6H_4-2-CH_3	**14.**	C_6H_4-3-CF_3	**19.**	C_6H_4-4-Cl
10.	C_6H_4-2-OCH_3	**15.**	C_6H_4-4-$NHCOCH_3$	**20.***	C_6H_4-4-NHC_2H_5

Reagents: (a) Bz.MeNH, $(CH_2O)_n$, *n*-propanol; (b) $NaBH_4$/MeOH; (c) NaH, *p*-chlorobenzotrifluoride, DMAC; (d) $ClCOOCH_3$, KOH, NH_2NH_2OH; (e) HCl; (f) K_2CO_3, EtOH.
*from the reduction of compound **15** by $LiAlH_4$ / THF.

The key intermediate *N*-methyl-3-phenyl-3-(4-trifluoromethylphenoxy) propylamine (**4**) was prepared from acetophenone by reported method.[14,15] Mannich reaction of acetophenone and benzylmethylamine furnished the benzylmethylamino-propiophenone (**1**), which on $NaBH_4$ reduction gave the hydroxy intermediate (**2**). Condensation of the hydroxy intermediate **2** with *p*-chlorobenzotrifluoride in presence of sodium hydride in dimethylacetamide[15] furnished (**3**), which on debenzylation gave the required key intermediate (**4**). Hydrochloride of (**4**) was condensed with appropriate 1-aryloxy-2,3-epoxypropanes (**5a-n**) in presence of potassium carbonate in absolute ethanol to furnish the desired substituted aryloxypropanolamines (**6-19, Scheme 1**) The 4-*N*-ethylaminoaryloxypropanol-amine (**20**) was prepared by $LiAlH_4$ reduction of the amido compound (**15**). The epoxy reactants **5a-n** were prepared by condensation of the required phenols with excess of epichlorohydrin in presence of potassium carbonate.[16]

Results and Discussion

All the compounds were tested for their effect on the gross behavior, antidepressant and anorexigenic activity by the standard methods.[17] The compounds, **6-20** showed no effect on the gross behaviour, however fluoxetine had shown sign of stimulation i.e. increased SMA (spontaneous motor activity), respiration and reactivity. In antireserpine tests all the compounds except (**7**) showed no activity, whereas fluoxetine showed 100% reversal of reserpine induced ptosis and sedation. The compounds **7, 9, 10, 15, 16** and **20** exhibited high degree of anorexia (56–72%) like fluoxetine but no appreciable antidepressant activity in most of the compounds except in the compound **7** with 4-CN group was observed.

In order to study the effect of different physicochemical and structural parameters on anorexigenic activity, the Quantitative Structural Activity Relationship (QSAR) studies have been carried out taking the percentage anorexigenic effect (%) as log [%/(100-%)] as dependent parameter, and different physicochemical parameters *viz.* hydrophobicity 'π', electronic sigma 'σ' and polar '*F*' and steric parameters '*MR*'[18] as independent parameters (**Table 1**). Among all these parameters, the best correlation R=0.405 was found only with electronic parameter 'σ' (**Eq.1**) for the fifteen compounds **6-20**.

$$\log [\%/(100-\%)] = -0.274(\pm 0.172)^{*}\sigma - 0.008; \quad (n=15, R= 0.405, s=0.239, F=2.548)\ldots\ldots \textbf{Eq.1}$$

The removal of the most deviating compound (outlier) number **7** with -CN group improved the correlation R=0.749 of anorexigenic activity very significantly with electronic parameters like 'σ' (**Eq. 2**) followed by polar *F* (R=0.541). However there was still a poor correlation with hydrophobicity (π) (R=0.244) and no correlation with steric parameter (*MR*) (**Table 2**). The **equation 2** describing the variation of anorexigenic activity with sigma parameter showed good statistical significance >99.75% ($F_{1,\ 12\ \alpha\ 0.0025}$ =14.5, $F_{1,\ 12}$ =15.372) with the correlation coefficient value R = 0.749 (**Eq.2**).

$$\log [\%/(100-\%)] = -0.475(\pm 0.121)^{*}\sigma - 0.029; \quad (n=14, R= 0.749, s=0.156, F=15.372)\ldots\ldots \textbf{Eq.2}$$

This equation well explains the variation in observed activity with sigma parameter (**Table 1**), thus indicating that the electron donating substituents with negative sigma value can enhance the anorexigenic activity. The outlier behavior of compound **7** may be due to the metabolic conversion of the CN group to $-CH_2NH_2$ (σ = -0.74) because the predicted activity value 0.322 for the CH_2NH_2 analog is close to the observed activity value 0.410 than that of the CN analog -0.342. Although such type of conversion is not reported in the literature, the **equation 3** derived using the CH_2NH_2 compound instead of compound **7** with CN group improved the correlation R=0.816 and statistical significance >99.95% ($F_{1,\ 13\ \alpha\ 0.0005}$ = 21.1, $F_{1,\ 13}$ =25.987).

$$\log [\%/(100-\%)] = -0.505(\pm 0.099)^{*}\sigma - 0.022 \quad (n=15, R= 0.816, s=0.151, F=25.987)\ldots\ldots \textbf{Eq.3}$$

(*The values in parentheses indicate standard error of regression coefficient)

Table 1: Physicochemical parameters and anorexigenic activity of aryloxypropanolamines **6-20**

Comp no.	Ar"R	Anorexigenic activity at 75 μmol/kg i.p. (% effect)	Log[%/ (100-%)]			π	MR	F	σ
			Observed	Calculated by eq. 2	Calculated by eq. 3				
6	2-naphthyl	40	-0.176	-0.010	-0.002	1.64	26.1	0.14	-0.04
7	C_6H_4-4-CN	72	0.410	0.322*	0.352**	-0.57	10.45	0.51	0.66
8	C_6H_5	52	0.035	-0.029	-0.022	0.0	5.15	0.0	0.0
9	C_6H_4-2-CH_3	60	0.176	0.052	0.064	0.56	9.77	-0.04	-0.17
10	C_6H_4-2-OMe	56	0.105	0.099	0.115	-0.02	11.99	0.26	-0.27
11	C_6H_4-4-COC_2H_5	36	-0.250	-0.266	-0.274	0.06	19.95	0.32	0.50
12	C_6H_4-4-CF_3	32	-0.327	-0.285	-0.294	0.88	9.14	0.38	0.54
13	C_6H_4-4-$COCH_3$	32	-0.327	-0.266	-0.274	-0.55	15.3	0.32	0.50
14	C_6H_4-3-CF_3	32	-0.327	-0.233	-0.239	0.88	9.14	0.38	0.43
15	C_6H_4-4-$NHCOCH_3$	60	0.176	-0.029	-0.022	-0.97	19.05	0.28	0.0
16	C_6H_4-4-Br	60	0.176	-0.138	-0.138	0.86	13.0	0.44	0.23
17	C_6H_4-4-OCH_3	52	0.035	0.099	0.115	-0.02	11.99	0.26	-0.27
18	C_6H_4-4-CHO	40	-0.176	-0.228	-0.234	-0.65	11.0	0.31	0.42
19	C_6H_4-4-Cl	28	-0.410	-0.138	-0.138	0.71	10.15	0.41	0.23
20	C_6H_4-4-NHC_2H_5	60	0.176	0.261	0.286	0.08	19.1	-0.11	-0.61
	Fluoxetine	72							

*Predicted for Ar"R = C_6H_4-4-CH_2NH_2, **Calculated for Ar"R = C_6H_4-4-CH_2NH_2

Table 2: Pearson correlation matrix for compounds **6, 8-20**

	PI	MR	F	S	log[%/(100-%)]
PI	1.000				
MR	0.073	1.000			
F	0.042	-0.111	1.000		
S	0.039	-0.181	0.724	1.000	
Log[%/(100-%)]	-0.244	0.067	-0.541	-0.749	1.000

Number of observations:14

Conclusion

These studies suggested that the SOSA approach has potential in optimizing the side activities by proper structural modification as observed above. The replacement of hydrogen in NH of $NHCH_3$ group in fluoxetine and its substitution by aryloxypropanol substructure resulted in the complete loss of antidepressant effect (the main activity) and in the retention of anorexigenic effect (the side activity). Further the dependence of anorexigenic activity on electronic parameter σ from the QSAR studies suggested that careful substitution by electron donating substituents may lead to the new molecules with enhanced anorexigenic activity.

Experimental

Chemistry - Melting points were determined in open capillaries in an electrically heated block and are uncorrected. IR spectra 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 300spectrometer (70 eV). Microanalyses were determined on Carlo Erba EA-1108 element analyzer within ±0.4% of the theoretical values. Thin layer chromatography was performed on 7.5×3.0cm. precoated silica gel plastic plates (Aldrich). For column chromatography, silica gel of 60-120 mesh from Qualigen Fine Chemicals was used.

General procedure for the preparation of 1-(substitutedaryloxy)-2,3-epoxypropane[16] **(5a-n).** A mixture of required phenol (50mmol), K_2CO_3 (60mmol) and epichlorohydrin (23g, 250mmol) was stirred at 120°C for 4-5h. After completion of reaction the solid was filtered, filtrate was diluted with water (50mL) and extracted with ethyl acetate. Organic layer was washed with water and concentrated to oil and chromatographed on a silica gel column to get the following epoxy propanes (**5a-n**):

S.No.	Compound **5a-n**	Yield(%)	mp(°C)
1	1-(*β*-Naphthyloxy)-2,3-epoxypropane (**5a**)	82	55
2	1-(4-Cyanoaryloxy)-2,3-epoxypropane (**5b**)	92	oil
3	1-Aryloxy-2,3-epoxypropane (**5c**)	74	oil
4	1-(2-Methylaryloxy)-2,3-epoxypropane (**5d**)	91	oil
5	1-(2-Methoxyaryloxy)-2,3-epoxypropane (**5e**)	93	oil
6	1-(4-Propionylaryloxy)-2,3-epoxypropane (**5f**)	87	49-50
7	1-(4-*α*,*α*,*α*-Trifluoromethylaryloxy)-2,3-epoxypropane (**5g**)	80	oil
8	1-(4-Acetylaryloxy)-2,3-epoxypropane (**5h**)	72	oil
9	1-(3-*α*,*α*,*α*-Trifluoromethylaryloxy)-2,3-epoxypropane (**5i**)	88	oil
10	1-(4-Acetamidoaryloxy)-2,3-epoxypropane (**5j**)	95	85
11	1-(4-Bromoaryloxy)-2,3epoxypropane (**5k**)	94	oil
12	1-(4-Methoxyaryloxy)-2,3-epoxypropane (**5l**)	73	39-40
13	1-(4-Formylaryloxy)-2,3-epoxypropane (**5m**)	82	oil
14	1-(4-Chloroaryloxy)-2,3-epoxypropane (**5n**)	79	oil

***N*-Methyl-3-phenyl-3-(4-trifluoromethyl)phenoxypropylamine (4).** A mixture of intermediate compound **3**[14,15] (5.9g, 14 mmol) and methylchloroformate (2.7g, 28mmol), in benzene (30mL) was refluxed for 12 h, cooled to r.t.. Reaction discontinued, sodium bicarbonate (5%, 10mL) was added, and benzene layer was separated and concentrated to oil. A solution of this oil in propanol (30mL), potassium hydroxide pellets (1.68g, 30mmol) and hydrazine hydrate (2.8g, 56mmol) was refluxed under stirring for 5h., cooled and filtered. Filtrate was concentrated, water (30mL) was added to it and extracted with ethyl acetate (3×30mL). Combined ethyl acetate extracts dried over anhyd.Na_2SO_4 and concentrated to oil which was taken in MeOH (30mL) and Conc. HCl (2mL) was added to it. Concentration of methanol gave the compound as oil, which was solidified on triturating with hexane/ethyl acetate mixture (2:1). Yield: 65%, mp: 151-153°C. ^{1}H NMR ($CDCl_3$, δ): 2.02-2.21(m, 2H, 2-CH_2), 2.41(s, 3H, N-CH_3), 2.69-2.76(t, 2H, *J*=6.6Hz, 1-CH_2), 5.26-5.32(m, 1H, 3-CH), 6.87-6.92(d, 2H, *J*=8.6Hz, ArH adjacent to O), 7.25-7.34(m, 5H, ArH), 7.40-7.44(d, 2H, *J*=8.6Hz, ArH adjacent to CF_3); MS (FAB): m/z 310 [$(M+1)^+$, 100%].

General procedure for the preparation of 1-(2" or 3" or 4"–substituted or unsubstituted aryloxy)-3-{*N*-methyl-*N*-[3'-aryl-3'-(4'"-α,α,α-trifluoromethylaryloxy) propyl]amino} propan-2-ol(6-20). A mixture of **4** (518mg, 1.5mmol), K_2CO_3 (621mg, 4.5mmol) and appropriate 1-(substituted) aryloxy-2,3- epoxypropane, **5a-n** (1.65 mmol) in absolute alcohol (20mL) was refluxed for 5h., cooled and filtered. Concentration of filtrate afforded the crude product as oil, which was purified on a silica gel column using $CHCl_3$ or $CHCl_3$.and MeOH (99:1 or 98:2%) as an eluent.

1-(2"-Naphthyloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4'"-α,α,α-trifluoromethylaryloxy)propyl) amino]propan-2-ol (6). Yield: 87%; ^{1}H NMR ($CDCl_3$): δ 1.99-2.26(m, 2H, NCH_2-$C\underline{H}_2$), 2.34(s, 3H, NMe), 2.59-2.71(m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 4.08-4.14(m, 3H, OH-C$\underline{H}$-$C\underline{H}_2$-O), 5.25-5.27(m, 1H, O-CH), 6.85-6.90(d, 2H, *J*=8.59Hz, ArH), 7.13-7.17 (m, 2H, ArH), 7.25-7.47(m, 8H, ArH), 7.68-7.78(m, 4H, ArH); MS (FAB): m/z 510[$(M+1)^+$, 100%]. Anal. Calcd. for $C_{30}H_{30}F_3NO_3$: C 70.73, H 5.89, N 2.75; found: C 71.06, H 6.28, N 2.37.

1-(4"-Cyanoaryloxy)-3-[*N*-methyl–*N*-(3'aryl-3'-(4'"-α,α,α-trifluoromethylaryloxy)-propyl)amino]propan-2-ol (7). Yield: 77%; ^{1}H NMR ($CDCl_3$): δ 1.98-2.22(m, 2H, NCH_2-$C\underline{H}_2$), 2.32(s, 3H, NMe), 2.51-2.71(m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.95-4.08(m, 3H, OH-C$\underline{H}$-$C\underline{H}_2$-O),

5.23-5.25(m, 1H, O-CH), 6.86-7.00(m, 4H, C-2"H, C-6"H, C-2‴H, C-6‴H), 7.26-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.7Hz, C-3‴H, C-5‴H), 7.54-7.58(d, 2H, *J*=8.6Hz, C-3"H, C-5"H); MS (FAB): m/z 485[$(M+1)^+$, 40%]. Anal. Calcd. for $C_{27}H_{27}F_3N_2O_3$: C 66.94, H 5.57, N 5.79; found: C 67.18, H 5.79, N 5.51.

1-Aryloxy-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoromethylaryloxy)propyl)amino] propan-2-ol (8). Yield: 70%; ^{1}H NMR ($CDCl_3$): δ 1.98-2.18(m, 2H, NCH_2-C<u>H</u>$_2$), 2.32(s, 3H, NMe), 2.51-2.70(m, 4H, C<u>H</u>$_2$-N-C<u>H</u>$_2$), 3.92-4.04(m, 3H, OH-C<u>H</u>-C<u>H</u>$_2$-O), 5.22-5.26(m, 1H, O-CH), 6.86-6.98(m, 5H, C-2"H, C-4"H, C-6"H, C-2‴H, C-6‴H), 7.23-7.32(m, 7H, ArH, C-3"H, C-5"H), 7.39-7.43(d, 2H, *J*=8.67Hz, C-3‴H, C-5‴H); MS (FAB): m/z 460 [$(M+1)^+$, 91%]. Anal. Calcd. for $C_{26}H_{28}F_3NO_3$: C 67.97, H 6.10, N 3.05; found: C 68.38, H 6.43, N 2.84.

1-(2"-Methylaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (9). Yield: 91%; ^{1}H NMR ($CDCl_3$): δ 2.05-2.23(m, 5H, NCH_2-C<u>H</u>$_2$, Ar"-CH_3), 2.32(s, 3H, NMe), 2.53-2.70(m, 4H, C<u>H</u>$_2$-N-C<u>H</u>$_2$), 3.91-4.04(m, 3H, OH-C<u>H</u>-C<u>H</u>$_2$-O), 5.23-5.27(m, 1H, O-CH), 6.86-6.90(d, 4H, *J*=8.31Hz, C-2"H, C-4"H, C-2‴H, C-6‴H), 7.09-7.16(m, 2H, C–3"H, C-5"H), 7.26-7.31(m, 5H, ArH), 7.39-7.43(d, 2H, *J*=8.61Hz, C-3‴H, C-5‴H); MS (FAB): m/z 474 [$(M+1)^+$, 100%]. Anal. Calcd. for $C_{27}H_{30}F_3NO_3$.HCl.¼ H_2O: C 63.04, H 6.13, N 2.72, found: C 62.77, H 5.83, N, 2.37.

1-(2"-Methoxyaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (10). Yield: 60%; ^{1}H NMR ($CDCl_3$): δ 1.96-2.22(m, 2H, NCH_2-C<u>H</u>$_2$), 2.31(s, 3H, NMe), 2.54-2.67(m, 4H, C<u>H</u>$_2$-N-C<u>H</u>$_2$), 3.83(s, 3H, OMe), 3.96-3.99(m, 3H, OH-C<u>H</u>-C<u>H</u>$_2$-O), 5.18-5.27(m, 1H, O-CH), 6.86-6.89(m, 6H, Ar"H, C-2‴H, C-6‴H), 7.26-7.31(m, 5H, ArH), 7.38-7.43(d, 2H, *J*=8.8Hz, C-3‴H, C-5‴H); MS (FAB): m/z 490 [$(M+1)^+$, 100%]. Anal. Calcd. for $C_{27}H_{30}F_3NO_4$.HCl: C 61.66; H 5.89, N 2.66; found: C 61.86, H 6.27, N 2.86.

1-(4"-Propionylaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoromethylaryloxy) propyl)amino]-propan-2-ol (11). Yield: 97%; ^{1}H NMR ($CDCl_3$): δ 1.17-1.24(t, 3H, *J*=7.26Hz, CO-CH_2-C<u>H</u>$_3$), 1.98-2.22(m, 2H, NCH_2-C<u>H</u>$_2$), 2.32(s, 3H, NMe), 2.52-2.64(m, 4H, C<u>H</u>$_2$-N-C<u>H</u>$_2$), 2.89-3.00(q, 2H, *J*=7.2Hz, $COCH_2$), 4.00-4.10(m, 3H, OH-C<u>H</u>-C<u>H</u>$_2$-O),

5.22-5.28(m, 1H, O-CH), 6.86-6.94(m, 4H, C-2"H, C-6"H, C-2‴H, C-6‴H), 7.26-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.4Hz, C-3‴H, C-5‴H), 7.90-7.94(d, 2H, *J*=8.7Hz, C-3"H, C-5"H); MS (FAB): m/z 516 [$(M+1)^+$, 100%]. Anal. Calcd. for $C_{29}H_{32}F_3NO_4$.HCl. ¼ H_2O: C 62.59, H 6.03, N 2.52; found: C 62.27, H 5.65, N 2.24.

1-(4"-α,α,α-Trifluoromethylaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoro methylaryloxy)propyl)amino]propan-2-ol (12). Yield: 70%; ^{1}H NMR ($CDCl_3$): δ 2.00-2.21(m, 2H, NCH_2-C$\underline{H_2}$), 2.32(s, 3H, NMe), 2.52-2.70(m, 4H, C$\underline{H_2}$-N-C$\underline{H_2}$), 3.98-4.08(m, 3H, OH-C$\underline{H}$-C$\underline{H_2}$-O), 5.22-5.26(m, 1H, O-CH), 6.86-7.01(m, 4H, C-2"H, C-6"H, C-2‴H, C-6‴H), 7.26-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.5Hz, C-3‴H, C-5‴H), 7.50-7.54(d, 2H, *J*=8.6Hz, C-3"H, C-5"H); MS (FAB): m/z 528 [$(M+1)^+$, 30%]. Anal. Calcd. for $C_{27}H_{27}F_6NO_3$.HCl.½ H_2O: C 56.49, H 4.86, N 2.45; found: C 56.10, H 4.51, N 2.17.

1-(4"-Acetylaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (13). Yield: 97%; ^{1}H NMR ($CDCl_3$): δ 1.98-2.22(m, 2H, NCH_2-C$\underline{H_2}$), 2.33(s, 3H, NMe), 2.55-2.71(m, 7H, C$\underline{H_2}$-N-C$\underline{H_2}$, COMe), 4.00-4.10(m, 3H, OH-C$\underline{H}$-C$\underline{H_2}$-O), 5.23-5.29(m, 1H, O-CH), 6.86-6.98(m, 4H, C-2"H, C-6"H, C-2‴, C-6‴ H), 7.26-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.6Hz, C-3‴H, C-5‴H) 7.89-7.93(d, 2H, *J*=8.7Hz, C-3"H, C-5"H); MS (FAB): m/z 502 [$(M+1)^+$, 100%]. Anal. Calcd. for $C_{28}H_{30}F_3NO_4$.¼ H_2O: C 66.47, H 6.03, N 2.77; found: C 66.49, H 6.39, N 2.45.

1-(3"-α,α,α-Trifluoromethylaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluorometh ylaryloxy)propyl)amino]propan-2-ol (14). Yield: 96%; ^{1}H NMR ($CDCl_3$): δ2.06-2.23(m, 2H, NCH_2-C$\underline{H_2}$), 2.32(s, 3H, NMe), 2.52-2.70(m, 4H, C$\underline{H_2}$-N-C$\underline{H_2}$), 3.95-4.07(m, 3H, OH-C$\underline{H}$-C$\underline{H_2}$-O), 5.24(m, 1H, O-CH), 6.86-6.90(d, 2H, *J*=8.6Hz, ArH), 7.03-7.43(m, 11H, ArH); MS (FAB): m/z 528 [$(M+1)^+$, 100%]. Anal. Calcd. for $C_{27}H_{27}F_6NO_3$: C 61.48, H 5.12, N 2.66; found: C 61.86, H 5.43, N 2.32.

1-(4"-Acetamidoaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4‴-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (15). Yield: 57%; ^{1}H NMR ($CDCl_3$): δ 1.97-2.22(m, 5H, NCH_2-C$\underline{H_2}$, COMe), 2.32(s, 3H, NMe), 2.51-2.71(m, 4H, C$\underline{H_2}$-N-C$\underline{H_2}$), 3.92-3.94(m, 3H, OH-C$\underline{H}$-C$\underline{H_2}$-O), 5.2-5.28(m, 1H, O-CH), 6.85-6.90(m, 4H, C-2"H, C-6"H, C-2‴H, C-6‴H), 7.26-7.34(m, 5H, ArH), 7.39-7.43(m, 4H, C-3"H, C-5"H, C-3‴H, C-5‴ H); MS (FAB): m/z 517

[$(M+1)^+$, 100%]. Anal. Calcd. for $C_{28}H_{31}F_3N_2O_4$: C 65.12, H 6.01, N 5.43; found: C 65.46, H 6.32, N 5.32.

1-(4"-Bromoaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4'''-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (16). Yield: 68%; ^{1}H NMR ($CDCl_3$): δ 2.05-2.20(m, 2H, NCH_2-$C\underline{H}_2$), 2.32 (s, 3H, NMe), 2.41-2.69(m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.88-4.00(m, 3H, OH-$C\underline{H}$-$C\underline{H}_2$-O), 5.22-5.25(m, 1H, O-CH), 6.75-6.90(m, 4H, C-2"H, C-6"H, C-2'''H, C-6'''H), 7.26-7.44(m, 9H, ArH, C-3"H, C-5"H, C-3'''H, C-5'''H); MS (FAB): m/z 538 [$(M)^+$, 73%]. Anal. Calcd. for $C_{26}H_{27}BrF_3NO_3$: C 57.99, H 5.02, N 2.60; found: C 58.39, H 5.35, N 2.39.

1-(4"-Methoxyaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4'''-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (17). Yield: 88%; ^{1}H NMR ($CDCl_3$): δ 1.98-2.26(m, 2H, NCH_2-$C\underline{H}_2$), 2.31(s, 3H, NMe), 2.49-2.69(m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.76(s, 3H, OMe), 3.89-3.99(m, 3H, OH-$C\underline{H}$-$C\underline{H}_2$-O), 5.22-5.26(m, 1H, O-CH), 6.81-6.90(m, 6H, C-2"H, C-3"H, C-5"H, C-6"H, C-2'''H, C-6'''H), 7.25-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.6Hz, C-3'''H, C-5'''H); MS (FAB): m/z 490 [$(M+1)^+$,100%]. Anal. Calcd. for $C_{27}H_{30}F_3NO_4$.HCl.½ H_2O: C 60.62, H 5.98, N 2.62; found: C 60.22, H 6.25, N 2.45.

1-(4"-Formylaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4'''-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (18) . Yield: 65%; ^{1}H NMR ($CDCl_3$): δ 1.99-2.22(m, 2H, NCH_2-$C\underline{H}_2$), 2.33 (s, 3H, NMe), 2.54-2.65(m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 4.02-4.19(m, 3H, OH-$C\underline{H}$-$C\underline{H}_2$-O), 5.2-5.27(m, 1H, O-CH), 6.86-6.90(d, 2H, *J*=8.7Hz, C-2'''H, C-6'''H), 7.01-7.05(d, 2H, *J*=8.7Hz, C-2"H, C-6"H), 7.26-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.8Hz, C-3'''H, C-5'''H), 7.80-7.86(m, 2H, C-3"H, C-5"H); MS (FAB): m/z 488 [$(M+1)^+$, 92%]. Anal. Calcd. for $C_{27}H_{28}F_3NO_4$. HCl.½ H_2O: C 60.85, H 5.63, N 2.63; found: C 60.78, H 5.54, N 2.33.

1-(4"-Chloroaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4'''-α,α,α-trifluoromethylaryloxy) propyl)amino]propan-2-ol (19). Yield: 96%; ^{1}H NMR ($CDCl_3$): δ 1.98-2.22(m, 2H, NCH_2-$C\underline{H}_2$), 2.31 (s, 3H, NMe), 2.50-2.69(m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.88-4.04(m, 3H, OH-$C\underline{H}$-$C\underline{H}_2$-O), 5.23(m, 1H, O-CH), 6.72-6.90(m, 4H, C-2"H, C-6"H, C-2'''H, C-6'''H), 7.10-7.44(m, 9H, ArH, C-3"H, C-5" H, C-3'''H, C-5'''H); MS(FAB) m/z: 494 [$(M)^+$,100%]. Anal Calcd. for $C_{26}H_{27}$ ClF_3N O_3.HCl.1H_2O: C 56.90, H 5.47, N 2.55; found: C 56.58, H 5.13, N 2.17.

1-(4"-*N*-ethylaminoaryloxy)-3-[*N*-methyl-*N*-(3'-aryl-3'-(4"'-α,α,α-trifluoromethyl aryloxy)propyl)amino]propan-2-ol (20). A solution of acetamido compound (**15**) (516 mg, 1mmol) dissolved in anhydrous THF (10mL) was added to a stirred and cooled suspension of $LiAlH_4$ (380mg, 10mmol) in anhydrous THF (20mL) within a period of 30 minutes. The mixture was stirred at low temp. for 30 minutes and refluxed for 5h., cooled in an ice bath and water (10mL) was added slowly to it. Reaction mixture was filtered through celite bed and concentrated to an oil. The oil was taken in ethyl acetate (30mL) and washed with distilled water (2×20mL), dried over anhyd. Na_2SO_4 and concentrated to give the required product (**20**) as an oil. Yield: 82%; ^{1}H NMR ($CDCl_3$): δ 1.23-1.27(m, 3H, NCH_2-C<u>H</u>$_3$), 1.97-2.22(m, 2H, NCH_2-C<u>H</u>$_2$), 2.31(s, 3H, NMe), 2.51-2.64(m, 4H, C<u>H</u>$_2$-N-C<u>H</u>$_2$), 3.04-3.15(q, 2H, *J*=7.12Hz, N<u>C</u>H_2-CH_3), 3.87-4.1(m, 3H, OH-C<u>H</u>-C<u>H</u>$_2$-O), 5.21-5.31(m, 1H, O-CH), 6.53-6.57(d, 2H, *J*=8.9Hz, C-3"H, C-5"H), 6.74-6.79(d, 2H, *J*=8.5Hz, C-2"H, C-6"H), 6.86-6.90(d, 2H, *J*=8.6Hz, C-2"'H, C-6"'H), 7.26-7.32(m, 5H, ArH), 7.39-7.44(d, 2H, *J*=8.9Hz, C-3"'H, C-5"'H); MS (FAB): m/z 503 [$(M+1)^+$, 86%]. Anal. Calcd. for $C_{28}H_{33}F_3N_2O_3.2HCl.½ H_2O$: C 57.53, H, 6.16, N 4.79; found: C 57.15, H 5.77, N 4.41.

Pharmacology

All the synthesized compounds (**6-20**) were tested for antidepressant and anorexigenic activities by standard methods.[17] The present study was carried out in a group of five Swiss mice (weighing 16-20g) of either sex. All the compounds were administered in a dose of 75 μmol/kg (*i.p.*), either as aqueous solution or suspension in gum accacia. After i.p. administration of the compounds in groups of five mice each, the animals were observed for gross behavioral effects. CNS depression was judged by reduced SMA, sedation, ptosis, crouching, catalepsy and autonomic effects. For anorexigenic activity groups of five mice each individually caged were pretreated with graded doses of the compounds and were offered milk (sweetened and reconstituted as 25% aqueous suspension from powdered milk). Each mouse was exposed to 0.5mL of this milk for 15 minutes. Control mice drank this quantity within 15 minutes. Any quantity of milk left after 15 minutes in the treated group indicate anorexigenic activity. The results were compared with those of fluoxetine (**Table 1**).

Acknowledgements

The authors thank Mr. Anoop Srivastava & Mr. A. S. Kushwaha for the technical assistance.

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