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MEDICINAL CHEMISTRY RESEARCH

SYNTHESIS OF THE RIGID ANALOGUES OF AN SSRI BENZENEPROPANAMINE†

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Abstract. Several 1-(substituted phenoxy)-3-{[4-(4-trifluoromethyl) phenoxy] piperidin-1-yl} propan-2-ols (str.II) were prepared in a six-step reaction sequence starting from methylamine and ethyl acrylate and evaluated for antidepressant activity. The compounds were fully characterized by spectral and elemental analyses, and were tested for their effect on gross behavior, antireserpine and anorexigenic activity. No effect was observed on gross behavior and some of them showed fluoxetine like antireserpine and anorexigenic activity.

Introduction

The development of a specific antidepressant has been one of the unmet medical needs in recent years[1]. Hence an antidepressant with unique and novel properties, i.e., reduced side effects, enhanced clinical efficacy with early onset action, is the need of the present time[2]. N-methyl-3- [(4-trifluoromethyl) phenoxy] benzenepropanamine, Fluoxetine (str.I)[3] has been widely used antidepressant drug with selective serotonin reuptake inhibitor (SSRI) mode of action. This suggest its efficacy and acceptability, still it has several side-effects[4] like delayed onset of action, slow elimination[5] in liver and renal impairments, accumulation in brain, anorexia and suicide ideation[6]. The anorectic side effect suggests that it might be affecting a range of 5-HT[7] receptors as well. Therefore, there is urgent need of a more specific SSRI type of antidepressant agent.

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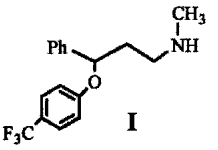
Keeping the above observations in consideration it was thought worthwhile to synthesize fluoxetine class of compounds with a rigid framework so as to restrict the free movement of the propylamine side chain. It has been carried out by linking the nitrogen atom and C-1 carbon atom through a two-methylene alkyl chain. Since the CNS activity of 2-amino propanols is well known,[8,9] a substituted phenoxy propan-2-ol side chain has also been attached at N-atom(str.II).



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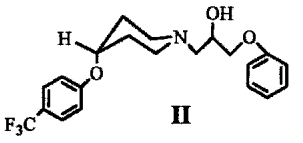


II

Chemistry

As shown in scheme 1, the Grignard reaction of N-methyl-4-piperidone(**1**) with PhMgBr gave **2**. N-methyl-4-piperidinol(**3**) was reacted with 4-chlorobenzotrifluoride in presence of sodium hydride to provide **4** which was N-demethylated(**6**) using ethyl chloroformate followed by alkaline hydrolysis of **5**. 4-(4-trifluoromethyl)phenoxypiperidine(**6**) was alkylated with 1,2-epoxy-3-substituted phenoxypropanes in DMSO to give final compounds(**7-19**).

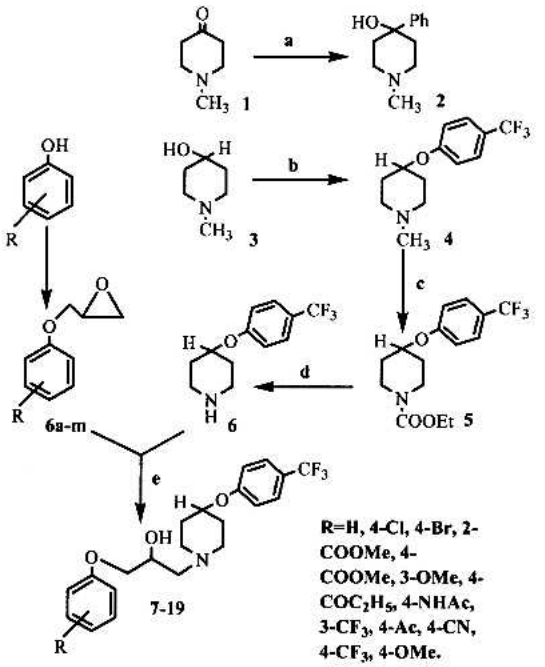
Results and Discussion

The compounds tested had no effect on gross behaviour, however, fluoxetine had shown signs of stimulation. In the antireserpine test, fluoxetine caused 100%, two compounds (**6** and **8**) exhibited 75% and compound **12** showed 50% reversal of reserpine induced ptosis, sedation and crouching. Whereas other compounds were inactive. Compounds **9** and **14** exhibited significant anorexia (77 and 78%) comparable to fluoxetine (81%) while nine compounds had moderate to good anorexigenic activity (46-67%). Three compounds (**6**, **8** and **12**) had both the antidepressant and anorexigenic activity like fluoxetine[10], while eight others showed only anorexigenic activity.

The activity results of compounds **2** and **6** (table 1) suggested that a phenoxy group, preferably with 4-trifluromethyl substitution was essential for these activities. The absence of activity in compound **4** which resembles most with the standard drug fluoxetine and fluoxetine like activity in **6** which is desmethyl derivative of **4** may be explained on the basis of metabolic transformations of fluoxetine[11], where fluoxetine and its demethylated metabolite both are biologically active. In case of compound **4** and **6**, the compound **4** is inactive and its demethylation might not be occurring.

The alkylation at N-atom of compound **6** with 3-phenoxyhydroxy propyl side chain has shown selectivity towards anorexigenic activity in compounds **7**, **9**, **12**, **14-17**, **19**. Compounds **9** and **14** had shown anorexigenic activity comparable to fluoxetine were devoid of antireserpine activity. Compounds **8** and **12** had both the antireserpine and anorexigenic activity.

The compounds **7-19** have shown an interesting structure activity relationship for the substituents in phenyl ring and in the 3-phenoxy-2-hydroxy propyl side chain. The substitution at position 4 by bromo(**9**) and acetyl(**14**) group enhanced the activity as compared to compound with unsubstituted phenyl ring(**7**), by chloro(**8**), 4-trifluoromethyl(**19**) the activity is retained, while with methoxycarbonyl at position 2 or 4(**10**, **11**), methoxy group at position 3 or 4(**12**, **13**), 4-propionyl(**15**), acetamido(**16**), cyano(**17**) at position 4 and trifluromethyl(**18**) at position 3, the anorexigenic activity was either decreased or completely lost.



Scheme 1. **a**: PhMgBr/THF ; **b** : NaH/p-chlorobenzotrifluoride/DMAC ; **c** : $ClCO_2Et$/Benzene ; **d** : KOH/EtOH ; **e** : DMSO

Conclusion

It may be inferred that the 4-(trifluoromethyl)phenoxy propylamine in a rigid framework (str.II) might be having some selectivity towards 5-HT receptors[7] involved for anorexia i.e., 5-HT_2. Secondly, its alkylation at nitrogen atom with 3-phenoxy 2-hydroxy propyl group may yield an appetite suppressant agent.

Experimental

Chemistry: Uncorrected melting points were taken on an electrically heated block. IR spectra (γ_{max}in cm^{-1}) of the compounds were taken on FTIR 8201 PC instrument and Perkin Elmer AC-1 spectrophotometer. ^{1}H-NMR spectra were recorded on Brucker DRX 200 MH_z spectrometer in deuterated solvents with TMS as internal reference(chemical shifts in δppm). Mass spectra were recorded on Jeol SX102/DA-6000 FAB mass spectrometer and Jeol (JMS

– D 300 spectrometer (70eV). Micro analysis were performed on Carlo Erba EA-1108 element analyzer. All compounds were analyzed of C, H, N and the results obtained were within ±0.4% of calculated values. Thin layer chromatography was performed on precoated silicagel plastic plates(Aldrich). Anhydrous sodium sulfate was used as drying agent. N-methyl-4-piperidone(**1**) and N-methyl-4-piperidinol(**3**) were commercially available. 1,2-epoxy-3-substituted phenoxy propanes (**6a-m**) [12], N-methyl-4-phenyl-4-piperidinol(**2**)[13], 4-(4-trifluoromethyl)phenoxy-N-methyl-piperidine(**4**)[13], 4-(4-trifluoromethyl)phenoxy-N-methoxycarbonyl-piperidine(**5**)[13], 4-(4-trifluoromethyl)phenoxy-piperidine(**6**)[13] were prepared by known procedures.

1-(Substitutedphenoxy)3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}2-propanols(7-19) General procedure : A mixture of **6**(2.2mmol) and 1, 2-epoxy-3-substituted phenoxy propane (**6a-m** ; 2.4mmol) in dry DMSO(3ml) was heated at 80-90°C for 24hrs. The reaction mixture was cooled to room temperature and treated with ice (20gm). After 30min. the residue was filtered off and washed well with water (5ml×4). The separated solid/oil were purified by recrystallization or usual column chromatography. The physical and spectroscopic data are given below:

1-(phenoxy)-3-{[4-(4-trifluoromethyl)phenoxy]-piperidin-1-yl}propan-2-ol (**7**): m.p. : 88-90°C, yield : 68%. IR(KBr) : 3410, 2944, 2368, 1610, 1500, 1465, 1159, 834. ^{1}H-NMR ($CDCl_3$):1.82-2.02(m, 4H, C*H*$_2$piperidinyl×2), 2.37-2.63(m, 4H, C*H*$_2$piperidinyl), 2.68-2.74(m, 1H, N-C*H*$_2$OH), 2.91-2.93(m, 1H, N-C*H*$_2$OH), 3.98-4.00(m, 2H, OC*H*$_2$), 4.04-4.10(m, 1H, C*H*OH), 4.41-4.44(m, 1H, *H*-4), 5.90-6.97(m, 4H, Ar*H* ortho to O), 7.23-7.32(m, 3H, Ar*H*), 7.50-7.55(m, 2H, Ar*H*). MS(m/z) : free base 396(M^++1), 302, 258. Anal. Calcd. for $C_{21}H_{24}F_3NO_3$:C 63.79, H 6.08, N 3.54; found: C 64.17, H 6.38, N 3.44.

1-(4-chloro)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (**8**): m.p.82^{0}C yield 76%. IR(KBr) : 3410, 2923, 2367, 1616, 1491, 1331, 1114, 1040. ^{1}H-NMR($CDCl_3$) : 2.37-2.58(m, 4H, C*H*$_2$piperidinyl), 1.83-2.00(m, 4H, C*H*$_2$piperidinyl×2), 2.63-2.69 (m, 1H, C*H*$_2$piperidinyl), 2.73-2.93(m, 2H, N-C*H*$_2$), 3.94-3.97(m, 2H, 2OC*H*$_2$), 4.04-4.11(m, 1H, C*H*)4.43-4.45(m, 1H, C*H*), 6.83-6.97(m, 4H, Ar*H*), 7.15-7.35(m, 2H, Ar*H*), 7.51-7.61(m, 2H, Ar*H*). MS(m/z) : 430(M^++1), 253. Anal. Calcd. For $C_{21}H_{23}ClF_3NO_3$.1/2 H_2O: C 57.47, H 5.47, N 3.19; found: C 57.39, H 5.58, N 3.32.

1-(4-bromo)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (9): m.p. : 101^{0}C, yield 52.6%. IR(KBr) : 3458, 2371, 1630, 1398, 1322, 1115. ^{1}H-NMR($CDCl_3$) : 2.41-2.58(m, 4H, C*H*$_2$piperidinyl), 2.25-2.58(m, 4H, C*H*$_2$piperidinyl×2), 2.6-2.75(m, 1H, N-C*H*$_2$), 2.8-2.95(m, 1H, N-C*H*$_2$), 3.94-3.96(m, 2H, 2OC*H*$_2$), 4.04-4.15(m, 1H, C*H*)4.43-4.45(m, 1H, C*H*), 6.73-6.83(m, 2H, Ar*H*), 6.93-6.97(d, 2H, Ar*H*), 7.35-7.39(m, 2H, Ar*H*), 7.51-7.55(m, 2H, Ar*H*). MS(m/z) : free base 475(M^++1), 474, 253(100%). Anal. Calcd. for $C_{21}H_{23}BrF_3NO_3$:C 53.16, H 4.85, N 2.95; found: C 53.20, H 5.22, N 2.70.

1-(2-methoxycarbonyl)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]-piperidin-1-yl}propan-2-ol (10) oil, yield : 55%. IR(KBr) : 3440, 3163, 2947, 1716, 1610. ^{1}H-NMR ($CDCl_3$):1.82-2.04(m, 4H, C*H*$_2$piperidinyl×2), 2.34-2.86(m, 6H, N-C*H*$_2$×3), 3.86(s, 3H, CO_2CH_3), 3.88-4.42(m, 4H, OC*H*$_2$, OC*H*&C*H*OH), 6.93-7.03(m, 4H, Ar*H* ortho & para to O), 7.44-7.55(m, 3H, Ar*H* ortho to CF_3 and para to CO_2CH_3), 7.80-7.84(d, 1H, Ar*H* ortho to CO_2CH_3, *J*=7.78Hz). MS(m/z) : 453(M^+), 257(100%). Anal. Calcd. for $C_{23}H_{26}F_3NO_5$:C 60.92, H 5.73, N 3.09; found: C 60.62, H 5.50, N 2.93.

1-(4-methoxycarbonyl)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]-piperidin-1-yl}propan-2-ol (11) m.p. 75-77°C, yield : 49%. IR(KBr) : 3404, 2958, 2895, 1710, 1612. ^{1}H-NMR($CDCl_3$):1.89-2.12(m, 4H, C*H*$_2$piperidinyl×2), 2.34-2.94(m, 6H, N-C*H*$_2$×3), 3.88(s, 3H, CO_2CH_3), 3.95-4.22(m, 3H, OC*H*$_2$&C*H*OH), 4.22-4.44(m, 1H, C*H*), 6.92-6.96(m, 4H, Ar*H* adjacent to O), 7.51-7.55(d, 2H, Ar*H* adjacent to CF_3, *J*=8.34Hz), 8.01-8.06(d, 2H, Ar*H* adjacent to CO_2CH_3, *J*=10.68Hz). MS(m/z) : 453(M^+), 257(100%). Anal. Calcd. For $C_{23}H_{26}F_3NO_5.H_2O$: C 58.59, H 5.94, N 2.97; found: C 58.29, H 5.76, N 2.72.

1-(3-methoxy)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (12): m.p.97^{0}C yield 59.4%. IR(KBr) : 3438, 2943, 1616, 1459, 1329, 1258, 1115. ^{1}H-NMR($CDCl_3$): 2.41-2.58(m, 4H, N-C*H*$_2$piperidinyl×2), 2.93-2.98(m, 1H, N-C*H*$_2$), 3.12-3.31 (m, 4H, N-C*H*$_2$), 3.51-3.54(m, 1H, N-C*H*$_2$), 4.36(s, 3H, OC*H*$_3$), 4.55-4.69(m, 4H, OC*H*$_2$, C*H*OH&OC*H*), 5.00-5.01(bs, 1H, O*H*), 7.08-7.11(d, 3H, Ar*H*), 7.52-7.55(d, 2H, Ar*H*), 7.73-7.83(m, 1H, Ar*H*), 8.09-8.12(d, 2H, Ar*H*). MS(m/z) : 426(M^++1), 425, 258. Anal. Calcd. for $C_{22}H_{26}F_3NO_4$:C 62.12, H 6.12, N 3.29; found: C 62.35, H 6.42, N 2.94.

1-(4-methoxy)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (13): m.p.75-76^{0}C, yield 81%. IR(KBr) : 3438, 2930, 2371, 1620, 1514, 1341. ^{1}H-

NMR($CDCl_3$) : 1.82-2.06(m, 4H, C*H*$_2$piperidinyl×2), 2.37-2.64(m, 4H, N-C*H*$_2$piperidinyl×2), 2.71-2.73(m, 1H, N-C*H*$_2$), 2.73-2.93 (m, 1H, N-C*H*$_2$), 3.76(m, 3H, OC*H*$_3$), 3.93-3.95(d, 2H, OC*H*$_2$), 4.04-4.08(m, 1H, C*H*OH), 4.43-4.44(m, 1H, C*H*), 6.79-6.84(d, 4H, Ar*H*), 6.90-6.97(m, 2H, Ar*H*), 7.51-7.55(d, 2H, Ar*H*). MS(m/z) : 426(M^++1), 258. Anal. Calcd. for $C_{22}H_{26}F_3NO_4$:C 62.12, H 6.12, N 3.29; found: C 62.44, H 6.42, N 3.31.

1-(4-acetyl)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (14): m.p.71-72^{0}C, yield 75%. IR(KBr) : 3451, 2945, 2362, 1665, 1613, 1336, 1260, 1113. ^{1}H-NMR($CDCl_3$); 1.87-2.06 (m, 4H, C*H*$_2$piperidinyl×2), 2.39-2.41 (m, 1H, N-C*H*$_2$), 2.57-2.73 (m, 7H, CO C*H*$_3$, N-C*H*$_2$piperidinyl×2), 2.94-2.97(m, 1H, N-C*H*$_2$), 4.04-4.14(m, 3H, OC*H*$_2$, C*H*OH), 6.95-6.97 (m, 4H, Ar*H*), 7.52-7.55(d, 2H, Ar*H*), 7.92-7.95 (d, 2H, Ar*H*). MS (m/z) : 438(M^++1), 276, 258. Anal. Calcd. For $C_{23}H_{26}F_3NO_4$.1/2 H_2O: C 61.88, H 6.05, N 3.14; found: C 61.90, H 6.33, N 2.75.

1-(4-propionyl)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (15): m.p.97^{0}C, yield 71%. IR(KBr) : 3427, 2930, 2363, 1678, 1609, 1337, 1239. ^{1}H-NMR($CDCl_3$) : 1.19-1.24(t, 3H, C*H*$_3$), 1.85-1.91(m, 2H, C*H*$_2$piperidinyl), 2.01-2.04(m, 2H, C*H*$_2$piperidinyl), 2.36-2.73(m, 5H, 2-C*H*$_2$piperidinyl, 1-N-C*H*$_2$), 2.73-2.97(m, 3H, CH_2C*H*$_3$, 1-N-C*H*$_2$), 4.05-4.14(m, 3H, OC*H*$_2$, C*H*OH), 4.40-4.50(m, 1H, C*H*), 6.94-6.97(d, 4H, Ar*H*), 7.52-7.55(d, 2H, Ar*H*), 7.93-7.96(d, 2H, Ar*H*). MS(m/z) : 452(M^++1), 391, 258. Anal. Calcd. for $C_{24}H_{28}F_3NO_4$:C 63.86, H 6.21, N 3.10; found: C 63.77, H 6.31, N 2.79.

1-(4-acetamido)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]-piperidin-1-yl}propan-2-ol (16) m.p. 167-69°C, yield : 67%. IR(KBr) : 3328, 2927, 2821, 1660, 1616. ^{1}H-NMR ($CDCl_3$&DMSO-d_6):1.84-1.95(m, 4H, C*H*$_2$piperidinyl), 2.10(s, 3H, COC*H*$_3$), 2.54-2.58(m, 6H, N-C*H*$_2$×3), 3.92-4.07(m, 3H, OC*H*$_2$&C*H*OH), 4.28-4.50(m, 1H, C*H*), 6.83-6.87(d, 2H, Ar*H* adjacent to O in 4-acetamido phenyl ring), 6.96-7.00(d, 2H, Ar*H* adjacent to O in 4- CF_3 phenyl ring), 7.45-7.50(d, 2H, Ar*H* adjacent to $NHCOCH_3$), 7.54-7.57(m, 2H, Ar*H* adjacent to CF_3). MS(m/z) : 453(M^++1), 452(M^+), 258(100%). Anal. Calcd. for $C_{23}H_{27}F_3N_2O_4$:C 61.02, H 5.97, N 6.19; found: C 60.92, H 5.66, N 5.97.

1-(4-cyano)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]-piperidin-1-yl}propan-2-ol (17) m.p. 95-97°C, yield : 59%. IR(KBr) : 3440, 3085, 2943, 2219, 1610. ^{1}H-NMR ($CDCl_3$):1.89-1.99(m, 4H, C*H*$_2$piperidinyl×2), 2.34-2.94(m, 6H, N-C*H*$_2$×3), 3.95-4.14(m, 3H,

OC*H*$_2$&C*H*OH), 4.14-4.45(m, 1H, C*H*), 6.93-7.00(m, 4H, Ar*H* adjacent to O), 7.42-7.61(m, 4H, Ar*H* adjacent to CN&CF_3). MS(m/z) : 421(M^++1), 420(M^+), 154(100%). Anal. Calcd. for $C_{22}H_{23}F_3N_2O_3$:C 62.86, H 5.48, N 6.66; found: C 62.98, H 5.68, N 6.28.

1-(3-trifluoromethyl)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]piperidin-1-yl}propan-2-ol (18): m.p.97^{0}C yield 72.0%. IR(KBr) : 3427, 2930, 2363, 1678, 1609, 1337, 1259. ^{1}H-NMR($CDCl_3$):1.877-1.94(m, 2H, C*H*$_2$piperidinyl), 2.03-2.06(m, 2H, C*H*$_2$piperidinyl), 2.38-2.44(m, 1H, N-C*H*$_2$), 2.60-2.76(m, 4H, N-C*H*$_2$piperidinyl×2), 2.97(m, 1H, N-C*H*$_2$), 4.05-4.06(d, 2H, OC*H*$_2$), 4.12-4.16(m, 1H, C*H*OH), 4.45-4.48(m, 1H, C*H*), 6.97-7.05(m, 2H, Ar*H*), 7.12-7.29(m, 3H, Ar*H*), 7.39-7.49(m, 1H, Ar*H*), 7.55-7.57(m, 2H, Ar*H*).MS(m/z):464(M^++1), 463, 258. Anal. Calcd. for $C_{22}H_{23}F_6NO_3$:C 57.02, H 4.96, N 3.02; found: C 57.21, H 4.76, N 2.82.

1-(4-trifluoromethyl)phenoxy-3-{[4-(4-trifluoromethyl)phenoxy]-piperidin-1-yl}propan-2-ol (19) m.p. 73-75°C, yield : 87%. IR(KBr) : 3365, 2945, 2817, 1618. ^{1}H-NMR ($CDCl_3$):1.80-2.12(m, 4H, C*H*$_2$piperidinyl×2), 2.29-2.94(m, 6H, N-C*H*$_2$×3), 4.02-4.22(m, 3H, OC*H*$_2$&C*H*OH), 4.43-4.46(m, 1H, C*H*), 6.87-7.01(m, 4H, Ar*H* adjacent to O), 7.52-7.55(m, 4H, Ar*H* adjacent to CF_3). MS(m/z) : 463(M^+), 257(100%). Anal. Calcd. for $C_{22}H_{23}F_6NO_3$:C 57.02, H 4.96, N 3.02; found: C 56.65, H 5.21, N 2.71.

Pharmacology

The study was carried out in albino mice (weighing between 16-20 gm) of either sex. Each group comprised of 5 animals. All the compounds and the standard drug fluoxetine were administered in a dose of 75 μmole/Kg intra peretonial (i.p.) as aqueous solution or aqueous suspension in gum acacia. Gross behavioural effects[14], antidepressant[15] and anorexigenic activity[15] were carried out by standard tests and saline treated control were seen concurrently. The results are given in table 1.

Table 1 ; Pharmacological data of compounds at 75μmol/Kg. i.p.

Compound No[a].	R	Dose (mg/Kg)	Antidepressant activity[b] (Reversal of Reserpine induced ptosis, sedation and crouching).	Anorexigenic activity	
				Milk left, SEM (% Anorexia)	% Activity against standard (Fluoxetine)
2	-	14.3	-	0.2320±0.08(46.4)	56.86
4	-	19.5	-	0.1180±0.05(23.6)	28.92
6	-	18.4	+++	0.3340±0.08(66.8)	81.86
7	H	29.6	-	0.3380±0.09(67.6)	82.84
8	4-Cl	32.2	+++	0.3080±0.07(61.6)	75.49
9	4-Br	35.5	-	0.3880±0.04(77.6)	95.09
10	2-CO_2Me	34.0	-	0.1760±0.08(35.2)	43.13
11	4-CO_2Me	34.0	-	0.1340±0.07(26.8)	32.84
12	3-OMe	31.8	++	0.2580±0.08(51.6)	63.23
13	4-OMe	31.8	-	0.1920±0.09(38.4)	47.05
14	4-$COCH_3$	32.7	-	0.3920±0.04(78.4)	96.07
15	4-COC_2H_5	33.8	-	0.2760±0.06(55.2)	67.64
16	4-NHAc	33.9	-	0.2520±0.08(50.4)	61.67
17	4-CN	31.5	-	0.2880±0.04(57.6)	70.58
18	3-CF_3	34.7	-	0.1560±0.05(31.2)	38.23
19	4-CF_3	34.7	-	0.3180±0.07(63.6)	77.94
Fluoxetine		25.9	++++	0.4080±0.04(81.6)	100.00

[a]No effect on gross behaviour ; [b](+)=25%, (-)= no effect ; [c]An anorexia of <40% was insignificant.

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