Med Chem Res (2008) 17:103–113
DOI 10.1007/s00044-007-9041-8

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Substituted urea/thiourea derived from fluoxetine as potent appetite suppressants

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Received: 18 October 2007 / Accepted: 31 October 2007 / Published online: 12 January 2008

Abstract A series of urea and thiourea analogues of fluoxetine (**5–17**) were synthesized and evaluated for their anorexigenic and antidepressant activities. The related conformationally restrained analogues (**20–23**) were also prepared for structure–activity relationship (SAR) studies. Many of these derivatives (**5, 6, 8, 10, 12, 13, 16,** and **23**) exhibited significant anorexigenic activity and interestingly were devoid of antidepressant activity, thus emerging as a promising tool for further research work.

Keywords Fluoxetine · Appetite suppressants · Antidepressants · SSRIs · Urea thiourea derivatives

Introduction

For several decades, pharmacologists have demonstrated the importance of central serotonergic neurotransmission (Garattini *et al.*, 1992; Kennett 1998) in the suppression of feeding behavior. Serotonin (5-hydroxytryptamine, 5-HT), a neurotransmitter, acts in the central nervous system to modulate the feeding behavior in an inhibitory manner (Blundell 1984) and possibly plays a role in the mediation of satiety (Shor-Posner *et al.*, 1986). Serotonergic drugs act either by releasing serotonin (Garattini *et al.*, 1992) or inhibiting the reuptake of serotonin

C.D.R.I. communication No 7022

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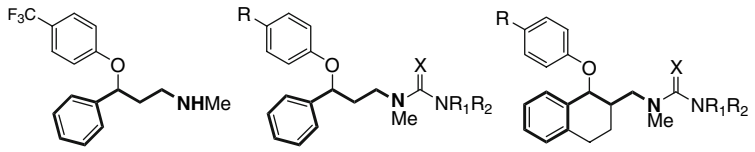
(SSRIs) (Kennett, 1998) into the synaptic cleft. In both cases the concentration of serotonin increases at presynaptic terminals to increase the sensation of satiety. Hence 5-HT-releasing agents and selective 5-HT uptake inhibitors have been suggested as antiobesity agents. Various SSRIs (Goldstein *et al.*, 1994; Wadden *et al.*, 1995; Fernstrom *et al.*, 1988) have been tested as antiobesity medications. Fluoxetine, arguably the most anorexigenic (Benfield *et al.*, 1986) of the SSRIs, has undergone considerable evaluation to determine its efficacy for weight loss. In addition to its SSRI activity, fluoxetine also has a direct agonist action at the 5-HT_{2C} receptor (Stahl, 1998) and it is well known that the direct activation of some 5-HT_{2C} receptors reduces food consumption (Curzon *et al.*, 1998).

Recently we reported that the replacement of hydrogen in the $NHCH_3$ group in fluoxetine and its substitution by various substructure (Bhandari *et al.*, 2005) resulted in a modest reduction in the antidepressant effect (the main activity) with the retention of the anorexigenic effect (the side activity). These results prompted us to take fluoxetine as an active pharmacophore for further diversification. Considering the anorexigenic activity of substituted urea/thiourea derivatives (Jackson 1976; Bhandari *et al.*, 2004), we incorporated this moiety onto fluoxetine and thus aimed to synthesize **1** as our target molecule. For structure–activity relationship (SAR) studies we also prepared the related 1-aryloxy-2-aminomethyltetrahydronaphthalene urea/thiourea derivatives (**2**) as conformationally rigid analogues of fluoxetine (Fig. 1).

Chemistry

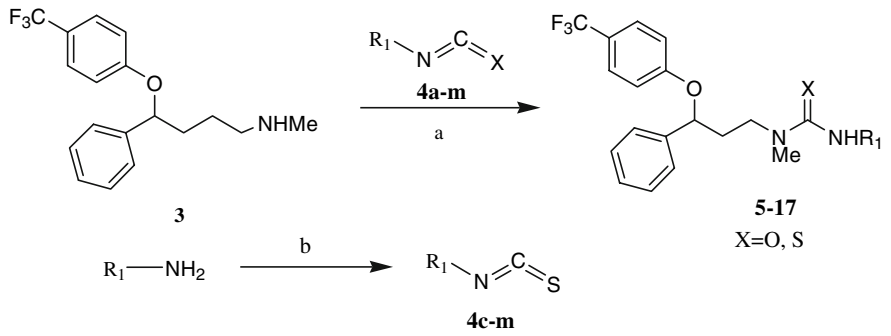
The synthesis route adopted for the preparation of the urea/thiourea derivatives of fluoxetine (**5–17**) and conformationally rigid analogues of fluoxetine (**20–23**) is depicted in Schemes 1 and 2.

Fluoxetine (**3**) was prepared starting from acetophenone in four steps as reported earlier (Bhandari *et al.*, 2005), was treated with different isocyanates (**4a, 4b**) and isothiocyanates (**4c–m**) to furnish the final urea and thioureas (**5–17**) (Scheme 1). The isothiocyanates (**4c-m**) used in Scheme 1 were synthesized from the corresponding primary amines using dicyclohexylcarbodiimide (DCC) and carbon disulphide (Ankersen *et al.*, 1998). The tetrahydronaphthalene urea/thiourea derivatives (**20–23**) as conformationally rigid analogues of fluoxetine were synthesized by the condensation of **19** (Bhandari *et al.*, 2006) with different isocyanates (**4a, 4b**) and isothiocyanates (**4c, 4i**) (Scheme 2).

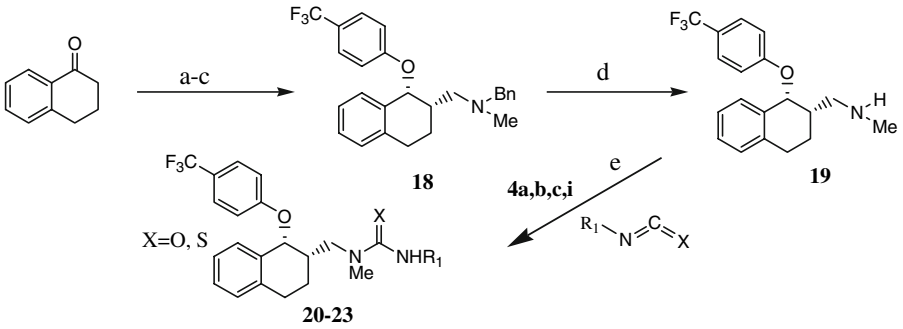


Fluoxetine **1** **2**

Fig. 1 Structures of fluoxetine and structures **1** and **2**



Scheme 1 Reagents and conditions: (a) CH_3CN; (b) DCC, CS_2, dry THF –10°C



Scheme 2 Reagents and conditions**:** (a) Bz.MeNH.HCl, $(CH_2O)_n$, *n*-propanol; (b) $NaBH_4$/MeOH; (c) NaH, *p*-fluorobenzotrifluoride, DMAC; (d) $ClCOOCH_3$, KOH, $NH_2NH_2H_2O$; (e) CH_3CN

Results and discussion

All the synthesized compounds (**5–17, 20–23**) were screened for their effect on gross behavior, appetite suppressant, and antidepressant activities by standard methods (Bhandari *et al.*, 2005). The results are summarized in Table 1 and compared with that of fluoxetine.

The compounds tested had no significant effect on the gross behavior whereas fluoxetine showed signs of stimulation. In the antidepressant test, all the compounds (**5, 7–12, 14–17,** and **20–23**) except **6** and **13** were found to be inactive. The standard fluoxetine exhibited 100% reversal of reserpine-induced ptosis, sedation, and crouching. Compounds **5, 6, 8, 10, 12, 13, 16,** and **23** were found to have significant anorexigenic activity ($P \leq 0.05$) with a significant decrease in milk intake (36.73% to 62.45%) in comparison to the control group (Table 1). None of the compounds exhibited better anorexigenic activity than fluoxetine. The most anorexigenic (62.45%) compound (**13**) also displayed a significant antidepressant activity. Compounds **12** and **23** emerged as the most active compounds with 59.18% and 62.24% anorexigenic activity, respectively. We have previously reported that compound **19** (Bhandari *et al.*, 2006), the rigid analogue of fluoxetine, showed

Table 1 Pharmacological data of urea/thiourea analogs of fluoxetine (**5–17, 20–23**) at 75 μmol/kg i. p

Compound	X	R_1	Milk intake (mean ± SEM)	Anorexigenic activity Decrease in milk intake from control (%)	Antidepressant activity [a] ptosis (% incidence)	Sedation and crouching (median score)
Control			0.46 ± 0.01		0	0
Reserpine					100	4
Fluoxetine			0.1 ± 0.06	78.49*	0•	0•
5	O	Cyclohexyl	0.20 ± 0.07	55.48*	80	4
6	S	2-phenethyl	0.28 ± 0.10	38.49*	40•	2•
7	S	benzyl	0.37 ± 0.07	19.57	100	4
Control			0.49 ± 0.01		0	0
8	S	*p*-tolyl	0.28 ± 0.06	42.86*	80	4
9	O	2-phenethyl	0.37 ± 0.07	23.67	100	4
10	S	Cyclohexyl	0.31 ± 0.04	36.73*	100	4
11	S	Phenyl	0.43 ± 0.03	11.02	100	4
12	S	Benzoyl	0.20 ± 0.02	59.18*	100	4
Control			0.49 ± 0.01		0	0
13	S	4-Methylcyclohexyl	0.18 ± 0.03	62.45*	60•	2•
14	S	3,4,5-trimethoxyphenyl	0.42 ± 0.04	13.06	100	4
15	S	Tert-butyl	0.38 ± 0.06	22.04	100	4
16	S	4-methoxy-phenyl	0.24 ± 0.06	50.20*	100	4
17	S	isopropyl	0.48 ± 0.01	0.82	100	4
Control			0.49 ± 0.01		0	0
20	S	2-phenethyl	0.48 ± 0.01	2.04	100	4
21	O	cyclohexyl	0.32 ± 0.07	33.88	100	4
22	O	2-phenethyl	0.48 ± 0.01	2.04	100	4
23	S	4-Methylcyclohexyl	0.18 ± 0.10	62.24*	80	4

*Significant anorexigenic activity ($P \leq 0.05$); •significant antidepressant activity; [a]the antidepressant activity of the fluoxetine and the compounds **5–17** and **20–23** was evaluated after 3 h of reserpine treatment; control: saline-treated mice

significant appetite suppression (66.9%) along with stimulant and antidepressant action. Conversion of its amino function into thiourea/urea resulted in the complete loss of the antidepressant activity and reduction in the anorexigenic activity (**20–23**). However in compound **23** the anorexigenic activity was retained (62.24%) and was comparable to that of **19**. The anorexigenic activity of the rigid analogue **23** may be attributed to the 4-methyl cyclohexyl function as its open chain counterpart (**13**) demonstrated the best anorexigenic activity profile (62.45%) among the synthesized compounds. These results indicate that substitution of H in NHMe of fluoxetine by urea/thiourea moieties resulted in th ecomplete loss of the antidepressant effect in most of the compounds whereas the anorexigenic activity was retained partially or significantly.

Conclusion

Seventeen urea and thiourea analogs of fluoxetine were synthesized as potential appetite suppressants, of which eight (**5, 6, 8, 10, 12, 13, 16,** and **23**) showed significant anorexigenic activity. All of these eight compounds (except **6** and **13,** in which the antidepressant activity was reduced to half) were devoid of undesired antidepressant effect. Compounds **23** and **12** displayed 62.24% and 59.18% anorexigenic activity, respectively, and were found to be the most active compounds of the series. These identified urea and thiourea derivatives will be very useful for further optimization work.

Experimental section

Chemistry

Melting points were determined in open capillaries in an electrically heated block and are uncorrected. Infrared (IR) spectra of all the compounds were recorded on a Perkin–Elmer AC–1 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Brucker WM 200 MHz spectrometer in deuterated solvent ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference. Fast atom bombardment (FAB) mass spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The electrospray mass spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. Microanalyses were determined on a Carlo Erba EA-1108 element analyzer within $\pm 0.4\%$ 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 Synthetic Chemicals and silica gel of 60–120 mesh from Qualigen Fine Chemicals were used. Differently substituted isocyanates (**4a, 4b**) were purchased from Aldrich. *N*-Methyl-3-phenyl-3-(4-trifluoromethylphenoxy) propanamine(fluoxetine) (**3**) (Bhandari *et al.*, 2005) and methyl-[1-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydro naphthalen-2-yl-methyl]-amine(**19**) (Bhandari *et al.*, 2006), were prepared by known procedures.

Substituted isothiocyanates (**4c–m**)

A mixture of dicyclohexylcarbodiimide (DCC) (3 mmol) and carbondisulfide (30 mmol) in tetrahydrofuran (THF) (4 mL) was cooled to –10°C in an ice-salt bath and treated dropwise with a solution of the appropriate amine (3 mmol) in THF (2 mL). The reaction mixture was allowed to attain room temperature and was stirred for 3 h. The reaction was monitored by TLC. Removal of the solvent under reduced pressure afforded a white solid, which was triturated with diethylether (2 mL) and the dicyclohexylthiourea was removed by filtration. The filtrate was evaporated to afford the desired isothiocyanates (**4c–m**) in excellent yield as an oil which was used as such for further reaction.

General procedure for the preparation of 3-substituted-1-methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-urea/thiourea (**5–17**) and 1-methyl-3-substituted-1-[1-(trifluoromethyl-phenoxy)-1,2,3,4-tetrahydronaphthalen-2-ylmethyl)urea/thiourea (**20–23**)

A mixture of compounds **3** or **19** (1 mmol) and differently substituted isocyanates (**4a**, **4b**)/isothiocyanates (**4c–m**) (1.2 mmol) in acetonitrile (5 mL) was stirred at room temperature for 6–7 h. The reaction was then discontinued and the solvent was distilled off to give the crude product, which was purified by either crystallization or column chromatography using 20–30% ethylacetate:hexane as an eluant to afford the desired ureas/thioureas (**5–17** and **20–23**), respectively.

3-Cyclohexyl-1-methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-urea (**5**)

Compound **3** with cyclohexyl isocyanate (**4a**); yield 83%; m.p. 78–80°C; MS (FAB) m/z: 435 ($(M + 1)^+$, 40%); ^{1}H NMR: δ 0.70–1.81 (m, 10H, cyclohexyl CH_2), 2.06–2.08 (m, 2H, NCH_2-CH_2), 2.78 (s, 3H, NMe), 3.35–3.50 (m, 3H, NCH_2, N-CH), 5.11–5.17 (m, 1H, O-CH), 6.80–6.84 (d, 2H, J = 8.54Hz, ArH *ortho* to O), 7.19–7.24 (m, 5H, ArH), 7.33–7.38 (d, 2H, J = 8.52Hz, ArH *ortho* to CF_3); IR (KBr): 3361, 2930, 2854, 1621, 1333, 1109 cm^{-1}. Analysis $C_{24}H_{29}F_3N_2O_2$ (C, H, N): calculated C 66.35, H 6.68, N 6.45, found C 66.62, H 6.50, N 6.34.

1-Methyl-3-phenethyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**6**)

Compound **3** with 2-phenylethyl isothiocyanate (**4c**); yield 77%; oil; MS (FAB) m/z: 473 ($(M + 1)^+$, 75%); ^{1}H NMR: δ 2.04–2.22 (m, 2H, NCH_2-CH_2), 2.81–2.89 (m, 2H, Ar-CH_2), 3.03 (s, 3H, NMe), 3.74–3.95 (m, 4H, Me-NCH_2, Ar-CH_2-CH_2-NH), 5.18–5.24 (m, 1H, O-CH), 6.82–6.87 (d, 2H, J = 8.66Hz, ArH *ortho* to O), 7.14–7.33 (m, 10H, ArH), 7.40–7.45 (d, 2H, J = 8.7 Hz, ArH *ortho* to CF_3); IR (neat): 3418, 2930, 2364, 1613, 1529, 1114 cm^{-1}. Analysis $C_{26}H_{27}F_3N_2OS$ (C, H, N): calculated C 66.10, H 5.72, N 5.93, found C 66.45, H 5.46, N 5.74.

3-Benzyl-1-methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**7**)

Compound **3** with benzyl isohtiocyanate (**4d**); yield 57%; oil; MS (ESI) m/z: 459 ($(M + 1)^+$, 50%); ^{1}H NMR: δ 2.15–2.21 (m, 2H, NCH_2-CH_2), 3.10 (s, 3H, NMe), 3.83–3.96 (m, 2H, NCH_2-CH_2), 4.53–4.62 (m, 1H, Ar-CH_2), 4.76–4.86 (m, 1H, Ar-CH_2), 5.15–5.21 (m, 1H, O-CH), 6.68–6.73 (d, 2H, J = 8.34Hz, ArH *ortho* to O), 7.19–7.33 (m, 14H, ArH); IR (neat): 3419, 2925, 2362, 1613, 1532, 1067 cm^{-1}. Analysis $C_{25}H_{25}F_3N_2OS{\cdot}1/4H_2O$ (C, H, N): calculated C 64.86, H 5.51, N 6.05, found C 64.55, H 5.33, N 5.66.

1-Methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-3-p-tolyl-thiourea (**8**)

Compound **3** with *p*-tolyl isothiocyanate (**4e**); yield 33%; oil; MS (ESI) m/z: 459 ($(M + 1)^+$, 7%), 460 ($(M + 2)^+$, 40%); ^{1}H NMR: δ 2.31–2.35 (m, 5H, Ar-CH_3, NCH_2-CH_2), 3.27 (s, 3H, NMe), 3.96–4.13 (m, 2H, NCH_2-CH_2), 5.29–5.35 (m, 1H, O-CH), 6.86–6.99 (m, 4H, ArH), 7.07–7.11 (d, 2H, J = 8.06Hz, ArH), 7.34 (m, 5H, ArH), 7.39–7.44 (d, 2H, J = 8.67 Hz, ArH *ortho* to CF_3); IR (neat): 3377, 2365, 1614, 1521, 1116 cm^{-1}. Analysis $C_{25}H_{25}F_3N_2OS$ (C, H, N): calculated C 65.50, H 5.46, N 6.11, found C 65.59, H 5.60, N 5.94.

1-Methyl-3-phenethyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-urea (**9**)

Compound **3** with 2-phenylethyl isocyanate (**4b**); yield 52%; oil; MS (FAB) m/z: 457 ($(M + 1)^+$, 50%), 295 (100%); ^{1}H NMR: δ 2.07–2.12 (m, 2H, (Me)-NCH_2-CH_2), 2.66–2.73 (m, 2H, Ar-CH_2), 2.31 (s, 3H, NMe), 3.28–3.45 (m, 4H, (Me)-NCH_2, Ar-CH_2-CH_2), 5.14–5.20 (m, 1H, O-CH), 6.82–6.86 (d, 2H, J = 8.5Hz, ArH *ortho* to O), 7.11–7.33 (m, 10H, ArH), 7.39–7.44 (d, 2H, J = 8.5Hz, ArH *ortho* to CF_3); IR (neat): 3372, 1629, 1526, 1248, 1114, 1067 cm^{-1}. Analysis $C_{26}H_{27}F_3N_2O_2$ (C, H, N): calculated C 68.42, H 5.92, N 6.14, found C 68.30, H 5.63, N 6.45.

3-Cyclohexyl-1-methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**10**)

Compound **3** with cyclohexyl isothiocyanate (**4f**); yield 67%; oil; MS (FAB) m/z: 451 ($(M + 1)^+$, 60%); ^{1}H NMR: δ 1.01–1.93 (m, 10H, cyclohexyl CH_2), 2.10–2.20 (m, 2H, NCH_2-CH_2), 3.05 (s, 3H, NMe), 3.90 (m, 2H, NCH_2), 4.2 (m, 1H, N-CH), 5.17–5.23 (m, 1H, O-CH), 6.81–6.85 (d, 2H, J = 8.64Hz, ArH *ortho* to O), 7.19–7.29 (m, 5H, ArH), 7.35–7.39 (d, 2H, J = 8.6Hz, ArH *ortho* to CF_3); IR (neat): 2931, 2855, 1615, 1528, 1112, 1068 cm^{-1}. Analysis $C_{24}H_{29}F_3N_2OS.H_2O$ (C, H, N): calculated C 61.54, H 6.41, N 5.98, found C 61.85, H 6.40, N 5.84.

1-Methyl-3-phenyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**11**)

Compound **3** with phenyl isothiocyanate (**4g**); yield 61%; m.p. 110–112°C; MS (FAB) m/z: 445 ($(M + 1)^+$, 100%); ^{1}H NMR: δ 2.31–2.40 (m, 2H, NCH_2-CH_2), 3.28 (s, 3H, NMe), 3.97–4.12 (m, 2H, NCH_2-CH_2), 5.29–5.36 (m, 1H, O-CH), 6.87–6.91 (d, 2H, J = 8.65Hz, ArH *ortho* to O), 7.08–7.36 (m, 10H, ArH), 7.40–7.44 (d, 2H, J = 8.54Hz, ArH *ortho* to CF_3); IR (KBr): 3306, 2362, 1595, 1529, 1111 cm^{-1}. Analysis $C_{24}H_{23}F_3N_2OS{\cdot}1/4H_2O$ (C, H, N): calculated C 64.21, H 5.23, N 6.24, found C 64.05, H 5.06, N 6.54.

3-Benzoyl-1-Methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**12**)

Compound **3** with benzoyl isothiocyanate (**4h**); yield 47%; oil; MS (FAB) m/z: 473 ($(M + 1)^+$, 15%); ^{1}H NMR: δ 2.29–2.37 (m, 2H, NCH_2-CH_2), 3.23 (s, 3H, NMe), 4.18–4.21 (m, 2H, NCH_2-CH_2), 5.46–5.49 (m, 1H, O-CH), 6.94–6.98 (d, 2H, J = 8.48Hz, ArH *ortho* to O), 7.26–7.60 (m, 10H, ArH), 7.83–7.86 (d, 2H, J = 7.4Hz, ArH); IR (neat): 2930, 2858, 1897, 1687, 1540, 1395, 1068 cm^{-1}. Analysis $C_{25}H_{23}F_3N_2O_2S$ (C, H, N): calculated C 63.55, H 4.87, N 5.93, found: C 63.23, H 5.15, N 5.70.

1-Methyl-3-(4-methyl-cyclohexyl)-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**13**)

Compound **3** with 4-methylcyclohexyl isothiocyanate (**4i**); yield 64%; oil; MS (ESI) m/z: 465 ($(M + 1)^+$, 100%), 466 ($(M + 2)^+$, 30%); ^{1}H NMR: δ 0.86–1.25 (m, 8H, cyclohexyl protons, CH-CH_3), 1.58–1.65 (m, 2H, cyclohexyl protons), 1.96–2.27 (m, 4H, cyclohexyl protons, O-CH-CH_2), 3.12–3.14 (s, 3H, NMe), 3.90–4.3 (m, 3H, N-CH_2, N-CH), 5.26–5.29 (m, 1H, O-CH), 6.88 (d, 2H, J = 8.36Hz, ArH *ortho* to O), 7.26–7.32 (m, 5H, ArH), 7.41–7.45 (d, 2H, J = 8.45Hz, ArH *ortho* to CF_3); IR (neat): 3754, 2929, 2856, 2115, 1615, 1524, 1163, 1116 cm^{-1}. Analysis $C_{25}H_{31}F_3N_2OS$ (C, H, N): calculated C 64.66, H 6.68, N 6.03, found C 64.54, H 6.77, N 6.24.

1-Methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-3-(3,4,5-trimethoxy-phenyl)-thiourea (**14**)

Compound **3** with 3,4,5-trimethoxy-phenyl isothiocyanate (**4j**); yield 51%; m.p. 122–125°C; MS (FAB) m/z: 535 ($(M + 1)^+$, 30%), 516 (100%); ^{1}H NMR: δ 2.34–2.37 (m, 2H, NCH_2-CH_2), 3.30 (s, 3H, NMe), 3.77 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 4.10 (m, 2H, N-CH_2), 5.33 (m, 1H, O-CH), 6.46 (s, 2H, ArH containing OMe grs), 6.89–6.93 (d, 2H, J = 8.38Hz, ArH *ortho* to O), 7.26–7.33 (m, 5H, ArH), 7.41–7.45 (d, 2H, J = 8.44Hz, ArH *ortho* to CF_3); IR (KBr): 3755, 3431, 2930, 1600, 1539, 1122 cm^{-1}. Analysis $C_{27}H_{29}F_3N_2O_4S{\cdot}1/4H_2O$ (C, H, N): calculated C 60.17, H 5.43, N 5.24, found C 60.06, H 5.77, N 4.96.

3-tert-Butyl-1-Methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**15**)

Compound **3** with *tert*-Butyl isothiocyanate (**4k**); yield 55%; oil; MS (FAB) m/z: 425 ($(M + 1)^+$, 80%), 424 (M^+, 40%); ^{1}H NMR: δ 1.49 (s, 9H, -C-$(CH_3)_3$), 2.28 (m, 2H, NCH_2-CH_2), 3.10 (s, 3H, NMe), 3.8–4.2 (m, 2H, NCH_2), 5.2–5.4 (m, 1H, O-CH), 6.87–6.92 (d, 2H, J = 8.62Hz, ArH *ortho* to O), 7.26–7.34 (m, 5H, ArH),

7.41–7.45 (d, 2H, J = 8.57 Hz, ArH *ortho* to CF_3); IR (neat): 2963, 1615, 1529. 1358, 1116, 1068 cm^{-1}. Analysis $C_{22}H_{27}F_3N_2OS{\cdot}H_2O$ (C, H, N): calculated C 60.97, H 6.24, N 6.47, found C 61.17, H 6.29, N 6.20.

3-(4-Methoxyphenyl)-1-methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**16**)

Compound **3** with 4-methoxy-phenyl isothiocyanate (**4l**); yield 89%; oil; MS (ESI) m/z: 475 ($(M + 1)^+$, 60%); ^{1}H NMR: δ 2.21–2.31 (m, 2H, NCH_2-CH_2), 3.19 (s, 3H, NMe), 3.70 (s, 3H, OCH_3), 3.90–4.05 (m, 2H, N-CH_2), 5.22–5.29 (m, 1H, O-CH), 6.71–6.94 (m, 6H, ArH), 7.18–7.36 (m, 7H, ArH); IR (neat): 3322, 2931, 2852, 1614, 1516, 1166 cm^{-1}. Analysis $C_{25}H_{25}F_3N_2O_2S{\cdot}H_2O$ (C, H, N): calculated C 63.29, H 5.27, N 5.91, found C 62.90, H 5.38, N 5.53.

3-Isopropyl-1-methyl-1-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-thiourea (**17**)

Compound **3** with isopropyl isothiocyanate (**4m**); yield 76%; oil; MS (ESI) m/z: 433 ($(M + Na)^+$, 35%), 411 ($(M + 1)^+$, 100%); ^{1}H NMR: δ 1.08–1.11 (d, 3H, J = 6.49Hz, -CH-CH_3), 1.17–1.20 (d, 3H, J = 6.50Hz, -CH-CH_3), 2.24–2.31 (m, 2H, NCH_2-CH_2), 3.12 (s, 3H, NMe), 3.88–4.01 (m, 2H, NCH_2), 4.53–4.60 (m, 1H, CH-$(Me)_2$), 5.24–5.30 (m, 1H, O-CH), 6.88–6.92 (d, 2H, J = 8.43Hz, ArH *ortho* to O), 7.26–7.32 (m, 5H, ArH), 7.41–7.46 (d, 2H, J = 8.50Hz, ArH *ortho* to CF_3); IR (neat): 3401, 2362, 1741, 1525, 1218 cm^{-1}. Analysis $C_{21}H_{25}F_3N_2OS.1/2H_2O$ (C, H, N): calculated C 60.14, H 6.21, N 6.68, found C 60.42, H 6.20, N 6.75.

1-Methyl-3-phenethyl-1-[1-(trifluoromethyl-phenoxy)-1,2,3,4-tetrahydronaphthalen-2-yl-methyl) thiourea (**20**)

Compound **19** with 2-phenylethyl isothiocyanate (**4c**); yield 58%; oil; MS (ESI) m/z: 499 ($(M + 1)^+$, 50%), 521 ($(M + Na)^+$, 100%); ^{1}H NMR: δ 1.65–1.68 (m, 1H, H-2), 2.04–2.06 (m, 1H, H-3), 2.58 (m, 1H, H-3), 2.87–2.92 (m, 4H, H-4, Ar-CH_2), 3.02 (s, 3H, N-CH_3), 3.70–4.17 (m, 4H, Ar-CH_2-CH_2, N-CH_2,), 5.32–5.35 (d, 1H, J = 5.94Hz, H-1), 7.00–7.05 (d, 2H, J = 8.6Hz, ArH *ortho* to O), 7.15–7.30 (m, 4H, ArH), 7.51–7.56 (d, 2H, J = 8.6Hz, ArH *ortho* to CF_3); IR (neat): 3425, 2932, 2363, 1613, 1527, 1327, 1117 cm^{-1}. Analysis $C_{28}H_{29}F_3N_2OS.1/2H_2O$ (C, H, N): calculated C 66.27, H 5.92, N 5.52, found C 66.43, H 4.63, N 5.27.

3-Cyclohexyl-1-methyl-1-[1-(4-trifluoromethyl-phenoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl-methyl) urea (**21**)

Compound **19** with cyclohexyl isocyanate (**4a**); yield 58%; m.p. 140–142°C; MS (ESI) m/z: 483 ($(M + Na)^+$, 100%), 484 ($(M + 1 + Na)^+$, 30%); ^{1}H NMR: δ 0.98–

1.37 (m, 5H, cyclohexyl CH_2), 1.64–1.89 (m, 6H, cyclohexyl CH_2, H-2), 2.10–2.15 (m, 1H, H-3), 2.47–2.50 (m, 1H, H-3), 2.87 (bs, 5H, N-CH_3, H-4), 3.31–3.37 (m, 2H, N-CH_2), 3.57 (m, 1H, cyclohexyl CH), 5.28–5.31 (d, 1H, J = 5.59Hz, H-1), 7.01–7.05 (d, 2H, J = 8.52Hz, ArH *ortho* to O), 7.19–7.26 (m, 4H, ArH), 7.52–7.57 (d, 2H, J = 8.46Hz, ArH *ortho* to CF_3); IR (KBr): 3307, 2927, 2855, 1616, 1340, 1068 cm^{-1}. Analysis $C_{26}H_{31}F_3N_2O_2$ .1/2H_2O (C, H, N): calculated C 66.52, H 6.82, N 5.97, found C 66.17, H 6.55, N 5.81.

1-Methyl-3-phenethyl-1-[1-(trifluoromethyl-phenoxy)-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl) urea (**22**)

Compound **19** with 2-phenylethyl isocyanate (**4b**); yield 60%; oil; MS (ESI) m/z: 505 ($(M + Na)^+$, 100%), 506 ($M + Na + 1^+$, 36%); ^{1}H NMR: δ 1.57–1.64 (m, 1H, H-2), 2.1 (m, 1H, H-3), 2.45 (m, 1H, H-3), 2.74–2.94 (m, 7H, H-4, N-CH_3, Ar-CH_2-CH_2-NH), 3.30–3.53 (m, 4H, MeN-CH_2, Ar-CH_2-CH_2-NH), 5.23–5.26 (d, 1H, J = 6.44Hz, H-1), 6.97–7.02 (d, 2H, J = 8.56Hz, ArH *ortho* to O), 7.19–7.34 (m, 9H, ArH), 7.51–7.55 (d, 2H, J = 8.24Hz, ArH *ortho* to CF_3); IR (neat): 3021, 2402, 1216, 1116cm^{-1}. Analysis $C_{28}H_{29}F_3N_2O_2$ (C, H, N): calculated C 69.70, H 6.01, N 5.80, found C 69.59, H 6.14, N 5.72.

1-Methyl-3-(4-methyl-cyclohexyl)-1-[1-(4-trifluoromethyl-phenoxy)-1,2,3,4-tetrahydro naphthlen-2-yl-methyl)thiourea (**23**)

Compound **19** with 4-methylcyclohexyl isothiocyanate (**4i**); yield 65%; oil; MS (ESI) m/z: 491 ($(M + 1)^+$, 50%); ^{1}H NMR: δ 0.87–1.38 (m, 8H, CH-CH_3, cyclohexyl protons), 1.58–1.78 (m, 3H, cyclohexyl protons, H-2), 2.13–2.17 (m, 3H, H-3, cyclohexyl protons), 2.68 (m, 1H, H-3), 2.86–2.93 (m, 2H, H-4), 3.12 (s, 3H, N-CH_3), 3.8 (m, 1H, NH-C*H*), 4.1 (m, 2H, NCH_2), 5.38–5.41 (d, 1H, J = 5.90Hz, H-1), 7.05–7.09 (d, 2H, J = 8.6Hz, ArH *ortho* to O), 7.16–7.26 (m, 4H, ArH), 7.52–7.57 (d, 2H, J = 8.48Hz, ArH *ortho* to CF_3); IR (neat): 3425, 2930, 2818, 1596, 1351, 1115 cm^{-1}. Analysis $C_{27}H_{33}F_3N_2OS$·1/4H_2O (C, H, N): calculated C 67.43, H 6.97, N 5.83, found C 67.77, H 6.75, N 5.62.

Pharmacology

The study was carried out in albino mice of either sex (weighing 16–20 g). Each group consisted of five animals. All the compounds and the standard drug fluoxetine were administered in a dose of 75 μmole/kg intraperitoneally (i.p.) as an aqueous solution or a suspension in gum acacia. Gross behavioral effects, antidepressant, and anorexigenic activities (Bhandari *et al.*, 2005; Bhandari *et al.*, 2006) were carried out by standard tests and saline-treated control was observed concurrently (Table 1). The antidepressant activity of the compounds was analyzed by the chi-square test with Yate's correction (one-sided P value) for ptosis and the Mann–Whitney U test

for sedation and crouching. For anorexigenic activity milk intake by the control and the treated group was noted and the significance the of difference between them was determined by the unpaired Student's *t*-test (two-tailed *p* value) with the Welch correction where required (Table 1).

Acknowledgements Financial assistance from Council of Scientific and Industrial Research, New Delhi (SS and LS) and the University Grant Commission (NS) is gratefully acknowledged.

References

Ankersen M, Dorwald F, Stidsen C, Crider A (1998) Constrained somatostatin agonists and antagonists. WO9818786

Benfield P, Heel RC, Lewis SP (1986) Fluoxetine-a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 32:481–508

Bhandari K, Srivastava S, Shankar G (2004) Synthesis of tetrahydronaphthyl thioureas as potent appetite suppressants. Bioorg Med Chem 12:4189–4196

Bhandari K, Srivastava S, Shankar G, Nath C (2005) Substituted propanolamines and alkylamines derived from fluoxetine as potent appetite suppressants. Bioorg Med Chem 13:1739–1747

Bhandari K, Srivastava S, Shankar G, Nath C (2006) Synthesis and appetite suppressant activity of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalenes as conformationally rigid analogues of fluoxetine. Bioorg Med Chem 14:2535–2544

Blundell JE (1984) Serotonin and appetite. Neuropharmacology 23:1537–51

Curzon G, Gibson EL, Oluyomi AO (1998) Appetite suppression by commonly used drugs depends on 5HT receptors but not on 5HT availability. Trends Pharmacol Sci 13:21–25

Fernstrom MH, Massoudi M, Kupfer DJ (1988) Fluvoxamine and weight loss. Biol Psychiatry 24:948–949

Garattini S, Bizzi A, Codegoni AM, Mennini T (1992) Progress report on the anorexia induced by drugs believed to mimic some of the effects of serotonin on the central nervous system. Am J Clin Nutr 55:160S–166S

Goldstein DJ, Rampey AH, Enas GG, Potvin JH, Fludzinski LA, Levine LR (1994) Fluoxetine: a randomized clinical trial in the treatment of obesity. Int J Obes Relat Metab Disord 18:129–135

Jackson JL (1976) Thiurea derivatives. US pat 3,985,898

Kennett GA (1998) 5-HT drugs and eating disorders. Drugs 1:456–470

Shor-Posner G, Grinker JA, Marinescu C, Brown O, Leibowitz SF (1986) Hypothalamic serotonin in the control of meal patterns and macronutrient selection. Brain Res Bull 17:663–671

Stahl SM (1998) Not so selective serotonin reuptake inhibitors. J Clin Psychiatry 59:343–344

Wadden TA, Bartlett SJ, Foster GD, Greenstein R, Wingate BJ, Stunkard AJ, Letizia KA (1995) Sertraline and relapse prevention training following treatment by very low calorie diet. Obes Res 3:549–557