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Synthesis of tetrahydronaphthyl thioureas as potent appetite suppressants☆

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Abstract—A series of thiourea derivatives (**7**–**23**, **25**–**27**) of 1-aminotetrahydronaphthalene (**4**) and 1-amino-2-hydroxytetrahydronaphthalene (**5**) were synthesized in single pot in 48–90% yield and evaluated for their anorexigenic activity. Among them compounds **10**, **14**, **15**, **16** and **22** exhibited significant anorexigenic activity without any antidepressant effect and provided a new structural lead for appetite suppressants.

1. Introduction

Obesity has become a serious health problem in modern world. Analysis of worldwide epidemiological data reveals that the frequency of this disorder has gone up steeply,[1,2] probably because of reduction in physical activity or due to bad eating and living habits. Health risks due to obesity lead to a series of serious events. Prevention of obesity is extremely important though difficult. Since obesity is the storage of excess energy, increasing satiety or altering the dietary preferences for complex carbohydrates relative to fat rich food can decrease the energy intake. Agents, which reduce body weight, have been actively sought after for many decades. Most marketed antiobesity drugs are appetite suppressants.[3,4] The appetite suppressants or anorectics act directly on the CNS and decrease food consumption by altering central adrenergic[5] or serotonergic[6] system. Activation of serotonergic system either by direct activation of serotonergic receptor[6] or by inhibiting serotonin reuptake[7] (SSRIs) has proved successful in suppressing appetite. Despite a rising worldwide epidemic of obesity there are currently only a very small number of antiobesity drugs available to manage the problem. Orlistat[8,9] (lipase inhibitor, reduces dietary fat absorption) and sibutramine[10] (appetite suppressant, inhibits reuptake of serotonin and norepinephrine) (Fig. 1) are the only two FDA approved drugs that are currently available for the long term treatment of obesity.[11,12] Both of these drugs are of limited efficacy and are associated with side effects.[13,14] Hence there is still need of a better drug with high therapeutic index and minimum side effects.

In view of the fact that several indanyl thioureas[15] (**1**), indanyl aminoalcohols[16] (**2**) and tetrahydronaphthyl aminoalcohols[17] (**3**) possess useful anorexigenic activity, it is of interest to synthesize the tetrahydronaphthyl thioureas (**7**–**23**, **25**–**27**) and evaluate them for anorexigenic activity. To add further point of diversity the thiourea were planned to be synthesized from various

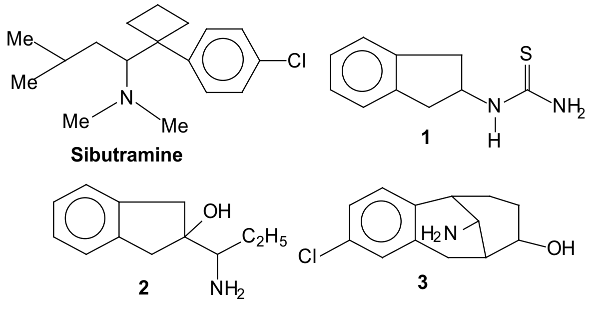

Figure 1. Representative appetite suppressants.

Keywords: Thiourea; Appetite suppressants; Synthesis.

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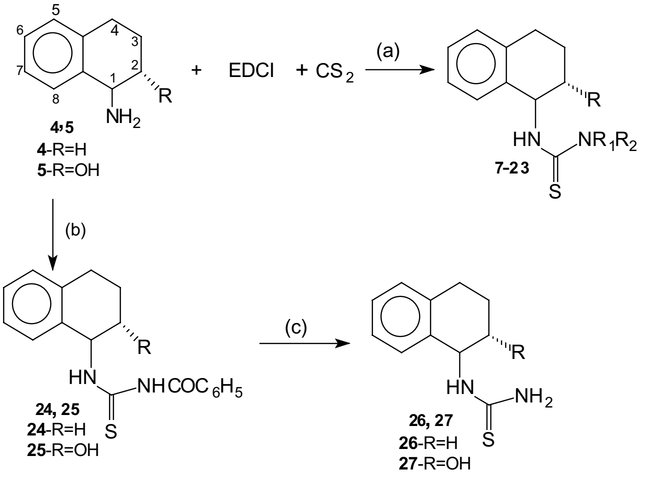
primary and secondary amines. These modifications were made for the purpose of obtaining compounds with the expected anorexigenic activity, but with possibly reduced side effects.

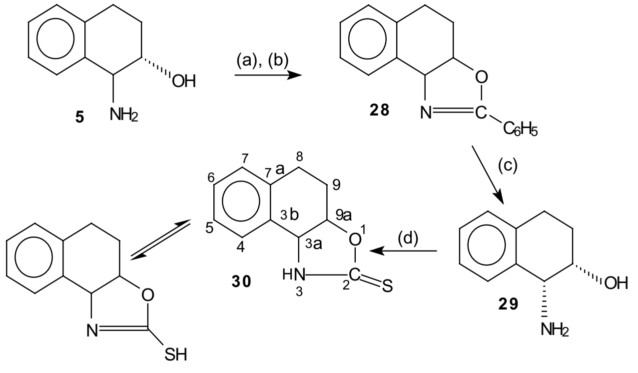
2. Result and discussion

2.1. Chemistry

The synthesis of compounds **7**–**23**, **25**–**27** was carried out according to Scheme 1. 1-Amino-1,2,3,4-tetrahydronaphthalene (**4**)/1-amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene[18] (**5**) was treated with a mixture of N-ethyl-N′-(3-dimethylaminopropyl)-carbodiimide (EDCI) and carbondisulfide in acetonitrile at low temperature, followed by the addition of secondary amines (**6a**–**j**). Subsequent work up of the reaction mixture and crystallization gave the desired products (**7**–**18**). This one pot synthesis afforded the final products (**7**–**18**) in good to excellent yield (48–90%). In case of compound no. **19**–**23**, primary amine (**6k**–**m**) was added after the isolation of the intermediate isothiocyanate. N-Benzoyl thiourea derivative (**24**, **25**) was prepared by treating the amino compound (**4**/**5**) with benzoyl isothiocyanate in acetone. Debenzoylation of **24** and **25**[19] gave **26** and **27**, respectively. Chemical and physical data of compounds are reported in the experimental section. The ^{1}H NMR spectra of the 2-hydroxytetrahydronaphthyl thioureas (**7**–**16**, **19**–**21**, **25**, **27**) showed a doublet at δ 5.9 with $J_{1\text{–}2} = 7\text{–}8$ Hz, indicative of a *trans* diaxial orientation.[20] Thus it indicated that the *trans* geometry[18] of the starting 1-amino-2-hydroxytetrahydronaphthalene (**5**) was maintained in the final thiourea compounds (**7**–**16**, **19**–**21**, **25**, **27**).



Scheme 1. Reagents and conditions: (a) HNR_1R_2 (**6a**–**m**), CH_3CN, −10 °C; (b) C_6H_5CONCS, dry acetone, reflux; (c) aq KOH, reflux, HNR_1R_2 = primary/secondary amine.



Scheme 2. Reagents and conditions: (a) PhCOCl, NaOH, rt; (b) $SOCl_2$, rt; (c) 6 N H_2SO_4, reflux; (d) EDCI, CS_2, dry acetone, −10 °C.

It was thought interesting to synthesize and evaluate the 2-hydroxytetrahydronaphthyl thioureas with *cis* geometry. Benzoylation of the *trans*-1-amino-2-hydroxytetrahydronaphthalene (**5**) followed by treatment with thionyl chloride gave the 2-phenyl oxazoline (**28**), which was hydrolyzed with 6 N H_2SO_4 to furnish the required *cis* amino alcohol[21] (**29**) (Scheme 2). The *cis* amino alcohol on treatment with EDCI, CS_2 and amines under similar conditions gave the thioxazoline derivative **30** instead of the required *cis* thioureas. The thioxazoline **30** remained unchanged on reaction with primary and secondary amines.

2.2. Pharmacology

The compounds (**7**–**23**, **25**–**27**) were tested for their effect on gross behaviour and anorexigenic activity by standard methods.[22] The results were compared to those of sibutramine (Table 1). The compounds tested have no effect on gross behaviour, however sibutramine had shown sign of stimulation. In antireserpine tests all the compounds showed no activity, where as sibutramine showed 100% reversal of reserpine induced ptosis and sedation. The significance of difference between the milk intake of treated and control group was determined by unpaired Students's *t* test (two tailed *P* value) with Welch correction wherever required. Comparison of mean ± standard error ($M \pm SE$) of milk intake of the control and treated groups (compounds and sibutramine treated) is shown in Figure 2.

The results indicate that replacement of five-membered ring of indanyl thiourea by six-membered ring and change of thiourea position (from 2 to 1) (**26**) retains the anorexigenic activity (42%). Introduction of a OH group at 2-position (**27**), resulted in loss of anorexigenic activity (13%). However thiourea substituted with various amine residues (**7**–**23**, **25**) exhibited variable anorexigenic activity.

Compounds **10**, **11**, **14**, **15**, **16**, **17**, **20**, **22**, **23** and **26** were found to have significant anorexigenic activity ($P \leqslant 0.05$) with significant decrease in milk intake (27–68%) as compared to milk intake in the control group (Table 1). None of the compounds had any remarkable effect on reserpine induced ptosis and sedation.

Table 1. In vivo anorexigenic activity of thiourea compounds (**7**–**23**, **25**–**27**) in Swiss mice model

S. no.	Compd. no.	R	NR_1R_2	Milk intake in 15 min (in mL)	% Decrease in milk intake (% anorexia)
	Control			2.4	
1	**7**	OH	4-Phenyl piperazino	1.65	31
2	**8**	OH	Anilino	1.55	35
3	**9**	OH	Pyrrolidino	2.15	10
4	**10**[*]	OH	Benzylmethylamino	1.15	52
5	**11**[*]	OH	4-[(3-Chloro)phenyl]piperazino	1.75	27
	Control			2.3	
6	**12**	OH	4-Methyl piperazino	1.5	35
7	**13**	OH	4-(2-Pyridyl) piperazino	1.95	15
8	**14**[*]	OH	4-[(4-Methyl)phenyl]piperazino	0.8	65
9	**15**[*]	OH	4-[(4-Fluoro)phenyl]piperazino	1.15	50
10	**16**[*]	OH	4-(3-α,α,α-Trifluorotolyl)piperazino	1.1	52
	Control			2.4	
11	**17**[*]	H	4-[(4-Fluoro)phenyl]piperazino	1.7	29
12	**18**	H	Benzylmethylamino	2.1	13
13	**19**	OH	4-Methylcyclohexylamino	1.45	40
14	**20**[*]	OH	Cyclohexylamino	1.3	46
15	**21**	OH	2-Phenylethylamino	1.6	33
	Control			2.4	
16	**22**[*]	H	Cyclohexylamino	0.75	69
17	**23**[*]	H	2-Phenylethylamino	1.25	48
18	**25**	OH	Benzamido	1.85	23
19	**26**[*]	H	NH_2	1.4	42
20	**27**	OH	NH_2	2.1	13
	Control			2.4	
21	Sibutramine[*]			0.4	83

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

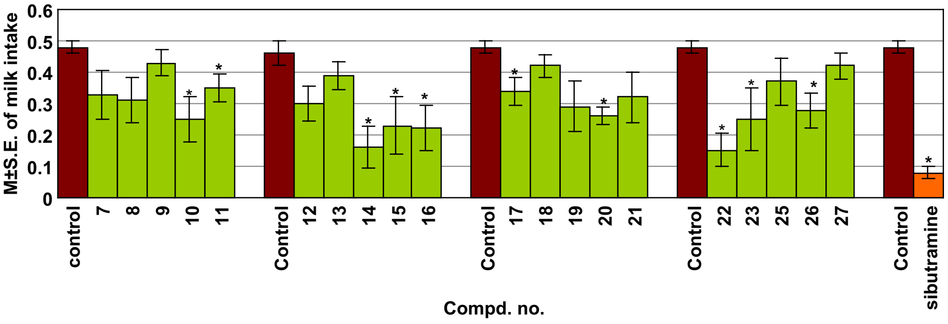


Figure 2. Comparison of mean ± standard error ($M \pm SE$) of milk intake of the tested compounds with sibutramine. *Significant differences against the control group ($P \leqslant 0.05$).

3. Conclusion

In summary we have synthesized the novel thiourea derivatives by adopting a versatile chemical pathway. Anorexigenic activity was evaluated and compared with the standard drug sibutramine. The results of biological activity confirm our assumption that the derivatives of tetrahydronaphthyl thiourea can have appetite suppressant activity. The results of our study depicted in Table 1, compound **14** (65%) and **22** (69%) exhibited very significant anorexigenic activity (sibutramine showed 83% activity). Compound no. **10**, **11**, **15**, **16**, **17**, **20**, **23** and **26** also showed significant activity. All these compounds were devoid of undesired antidepressant effect. Derivatives of tetrahydronaphthylthiourea may constitute a new chemical tool for further research work.

4. Experimental

4.1. Chemistry

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

4.1.2. 1-Amino-1,2,3,4-tetrahydronaphthalene (4). A mixture of hydroxylamine hydrochloride (0.517 g, 8.22 mmol) and sodium acetate trihydrate (1.12 g, 8.22 mmol) in water (7 mL) was added dropwise to stirred and refluxing solution of α-tetralone (1 g, 6.85 mmol) in methanol (15 mL). The reaction mixture was allowed to reflux for 6 h. The solid oxime separated was filtered, washed with water and dried.

To a solution of the oxime (1.04 g) obtained above in dry *n*-propanol (40 mL) was added sodium metal (2.2 g) over a period of 0.5 h under reflux. The reaction mixture was heated under reflux for 0.5 h, cooled to rt and water (20 mL) was added. Propanol layer was separated and distilled under reduced pressure. The residue obtained was triturated with water (20 mL) and extracted with chloroform (15 mL × 3). The extract was washed thrice with water (10 mL × 3) and dried (anhydrous Na_2SO_4). The organic layer was concentrated under reduced pressure to afford the product compound **5** as an oil. Yield: 94%, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.64–1.99 (m, 4H, H-3, H-2), 2.72–2.78 (m, 2H, H-4), 3.94–4.00 (t, 1H, $J = 5.66$ Hz, $J = 5.14$ Hz, H-1), 7.04–7.27 (m, 3H, ArH), 7.36–7.41 (m, 1H, ArH); MS (FAB) *m/z*: 148 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3371, 3015, 2932, 1597, 1449, 1217, 758.

4.1.3. *trans*-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene (5). It was prepared by known methods reported in the literature.[18] Yield: 82%, mp = 105 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.76–1.92 (m, 1H, H-3), 2.16–2.25 (m, 1H, H-3), 2.80–2.94 (m, 2H, H-4), 3.53–3.61 (m, 1H, H-2), 3.65–3.68 (d, 1H, $J = 8.7$ Hz, H-1), 7.08–7.46 (m, 4H, ArH); MS (FAB) *m/z*: 164 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3320, 3290, 3030, 2920, 1600, 1485, 1317, 1060, 1005. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.93; H, 7.61; N, 8.65.

4.1.4. General procedure for preparation of compounds (7–18). A mixture of N-ethyl-N′-(3-dimethylaminopropyl)carbodiimidehydrochloride (EDCI) (117.5 mg, 0.613 mmol) and carbondisulfide (466 mg, 6.132 mmol) in acetonitrile (1.5 mL) was cooled to −10 °C in an ice-salt bath and treated dropwise with a solution of compound **4/5** (0.613 mmol) in acetonitrile (1.5 mL). The reaction mixture was allowed to attain the rt and was stirred for 3 h. Reaction was monitored by TLC and solution of corresponding amine (**6a–j**) (0.613 mmol) in 1.5 mL acetonitrile was added dropwise to the reaction mixture and allowed to stir for 5 h. The solvent was distilled off, added 15 mL of water and the compound was extracted with CH_2Cl_2 (10 mL × 3). Combined organic extracts were dried over Na_2SO_4 and distilled to afford the desired compound (**7–18**). These compounds were purified by crystallization with CH_2Cl_2 and hexane.

4.1.5. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(4-phenylpiperazine)-1-carbothioamide (7). With **5** and 1-phenylpiperazine (**6a**). Yield: 83%, mp = 180–6 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96–2.21 (m, 2H, H-3), 2.86–2.91 (m, 2H, H-4), 3.32–3.37 (t, 4H, $J = 5.2$ Hz, piperazinyl H's adjacent to phenyl ring), 3.97–4.12 (m, 5H, piperazinyl H's adjacent to thiourea group, H-2), 5.91–5.95 (d, 1H, $J = 8.02$ Hz, H-1), 6.87–6.93 (m, 3H, ArH), 7.12–7.33 (m, 6H, ArH); MS (FAB) *m/z*: 368 ($(M+1)^+$, 16%); IR (KBr, cm^{-1}): 3754, 3446, 2914, 2373, 1632, 1549, 1421, 1351, 1223, 1027, 750. Anal. Calcd for $C_{21}H_{25}N_3OS{\cdot}0.25H_2O$: C, 67.83; H, 6.86; N, 11.31. Found: C, 68.19; H, 6.58; N, 11.52.

4.1.6. N-Phenyl-N′-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (8). With **5** and aniline (**6b**). Yield: 48%, mp = 129–30 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.92–2.16 (m, 2H, H-3), 2.80–2.88 (m, 2H, H-4), 3.86–3.97 (m, 1H, H-2), 5.81 (m, 1H, H-1), 7.09–7.44 (m, 9H, ArH); MS (FAB) *m/z*: 299 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3759, 3465, 3367, 3197, 2929, 2374, 1541, 1380, 1319, 1242, 1062, 746. Anal. Calcd for $C_{17}H_{18}N_2OS{\cdot}0.375H_2O$: C, 66.94; H, 6.15; N, 9.19. Found: C, 67.23; H, 6.54; N, 8.89.

4.1.7. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-pyrrolidine-1-carbothioamide (9). With **5** and pyrrolidine (**6c**). Yield: 89.3%, mp = 185–8 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.86–2.22 (m, 6H, H-3, N–CH_2–CH_2–CH_2), 2.87–2.93 (m, 2H, H-4), 3.2–3.9 (m, 4H, CH_2–N–CH_2), 3.93–4.04 (m, 1H, H-2), 5.84–5.92 (d, 1H, $J = 7.9$ Hz, H-1), 7.14–7.36 (m, 4H, ArH); MS (FAB) *m/z*: 277 ($(M+1)^+$, 10%); IR (KBr, cm^{-1}): 3753, 3421,2932, 2368,1633, 1559, 1427, 1355, 1040, 748. Anal. Calcd for $C_{15}H_{20}N_2OS{\cdot}0.75H_2O$: C, 62.18; H, 7.43; N, 9.67. Found: C, 62.51; H, 7.28; N, 9.28.

4.1.8. N-Benzyl-N-methyl-N′-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (10). With **5** and benzylmethylamine (**6d**). Yield: 89.8%, mp = 140 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96–2.16 (m, 2H, H-3), 2.82–2.87 (m, 2H, H-4), 3.25 (s, 3H, N–Me), 3.92–4.01 (m, 1H, H-2), 5.05–5.09 (d, 2H, $J = 8$ Hz, ArCH_2), 5.89–5.92 (d, 1H, $J = 6.9$ Hz, H-1), 7.12–7.20 (m, 4H, ArH), 7.31–7.41 (m, 5H, ArH); MS (FAB) *m/z*: 327 ($(M+1)^+$, 55%); IR (KBr, cm^{-1}): 3755, 3416, 2923, 2373, 1633, 1549, 1357, 1216, 1063, 1037, 745. Anal. Calcd for $C_{19}H_{22}N_2OS{\cdot}1.4CS_2$: C, 6.48; H, 5.45; N, 6.98. Found: C, 56.61; H, 5.09; N, 6.48.

4.1.9. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(3-chlorophenylpiperazine)-1-carbothioamide (11). With **5** and 1-[(3-chloro)phenyl]piperazine (**6e**). Yield: 89%, mp = 202–5 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.88–2.22 (m, 2H, H-3), 2.89–2.91 (m, 2H, H-4), 3.34–3.39 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.98–4.05 (m, 5H, piperazinyl H's adjacent to thiourea group, H-2), 5.90–5.94 (d, 1H, $J = 7.3$ Hz, H-1), 6.72–6.77 (d, 1H, $J = 8.6$ Hz, ArH), 6.83–6.92 (m, 2H, ArH), 7.19–7.46

(m, 5H, ArH); MS (FAB) *m/z*: 401 (M^+, 2%), 403 ($(M+2)^+$, 18%); IR (KBr, cm^{-1}): 3387, 3298, 2835, 1597, 1551, 1423, 1349, 1218, 1028. Anal. Calcd for $C_{21}H_{24}ClN_3OS{\cdot}1.25H_2O$: C, 59.43; H, 6.25; N, 9.91. Found: C, 59.26; H, 6.29; N, 9.82.

4.1.10. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(4-methylpiperazine)-1-carbothioamide (12). With **5** and 2-methylpiperazine (**6f**). Yield: 88%, mp = 160 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.96–2.16 (m, 2H, H-3), 2.34 (s, 3H, N-Me), 2.47–2.52 (t, 4H, $J = 5$ Hz, CH_2–N(Me)–CH_2), 2.87–2.89 (m, 2H, H-4), 3.8–3.89 (m, 4H, CH_2–N–CH_2), 3.91–4.04 (m, 1H, H-2), 5.89–5.93 (d, 1H, $J = 7.4$ Hz, H-1), 7.14–7.26 (m, 4H, ArH); MS (FAB) *m/z*: 306 ($(M+1)^+$, 27%); IR (KBr, cm^{-1}): 3754, 3418, 3251, 2933, 2367, 1627, 1558, 1422, 1038, 848. Anal. Calcd for $C_{16}H_{23}N_3OS{\cdot}3.5H_2O$: C, 52.17; H, 8.15; N, 11.41. Found: C, 52.38; H, 7.92; N, 10.95.

4.1.11. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(4-(2-pyridyl)piperazine)-1-carbothioamide (13). With **5** and 1-(2-pyridyl)piperazine (**6g**). Yield: 73%, mp = 163–5 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.97–2.17 (m, 2H, H-3), 2.86–2.93 (m, 2H, H-4), 3.73–3.79 (m, 4H, piperazinyl H's adjacent to pyridine ring), 3.97–4.06 (m, 5H, piperazinyl H's adjacent to thiourea group, H-2), 5.91–5.95 (d, 1H, $J = 7.7$ Hz, H-1), 6.57–6.70 (m, 2H, pyridinyl H's adjacent to piperazine), 7.15–7.29 (m, 4H, ArH), 7.49–7.57 (m, 1H, pyridinyl H adjacent to N), 8.17–8.19 (m, 1H, pyridinyl H adjacent to N); MS (FAB) *m/z*: 369 ($(M+1)^+$, 28%); IR (KBr, cm^{-1}): 3757, 3410, 3224, 3062, 2923, 2371, 1597, 1550, 1489, 1429, 1230, 1037, 760. Anal. Calcd for $C_{20}H_{33}N_4OS{\cdot}0.25CS_2$: C, 62.09; H, 6.20; N, 14.47. Found: C, 62.31; H, 5.88; N, 14.56.

4.1.12. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(4-tolylpiperazine)-1-carbothioamide (14). With **5** and 1-[(4-methyl)phenyl]piperazine (**6h**). Yield: 65%, mp = 205–7 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.98–2.17 (m, 2H, H-3), 2.28 (s, 3H, Ar-CH_3), 2.86–2.91 (m, 2H, H-4), 3.17–3.29 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.93–4.06 (m, 5H, piperazinyl H's adjacent to thiourea group, H-2), 5.91–5.95 (d, 1H, $J = 7.9$ Hz, H-1), 6.80–6.85 (d, 2H, $J = 8.5$ Hz, ArH), 7.08–7.36 (m, 6H, ArH); MS (FAB) *m/z*: 382 ($(M+1)^+$, 45%); IR (KBr, cm^{-1}): 3753, 3420, 3237, 2931, 2371, 1620, 1549, 1425, 1351, 1223, 1037. Anal. Calcd for $C_{22}H_{27}N_3OS{\cdot}0.75H_2O$: C, 66.92; H, 7.22; N, 10.65. Found: C, 67.31; H, 7.13; N, 10.47.

4.1.13. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(4-fluorophenylpiperazine)-1-carbothioamide (15). With **5** and 1-[(4-fluoro)phenyl]piperazine (**6i**). Yield: 89%, mp = 188–90 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.95–2.25 (m, 2H, H-3), 2.91 (m, 2H, H-4), 3.20–3.25 (m, 4H, piperazinyl H's adjacent to phenyl ring), 4.02–4.11 (m, 5H, piperazinyl H's adjacent to thiourea group, H-2), 5.91–5.95 (d, 1H, $J = 7.2$ Hz, H-1), 6.88–7.04 (m, 4H, ArH), 7.17–7.36 (m, 4H, ArH); MS (FAB) *m/z*: 386 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3755, 3457, 2371, 1634, 1512, 1220, 1030. Anal. Calcd for $C_{21}H_{24}FN_3OS{\cdot}1.15CS_2$: C, 58.81; H, 4.45; N, 8.89. Found: C, 58.89; H, 4.36; N, 8.47.

4.1.14. 2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl-2-(3-α,α,α-trifluoromethylphenyl piperazine)-1-carbothioamide (16). With **5** and 1-(3-α,α,α-trifluorotolyl)piperazine (**6j**). Yield: 50%, mp = 180–2 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.9–2.26 (m, 2H, H-3), 2.89–2.99 (m, 2H, H-4), 3.39–3.44 (t, 4H, $J = 5.3$ Hz, piperazinyl H's adjacent to phenyl ring), 4.06–4.08 (m, 5H, piperazinyl H's adjacent to thiourea group, H-2), 5.89–5.92 (d, 1H, $J = 7.4$ Hz, H-1), 7.00–7.42 (m, 8H, ArH); MS (FAB) *m/z*: 436 ($(M+1)^+$, 34%); IR (KBr, cm^{-1}): 3752, 3438, 2931, 2374, 1617, 1369, 1122, 698. Anal. Calcd for $C_{22}H_{24}F_3N_3OS{\cdot}0.4CS_2$: C, 57.76; H, 5.16; N, 9.02. Found: C, 57.61; H, 4.83; N, 9.37.

4.1.15. 1,2,3,4-Tetrahydronaphthalen-1-yl-2-(4-fluorophenylpiperazine)-1-carbothioamide (17). With **4** and 1-[(4-fluoro)phenyl]piperazine (**6i**). Yield: 48%, mp = 115–20 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.84–1.98 (m, 3H, H-2, H-3), 2.17 (m, 1H, H-3), 2.80 (m, 2H, H-4), 3.16–3.18 (m, 4H, piperazinyl H's adjacent to phenyl ring), 3.95–3.97 (m, 4H, piperazinyl H's adjacent to thiourea group), 5.85 (m, 1H, H-1), 6.81–7.01 (m, 4H, ArH), 7.15–7.24 (m, 3H, ArH), 7.32 (m, 1H, ArH); MS (FAB) *m/z*: 370 ($(M+1)^+$, 60%); IR (KBr, cm^{-1}): 3413, 3248, 2932, 2835, 1508, 1415, 1347, 1221, 1153, 1020, 819. Anal. Calcd for $C_{21}H_{24}FN_3S{\cdot}1.15H_2O$: C,64.67; H, 6.75; N, 10.78. Found: C, 64.52; H, 6.98; N, 10.92.

4.1.16. N-Benzyl-N-methyl-N′-(1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (18). With **4** and benzylmethylamine (**6d**). Yield: 72%, oil, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.67–1.90 (m, 3H, H-2, H-3), 2.13–2.20 (m, 1H, H-3), 2.74–2.79 (m, 2H, H-4), 3.18 (s, 3H, N-Me), 5.03–5.06 (d, 2H, $J = 5.98$ Hz, N–CH_2), 5.81 (m, 1H, H-1), 7.08–7.17 (m, 3H, ArH), 7.24–7.38 (m, 6H, ArH); MS (FAB) *m/z*: 311 ($(M+1)^+$, 100%); IR (neat, cm^{-1}): 3406, 3315, 2929, 1523, 1351, 1211, 1081, 746. Anal. Calcd for $C_{19}H_{22}N_2S{\cdot}H_2O$: C, 69.51; H, 7.01; N, 8.54. Found: C, 69.62; H, 7.30; N, 8.74.

4.1.17. General procedure for preparation of compounds (19–23). A mixture of N-ethyl-N′-(3-dimethylaminopropyl)-carbodiimidehydrochloride (EDCI) (117.5 mg, 0.613 mmol) and carbondisulfide (466 mg, 6.13 mmol) in acetonitrile (1.5 mL) was cooled to −10 °C in an ice-salt bath and treated dropwise with a solution of compound **4**/**5** (0.613 mmol) in acetonitrile (1.5 mL). The reaction mixture was allowed to attain the rt and was stirred for 3 h. Reaction was monitored by TLC. Removal of the solvent under reduced pressure afforded a white solid. Water (15 mL) was added to it and the compound was extracted with dichloromethane (10 mL × 3). Combined dichloromethane extracts were dried (anhyd Na_2SO_4)

and concentrated to furnish the isothiocyanate as white solid. To the above isothiocyanate solution in acetonitrile (4 mL) was added appropriate amine (**6k**–**m**) (0.613 mmol) in acetonitrile (1.5 mL) dropwise and allowed to stir for 5 h. The solvent was distilled off to afford an oil, which was crystallized with CH_2Cl_2 and hexane to furnish the desired compound (**19**–**21**).

4.1.18. N-(4-Methylcyclohex-1-yl)-N′-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (19). With **5** and 4-methylcyclohexylamine (**6k**). Yield: 69%, mp = 45–8 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87–0.92 (m, 3H, CH_3), 1.05–1.29 (m, 5H, cylcohexyl H's), 1.67–1.76 (m, 2H, cylcohexyl H's), 1.8–2.14 (m, 4H, H-3, cylcohexyl H's), 2.86–2.92 (m, 2H, H-4), 3.96–4.13 (m, 2H, H-2, cyclohexyl H adjacent to thiourea group), 6.13 (m, 1H, H-1), 7.12–7.78 (m, 4H, ArH); MS (FAB) m/z: 319 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3400, 2928, 2366, 1636, 1544, 1221, 761. Anal. Calcd for $C_{18}H_{26}N_2OS{\cdot}1.2H_2O$: C, 63.60; H, 8.36; N, 12.37. Found: C, 63.33; H, 8.52; N, 12.51.

4.1.19. N-Cyclohexyl-N′-(2-hydroxy-1,2,3,4-tetra hydronaphthalen-1-yl)-thiourea (20). With **5** and cyclohexylamine (**6l**). Yield: 82%, mp = 130 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.15–1.39 (m, 6H, cylcohexyl H's), 1.61–1.67 (m, 2H, cylcohexyl H's), 1.94–2.14 (m, 4H, H-3, cylcohexyl H's), 2.86–2.93 (m, 2H, H-4), 3.5 (m, 1H, cyclohexyl H adjacent to thiourea group), 3.96 (m, 1H, H-2), 5.9 (m, 1H, H-1), 7.12–7.14 (m, 1H, ArH), 7.20–7.24 (m, 2H, ArH), 7.32–7.34 (m, 1H, ArH); MS (FAB) m/z: 305 ($(M+1)^+$, 45%); IR (KBr, cm^{-1}): 3870, 3408, 2930, 2854, 2371, 1631, 1544, 1338, 1231, 1063, 751. Anal. Calcd for $C_{17}H_{24}N_2OS{\cdot}1.1CS_2$: C, 65.85; H, 65.85; N, 8.99. Found: C, 65.95; H, 7.26; N, 9.13.

4.1.20. N-(2-Phenylethyl)-N′-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (21). With **5** and 2-phenylethylamine (**6m**). Yield: 89.1%, mp = 97–8 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.78–1.98 (m, 1H, H-3), 2.06 (m, 1H, H-3), 2.82–2.88 (m, 2H, H-4), 2.92–2.99 (t, 2H, $J = 6.8$ Hz, $ArCH_2$), 3.81–3.86 (m, 3H, NH–$CH2$, H-2), 5.9 (m, 1H, H-1), 7.12–7.35 (m, 9H, ArH); MS (FAB) m/z: 327 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3757, 3348, 3270, 3092, 2925, 2365, 1581, 1432, 1343, 1041, 703. Anal. Calcd for $C_{19}H_{22}N_2OS{\cdot}1.5H_2O$: C, 64.59; H, 7.08; N, 7.93. Found: C, 64.36; H, 7.32; N, 7.59.

4.1.21. N-Cyclohexyl-N′-(1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (22). With **4** and cyclohexylamine (**l6**). Yield: 65%, mp = 144 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.18–1.42 (m, 6H, cylcohexyl H's), 1.68 (m, 2H, cyclohexyl H's), 1.86–2.01 (m, 5H, H-2, H-3, cyclohexyl H's), 2.13–2.17 (m, 1H, H-3), 2.80 (m, 2H, H-4), 3.61 (m, 1H, cyclohexyl H adjacent to thiourea group), 5.54 (m, 1H, H-1), 7.12–7.22 (m, 3H, ArH), 7.33–7.37 (m, 1H, ArH); MS (FAB) m/z: 289 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3751, 3431, 3239, 2929, 2851, 2363, 1544, 1337, 1076. Anal. Calcd for $C_{17}H_{24}N_2S{\cdot}0.5H_2O$: C, 68.69; H, 8.42; N, 9.43. Found: C, 68.83; H, 8.59; N, 9.45.

4.1.22. N-(2-Phenylethyl)-N′-(1,2,3,4-tetrahydronaphthalen-1-yl)thiourea (23). With **4** and 2-phenylethylamine (**6m**). Yield: 90%, mp = 72–5 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.80–1.82 (m, 3H, H-2, H-3), 1.98–2.1 (m, 1H, H-3), 2.75 (m, 2H, H-4), 2.88–2.95 (t, 2H, $J = 6.9$ Hz, $ArCH_2$), 3.68 (m, 2H, NH–CH_2), 5.3 (m, 1H, H-1), 7.09–7.3 (m, 9H, ArH); MS (FAB) m/z: 295 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3323, 2930, 2863, 1619, 1246, 752. Anal. Calcd for $C_{19}H_{22}N_2S{\cdot}1.2H_2O$: C, 68.76; H, 7.36; N, 8.44. Found: C, 69.12; H, 7.22; N, 8.57.

4.1.23. N-Benzoyl-N′-(1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (24). A solution of compound **4** (500 mg, 3.40 mmol) in dry acetone (10 mL) was treated with benzoylisothiocyanate (610 mg, 3.74 mmol). The reaction mixture was stirred for 0.5 h and refluxed for 1.5 h, solvent was distilled off in a rotavapour and residue was poured in ice. The oily residue was extracted with CH_2Cl_2 (3 × 30 mL). Organic layer was washed with D.W. (30 mL × 2), dried (Na_2SO_4) and concentrated to give **24** as an oil. Yield: 60%, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.89–1.93 (m, 2H, H-2), 2.1 (m, 1H, H-3), 2.17 (m, 1H, H-3), 2.83–2.87 (m, 2H, H-4), 5.75 (m, 1H, H-1), 7.14–7.19 (m, 2H, ArH), 7.48–7.53 (m, 4H, ArH), 7.62 (m, 1H, ArH), 7.81–7.84 (m, 2H, ArH); MS (FAB) m/z: 311 ($(M+1)^+$, 30%); IR (neat, cm^{-1}): 3233, 2932, 2365, 1668, 1520, 1262, 1157, 712. Anal. Calcd for $C_{18}H_{18}N_2OS{\cdot}1.2H_2O$: C, 65.14; H, 6.15; N, 8.44. Found: C, 64.93 H, 6.16; N, 8.66.

4.1.24. N-Benzoyl-N′-(2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (25). It was prepared by known methods reported in the literature.[19] Yield: 65%, mp = 138–40 °C (140–141 °C reported in the literature). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.25; H, 5.52; N, 8.59. Found: C, 66.52; H, 5.45; N, 8.67.

4.1.25. N-(1,2,3,4-Tetrahydronaphthalen-1-yl)-thiourea (26). To solution of compound no. **24** (378 mg, 1.22 mmol) in alcohol (1.5 mL) was added 5 mL 10% KOH and the reaction mixture was heated and stirred at 100 °C for 1 h. After cooling, the separated solid was filtered, washed with water and dried. Yield: 70%, mp = 95–97 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.85–2.11 (m, 4H, H-2, H-3), 2.78–2.80 (m, 2H, H-4), 6.43 (m, 1H, H-1), 7.10–7.72 (m, 4H, ArH); MS (FAB) m/z: 207 ($(M+1)^+$, 55%); IR (KBr, cm^{-1}): 3406, 3272, 2929, 2263, 1619, 1554, 1408, 1358, 1111. Anal. Calcd for $C_{18}H_{18}N_2OS{\cdot}1.5H_2O$: C,56.65; H, 7.29; N, 12.02. Found: C, 56.83; H, 6.95; N, 12.31.

4.1.26. N-(2-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thiourea (27). It was prepared by known methods reported in the literature.[19] Yield: 84%, mp = 195–97 °C

(203–205 °C reported in lit.). Anal. Calcd for $C_{11}H_{15}N_2S{\cdot}0.12H_2O$: C, 58.89; H, 6.35; N, 12.49. Found: C, 59.26; H, 6.76; N, 12.12.

4.1.27. 2-Phenyl-3a,8,9,9a-tetrahydronaphtho[1,2-*d*]oxazole (28). To stirred solution of compound no. **5** (1 g, 6.135 mmol) in 12.5 mL of water was added 5 mL of 5% KOH followed by a solution of benzoyl chloride (0.948 g, 6.748 mmol) in 5 mL of benzene. The reaction mixture was allowed to stir for 3 h, the product was collected by filtration and dried. The crude hydroxylamide (1.466 g) was suspended in 20 mL of CH_2Cl_2 and cooled in an ice bath. To this was added of $SOCl_2$ (6.9 mL). The reaction mixture was allowed to stir at rt for 7 h, concentrated to dryness. Residual solid was made alkaline with KOH soln (10 mL, 10%) and extracted with CH_2Cl_2 (25 mL × 4). The combined organic extracts were dried over Na_2SO_4 and the solvent was distilled off to afford the desired compound **28** as an oil, yield: 65%, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.90–1.98 (m, 1H, H-9), 2.23–2.25 (m, 1H, H-9), 2.55–2.78 (m, 2H, H-8), 5.18–5.25 (m, 1H, H-9a), 5.37–5.42 (d, 1H, $J = 9.6$ Hz, H-3a), 7.09–7.57 (m, 7H, ArH), 7.92–7.96 (m, 2H, ArH); MS (FAB) *m/z*: 250 ($(M+1)^+$, 100%); IR (neat, cm^{-1}): 29 41, 2852, 1718, 1644, 1580, 1451, 1343, 1085.

4.1.28. *cis*-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene[21] (29). A mixture of **28** (1 g, 4 mmol), concd H_2SO_4 (2 mL) and H_2O (10 mL) was refluxed under stirring for 11 h, then cooled (ice bath) and the pH >10 was adjusted with 10 N NaOH. The reaction mixture was extracted with CH_2Cl_2 (15 mL × 3). Combined organic extracts were dried over Na_2SO_4 and concentrated to yield **29** as white solid. Yield: 88%, mp = 105–106 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.75–1.85 (m, 1H, H-3), 1.88–1.94 (m, 1H, H-3), 2.76–2.89 (m, 2H, H-4), 3.83–3.87 (m, 1H, H-2), 3.90–3.91 (d, 1H, $J = 2.3$ Hz, H-1), 7.07–7.33 (m, 4H, ArH); MS (FAB) *m/z*: 164 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3320, 3270, 3050, 2900, 1590, 1475, 1355, 1060, 1010. Anal. Calcd for $C_{10}H_{13}NO{\cdot}0.25H_2O$: C, 71.64; H, 8.06; N, 8.36. Found: C, 71.25; H, 8.01; N, 8.42.

4.1.29. 3a,8,9,9a-Tetrahydronaphtho[1,2-*d*]oxazole-2-thione (30). A mixture of N-ethyl-N′-(3-dimethylaminopropyl)-carbodiimidehydrochloride (EDCI) (117.5 mg, 0.613 mmol) and carbondisulfide (466 mg, 6.132 mmol) in acetonitrile (1.5 mL) was cooled to −10 °C in an ice-salt bath and treated dropwise with a solution of compound **29** (100 mg, 0.613 mmol) in acetonitrile (1.5 mL). The reaction mixture was allowed to attain the rt and was stirred for 3 h. Reaction was monitored by TLC. The solvent was distilled off and the crude was purified by column chromatography on silica gel using hexane–ethylacetate (89:11) as an eluent. Yield: 50%, mp = 175–178 °C, ^1H NMR ($CDCl_3$, 200 MHz): δ 1.76–1.89 (m, 1H, H-9), 2.38–2.46 (m, 1H, H-9), 2.63–2.73 (m, 1H, H-8), 2.83–2.91 (m, 1H, H-8), 5.12–5.16 (d, 1H, $J = 8.96$ Hz, H-3a), 5.40–5.46 (m, IH, H-9a), 7.15–7.56 (m, 3H, ArH), 7.56 (m, 1H, ArH); MS (FAB) *m/z*: 206 ($(M+1)^+$, 100%); IR (KBr, cm^{-1}): 3426, 3143, 2956, 2833, 2365, 1592, 1524, 1364, 1263, 1178. Anal. Calcd for $C_{11}H_{11}NOS{\cdot}0.2H_2O$: C, 63.28; H, 5.47; N, 6.71. Found: C, 63.32; H, 5.49; N, 6.6.

4.2. Pharmacology

The present study was carried out in Swiss mice (weighing 16–20 g) of either sex. Swiss mice were fasted for 24 h before the administration of drugs. Each group comprises of five animals. The compounds were administered in a dose of 75 μmol/kg (ip), as aqueous suspension in gum acacia. The animals were observed for gross behavioural effects after ip administration of the compounds. The animals were observed continuously for 3 h after administration of the compounds, then every 30 min for next 3 h and finally after 24 h. CNS stimulation is judged by increased spontaneous motor activity (SMA), piloerection, exopthalamous, clonic and/or tonic convulsions; CNS depression was judged by reduced SMA, sedation, ptosis, crouching, catalepsy and autonomic effects by piloerection, urination, defecation, salivation, lachrymation etc. For anorexigenic activity groups of five mice each individually caged were pretreated with graded doses of the compounds and after 1 h were offered milk (sweetened and reconstituted as 25% aqueous suspension from powdered milk). Each mouse is exposed to 0.5 mL of this milk for 15 min. Control mice drank this quantity within 15 min. Any quantity of milk left after 15 min in the treated group indicate anorexigenic activity.

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References and notes

1. Hyattsville, M. D. National Center for Health Statistics. *Health E-Stats* **2000**.
2. Flegal, K. M.; Carroll, M. D.; Ogden, C. L.; Johnson, C. L. *JAMA* **2002**, *288*, 1723–1727.
3. Bray, G. A. In *Nutrition, Endocrinology, and Diseases*; Bray, G. A., Ryan, D. H., Eds.; Pennington Center Nutrition Series; Lousiana State University Press: Baton Rouge, 1995; Vol. 4, pp 131–176.
4. Atkinson, R. L. *Annu. Rev. Nutr.* **1997**, *17*, 383–403.
5. Triscari, J.; Tilley, J.; Hogan, S. *Annu. Rep. Med. Chem.* **1988**, *23*, 191–200.
6. Garattini, S.; Bizzi, A.; Codegoni, A. M.; Mennini, T. *Am. J. Clin. Nutr.* **1992**, *55*, 160S–166S.
7. Kennett, G. A. *Drugs* **1998**, *1*, 456–470.
8. Malone, M. *Drugs* **1998**, *1*, 232–235.
9. Daniel, W. L.; Matthew, C. L.; Marina, R. A.; Patricia, G. *Drugs of the Future* **2001**, *26*(9), 873–881.
10. Connoley, I. P.; Frost, I.; Heal, D. J.; Stock, M. J. *Br. J. Pharmacol.* **1996**, *117*, 170.
11. Bray, G. A. *Rev. Endocrine Metab. Disord.* **2001**, *2*(4), 403–418.

12. Hauner, H. *Int. J. Obes.* **2001**, *25*(Suppl. 1), S102–S106.
13. King, D. J.; Devaney, N. *Br. J. Pharmacol.* **1988**, *26*, 607–611.
14. Drent, M. L.; Larsson, I.; Oisson, J. W.; Quaade, F.; Czubayko, F.; Bergmann, K. V.; Strobel, W.; Sjostrom, L.; Veen, E. A. V. *Int. J. Obes. Relat. Metab. Disord.* **1995**, *19*, 221.
15. Jackson, J. L. U.S. Patent 3,985,898, 1976; *Chem. Abstr.* **1977**, *86*, 434–444.
16. Hewett, C. L.; Savage, D. S.; Redpath, J.; Sleigh, T.; Rae, D. R. Ger. Patent 2,618,721, 1976; *Chem. Abstr.* **1977**, *86*, 89479.
17. Maillard, J. G. Ger. Patent 2,422,879, 1975; *Chem. Abstr.* **1975**, *82*, 155958.
18. Bhandari, K.; Sharma, V. L.; Singh, C. M.; Shanker, G.; Singh, H. K. *Ind. J. Chem.* **2000**, *39B*, 468–471.
19. Shukla, U. K.; Singh, R.; Khanna, J. M.; Saxena, A. K.; Singh, H. K.; Sur, R. N.; Dhawan, B. N.; Anand, N. *Collect. Czech. Chem. Commun.* **1992**, *57*, 415–424.
20. Delegado, A.; Garcia, J. M.; Mauleon, D.; Minguillon, C.; Subirats, J. R. *Can. J. Chem.* **1988**, *66*, 517–527.
21. Bellucci, C. M.; Bergamini, A.; Cozzi, P. G.; Papa, A.; Tagliavini, E.; Ronchi, A. U. *Tetrahedron: Asymmetry* **1997**, *8*(6), 895–902.
22. Dua, P.R. UNESCO-CDRI Workshop on the use of pharmacological techniques for the study of natural products, held at CDRI, Lucknow, India, 1992; p 130.