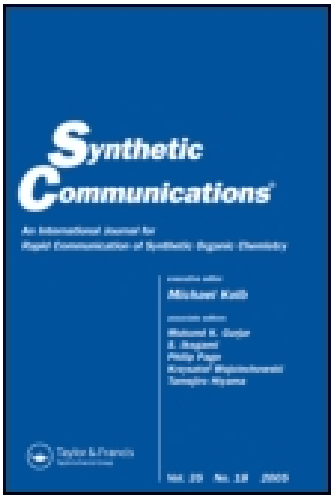

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Synthesis of Symmetrical and Asymmetrical Phenethyl Thiourea Compounds as Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase

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Synthesis of Symmetrical and Asymmetrical Phenethyl Thiourea Compounds as Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase

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Abstract: Synthesis of symmetrical and asymmetrical phenethyl thioureas was accomplished in two steps with an overall yield of 75–80%. Condensation of a substituted phenethyl amine with thiocarbonyldiimidazole, followed by treatment with one more equivalent of the phenethylamine in DMF, yielded the desired symmetrical phenethyl thiourea compound as a crystalline solid. In the case of asymmetrical thiourea derivatives, different amines were selected and condensed using a similar procedure. A series of 45 thioureas was synthesized.

Keywords: Thiourea, NNRTI, HIV

INTRODUCTION

Several thiourea compounds have been observed to inhibit HIV reverse transcriptase (RT).[1–16] In a systematic search for nonnucleoside inhibitors of

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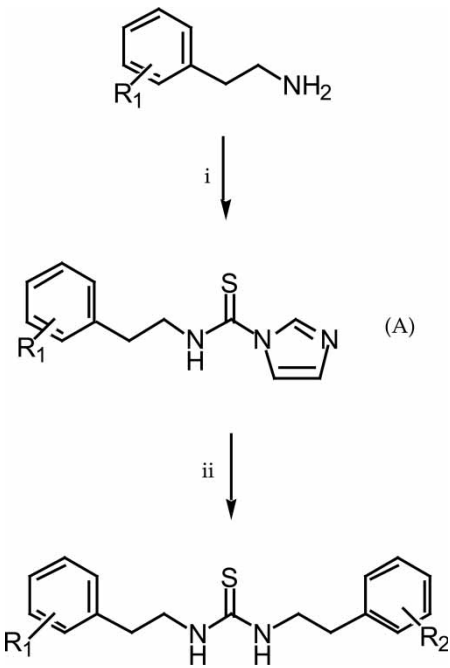
HIV RT, we prepared 45 substituted phenethyl thiourea derivatives with various substitutions on the phenyl ring.

MATERIALS AND METHODS

All chemicals were purchased from Aldrich (Milwaukee, WI) and were used without further purification. Unless otherwise noted, each reaction vessel was secured with a rubber septa, and the reaction was performed under a nitrogen atmosphere. NMR spectra were obtained on a 300-MHz Varian Mercury 300 instrument at ambient temperature in $CDCl_3$. Chemical shifts are reported as δ values in parts per million downfield from tetramethylsilane (TMS, $\delta = 0.0$ ppm) as an internal standard in the case of $CDCl_3$, and $\delta = 77.0$ ppm for ^{13}C NMR spectra. ^{19}F NMR spectra were obtained using either of these solvents and a capillary containing 0.1% trifluoroacetic acid in water, which served as the internal standard ($\delta = 0.0$ ppm). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad peak. FT-IR spectra were recorded on a Nicolet Protégé 460 spectrometer as KBr pellets. Mass spectra were performed on a



Scheme 1. Synthesis of substituted phenethyl thioureas: i) ACN, thiodicarbonyldiimidazole, 0°C for 1–2 h, rt for 20 h, and ii) anhydrous DMF, $R_2CH_2CH_2NH_2$, 100°C, 20 h.

Hewlett Packard MALDI-TOF spectrometer (Model G2025 MALDI-TOF). Melting points were determined using a Melt John's apparatus and are uncorrected. HPLC was done using a Hewlett Packard 1100-series instrument that consisted of a automatic sampler, a electronic degasser, a thermostatic control unit, and a diode array detector in conjunction with Chemstation software. The column used was an analytical Lichrospher RP–18 column (5 μm, 4.6 × 250 mm) (Hewlett Packard), and the eluent was methanol. The flow rate was maintained at 1.0 mL/min and the detection wavelength was set at 275 nm. The column was maintained at room temperature throughout the analysis. Column chromatography was performed using silica gel (60 mesh) obtained from the Baker Company. The solvents used for elution was ethyl acetate and hexane.

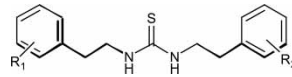
RESULTS AND DISCUSSION

The thiourea compounds were prepared by condensing appropriately phenyl-substituted phenylethyl amines and thiocarbonyldiimidazole in acetonitrile medium at 0°C (ice bath) for 15 h to yield the corresponding phenethyl-substituted thicarbonylimidazole as an intermediate. Treatment of the intermediate with one more equivalent of the substituted phenylethyl amine in dimethylformamide at 100°C for 20 h over an oil bath furnished the required symmetrical thiourea derivatives (Table 1) (Scheme 1). Condensation of the thiocarbonylimidazole intermediate with other amines furnished the asymmetrical thiourea compounds. (Table 2). Use of the thiocarbonyldiimidazole methodology is simple and is an advantageous alternative to isothiocyante method used in the past.[17,18] Isothiocyantes are more difficult to handle because of their reactive nature as compared with their comparative thiocarbonyldiimidazole precursors.

GENERAL SYNTHETIC PROCEDURE

The following is a synthetic procedure for **1** and is a representative synthetic procedure for the compounds described in this article. Thiodicarbonyldimidazole (1.78 g, 1 mmol) was dissolved in anhydrous acetonitrile (75 mL) in a 250-ml, round-bottomed flask with an addition funnel and a magnetic stir bar. The contents were stirred for 30 min. The flask was cooled with an external ice bath, and the addition funnel was charged with phenethyl amine (1.21 g, 1.0 mmol). The amine was added dropwise with stirring. After completion of addition, the mixture was allowed to stir at room temperature for 15 h, which was followed by removal of the solvent by rotary evaporation under vacuum, yielding the thiocarbonylimidzole intermediate. This was directly used for the next step without further purification.

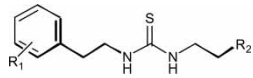
Table 1. Structures of PETT derivatives



Compound	R_1	R_2
1	H	H
2	2-Chloro	4-Bromo
3	2-Chloro	2-Chloro
4	2-Chloro	3-Chloro
5	2-Chloro	4-Chloro
6	2-Chloro	2-Fluoro
7	2-Chloro	4-Hydroxy
8	2-Chloro	2-Methoxy
9	2-Chloro	3-Methoxy
10	2-Chloro	2,5-Dimethoxy
11	2-Chloro	3,4-Dimethoxy
12	2-Chloro	4-Methyl
13	3-Chloro	4-Bromo
14	3-Chloro	3-Chloro
15	3-Chloro	2-Fluoro
16	3-Chloro	4-Hydroxy
17	3-Chloro	2-Methoxy
18	3-Chloro	3-Methoxy
19	3-Chloro	2,5-Dimethoxy
20	3-Chloro	3,4-Dimethoxy
21	3-Chloro	4-Methyl
22	4-Chloro	4-Bromo
23	4-Chloro	2-Fluoro
24	4-Chloro	4-Hydroxy
25	4-Chloro	2-Methoxy
26	4-Chloro	3-Methoxy
27	4-Chloro	2,5-Dimethoxy
28	4-Chloro	3,4-Dimethoxy
29	4-Chloro	4-Methyl
30	2-Fluoro	4-Bromo
31	2-Fluoro	2-Fluoro
32	2-Fluoro	4-Hydroxy
33	2-Fluoro	2-Methoxy
34	2-Fluoro	3-Methoxy
35	2-Fluoro	2,5-Dimethoxy
36	2-Fluoro	3,4-Dimethoxy
37	2-Fluoro	4-Methyl

The crude thicarbonylimidazole intermediate was dissolved in anhydrous dimethylformamide (50 mL) in a 250-mL, round-bottomed flask with a condenser and a magnetic stir bar. Using a dry syringe, one equivalent of phenethylamine (1.22 g, 1 mmol) was added and the mixture heated over an oil

Table 2. Structures of PETT derivatives



Compound	R_1	R_2
38	2-Chloro	1-Cyclohexene
39	2-Chloro	3-Indole
40	3-Chloro	1-Cyclohexene
41	3-Chloro	3-Indole
42	4-Chloro	1-Cyclohexene
43	4-Chloro	3-Indole
44	2-Fluoro	1-Cyclohexene
45	2-Fluoro	3-Indole

bath at 100°C for 20 h. The solution was allowed cool to room temperature and then poured into crushed ice. The solution was stirred for 45 min, during which a precipitate was formed. The precipitate was filtered and washed with 3×200 ml of water and dried under vacuum. The product was further purified by column chromatography using ethyl acetate/hexanes as eluent. Further purification of the product was achieved by crystallization in ethanol to furnish **1** as a crystalline solid in 65% yield. A similar procedure was followed for all the other thioureas described in Tables 1 and 2.

PHYSICAL DATA FOR SYNTHESIZED COMPOUNDS 1–45

N-[2-(Phenethyl)]-N′-[2-(Phenethyl)]thiourea (1). Yield: 65%; mp 82–85°C; UV ($CHCl_3$) λ_{max}: 218, 254 nm; IR (KBr) ν 3275, 3205, 3051, 2928, 2862, 1562, 1494, 1450, 1379, 1346, 1311, 1284, 1136, 1001, 908, 752, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.10 (m, 10H), 5.83 (bs, 2H), 3.64 (bs, 4H), 2.88–2.83 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 138.2, 128.8, 128.7, 126.7, 45.3, 35.0; MS: Found 285 (M+1), calcd.: 284; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{20}N_2S$: C, 71.79; H, 7.09; N, 9.85. Found: C, 71.95; H, 7.17; N, 9.78.

N-[2-(2-Chlorophenethyl)]-N′-[2-(4-Bromophenethyl)]-thiourea (2). Yield: 97%; mp 88–89°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3401, 3255, 3060, 3022, 2931, 2863, 1550, 1488, 1475, 1442, 1384, 1346, 1280, 1186, 1120, 1072, 1053, 1010, 808, 752, 676, 528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.05 (m, 8H), 6.00 (s, 1H), 5.87 (s, 1H), 3.64 (q, 4H), 3.01–2.97 (t, 2H), 2.86–2.81 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.6, 137.2, 135.7, 133.8, 131.7, 131.0, 130.4, 129.6, 128.3, 127.2, 120.5, 45.2, 43.7, 31.5, 32.9; MALDI-TOF found: 398.9; (M+1), calcd.: 397.8. HPLC: Rt: 2.5 min, single

peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SBrCl$: C, 51.33; H, 4.56; N, 7.04. Found: C, 51.42; H, 4.46; N, 6.96.

N-[2-(2-Chlorophenethyl)]-N′-[2-(2-Chlorophenethyl)]-thiourea (3). Yield: 62%; mp 112–113°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3407, 3270, 3056, 3041, 2931, 2865, 1550, 1475, 1442, 1384, 1346, 1301, 1280, 1188, 1053, 999, 941, 750, 675, 594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.13 (m, 8H), 6.21 (s, 2H), 3.65 (q, 4H), 3.02–2.97 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.4, 135.7, 133.7, 130.9, 129.4, 128.1, 127.0, 43.6, 32.8; MALDI-TOF found: 354.0 (M+1), calcd.: 353.3; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SCl_2$: C, 57.79; H, 5.13; N, 7.93. Found: C, 57.80; H, 5.05; N, 7.83.

N-[2-(2-Chlorophenethyl)]-N′-[2-(3-Chlorophenethyl)]-thiourea (4). Yield: 94%; mp 71–72°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3405, 3251, 3062, 3020, 2933, 2865, 1687, 1598, 1560, 1442, 1384, 1346, 1297, 1203, 1080, 1053, 999, 908, 823, 783, 754, 684, 555, 441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.05 (m, 8H), 6.29 (s, 1H), 6.20 (s, 1H), 3.63 (q, 4H), 2.99–2.95 (t, 2H), 2.86–2.81 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.3, 140.2, 135.6, 134.1, 133.6, 130.8, 129.8, 129.4, 128.6, 128.1, 127.0, 126.8, 126.6, 445.1, 43.5, 34.7, 32.8; MALDI-TOF found: 354.3 (M+1), calcd.: 353.3; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SCl_2$: C, 57.79; H, 5.13; N, 7.93. Found: C, 57.38; H, 5.23; N, 7.91.

N-[2-(2-Chlorophenethyl)]-N′-[2-(4-Chlorophenethyl)]-thiourea (5). Yield: 77%; mp 85–86°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3403, 3253, 3062, 2933, 2865, 1664, 1552, 1492, 1442, 1346, 1299, 1188, 1091, 1053, 1016, 943, 811, 754, 376, 509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.09 (m, 8H), 5.98 (s, 1H), 5.86 (s, 1H), 3.63 (q, 4H), 3.02–2.97 (t, 2H), 2.88–2.83 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.7, 136.7, 135.7, 133.8, 132.5, 131.0, 130.0, 129.6, 128.8, 128.3, 127.2, 45.3, 43.7, 34.5, 32.9; MALDI-TOF found: 353.8 (M+1), calcd.: 353.3; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SCl_2$: C, 57.79; H, 5.13; N, 7.93. Found: C, 57.64; H, 5.08; N, 8.13.

N-[2-(2-Chlorophenethyl)]-N′-[2-(2-Fluorophenethyl)]-thiourea (6). Yield: 63%; mp 74–75°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3407, 3253, 3064, 2935, 2867, 1552, 1492, 1456, 1348, 1284, 1230, 1188, 1120, 1053, 1000, 910, 754, 675, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–6.98 (m, 8H), 6.21 (s, 2H), 3.64 (q, 4H), 3.01–2.96 (t, 2H), 2.93–2.88 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.4, 161.5, 159.63, 135.7, 133.7, 130.94, 130.86, 129.4, 128.4, 128.3, 128.0, 127.0, 125.1, 124.9, 124.21, 124.17, 115.3, 115.0, 44.1, 43.6, 32.8, 28.6; ^{19}F NMR ($CDCl_3$) δ −42.74, −42.72; MALDI-TOF found: 337.4 (M+1), calcd.: 336.9; HPLC: Rt: 2.3 min, single peak with purity

100%; Anal. calcd. for $C_{17}H_{18}N_2SCl$ F: C, 60.62; H, 5.39; N, 8.32. Found: C, 60.74; H, 5.38; N, 8.38.

N-[2-(2-Chlorophenethyl)]-N′-[2-(4-Hydroxyphenethyl)]-thiourea (7). Yield: 93%; mp 111–112°C; UV ($CHCl_3$) λ_{max}: 255, 284 nm; IR (KBr) ν 3396, 3070, 3016, 2939, 2865, 1612, 1556, 1513, 1475, 1442, 1346, 1218, 1172, 1107, 1053, 948, 827, 754, 667, 559, 459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–6.76 (m, 8H), 5.98 (s, 1H), 5.87 (s, 2H), 3.59 (s, 4H), 2.99–2.95 (t, 2H), 2.79–2.74 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.2, 154.6, 135.8, 133.8, 131.0, 129.7, 129.6, 128.3, 127.2, 115.7, 45.5, 43.9, 34.1, 32.9; MALDI-TOF found: 336.9 (M + 2), calcd.: 334.9; HPLC: Rt: 2.1 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{19}N_2SOCl$: C, 60.98; H, 5.72; N, 8.37. Found: C, 60.68; H, 5.83; N, 8.41.

N-[2-(2-Chlorophenethyl)]-N′-[2-(2-Methoxyphenethyl)]-thiourea (8). Yield: 66%; mp 73–74°C; UV ($CHCl_3$) λ_{max}: 256, 264 nm; IR (KBr) ν 3355, 3251, 3062, 3006, 2937, 2834, 1600, 1552, 1492, 1475, 1438, 1346, 1290, 1243, 1124, 1053, 1031, 752, 675, 462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–6.81 (m, 8H), 6.56 (s, 1H), 6.29 (s, 1H), 3.73 (s, 3H), 3.49 (q, 4H), 3.16–3.01 (t, 2H), 2.86–2.82 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.0, 156.9, 136.0, 133.6, 131.0, 130.3, 129.3, 127.9, 126.9, 120.8, 110.2, 55.16, 44.0, 32.8, 29.7; MALDI-TOF found: 349.9 (M+1), calcd.: 348.9; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOCl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.17; H, 5.98; N, 7.78.

N-[2-(2-Chlorophenethyl)]-N′-[2-(3-Methoxyphenethyl)]-thiourea (9). Yield: 56%; mp 64–65°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3251, 3058, 3010, 2935, 2865, 2833, 1594, 1550, 1488, 1475, 1438, 1384, 1346, 1259, 1189, 1153, 1053, 1002, 871, 777, 754, 696, 570, 451 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–6.73 (m, 8H), 6.17 (s, 2H), 3.75 (s, 3H), 3.62 (q, 4H), 2.97–2.93 (t, 2H), 2.84–2.80 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.3, 159.5, 139.7, 135.7, 133.6, 130.8, 129.5, 129.3, 128.0, 126.9, 120.8, 114.2, 111.8, 55.0, 45.2, 43.6, 35.0, 32.7; MALDI-TOF found: 349.6 (M+1), calcd.: 348.9; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOCl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.62; H, 6.01; N, 7.92.

N-[2-(2-Chlorophenethyl)]-N′-[2-(2,5-Dimethoxyphenethyl)]-thiourea (10). Yield: 31%; mp 55–56°C; UV ($CHCl_3$) λ_{max}: 254, 295 nm; IR (KBr) ν 3349, 3257, 3064, 2998, 2937, 2833, 1552, 1500, 1465, 1442, 1346, 1282, 1224, 1180, 1128, 1051, 867, 802, 754, 709, 675, 455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–6.70 (m, 7H), 6.37 (s, 1H), 6.04 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.47 (q, 4H), 3.08–3.03 (t, 2H), 2.85–2.80 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.3, 153.7, 151.2, 133.8, 131.2, 129.5, 128.2, 127.1, 116.8, 112.2, 111.4, 55.9, 55.7, 32.9, 30.1; MALDI-TOF found: 379.8 (M+1), calcd.: 378.9; HPLC: Rt: 24 min, single peak with purity 100%; Anal. calcd.

for $C_{19}H_{23}N_2SO_2Cl$: C, 60.23; H, 6.12; N, 7.39. Found: C, 60.09; H, 6.16; N, 7.22.

N-[2-(2-Chlorophenethyl)]-N′-[2-(3,4-Dimethoxyphenethyl)]-thiourea (11). Yield: 68%; mp 139–140°C; UV ($CHCl_3$) λ_{max}: 253, 283 nm; IR (KBr) ν 3345, 3064, 3014, 2935, 2869, 2834, 1606, 1553, 1515, 1473, 1442, 1419, 1346, 1261, 1236, 1191, 1141, 1053, 1027, 808, 754, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–6.70 (m, 7H), 6.12 (s, 2H), 3.80 (s, 6H), 3.66 (q, 4H), 3.00–2.95 (t, 2H), 2.84–2.79 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.5, 148.7, 154.4, 135.8, 133.7, 130.8, 129.4, 128.0, 126.9, 120.7, 111.6, 111.2, 55.7, 45.4, 43.7, 34.6, 32.8; MALDI-TOF found: 380.2 (M+1), calcd.: 378.9; HPLC: Rt: 2.2 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{23}N_2SO_2Cl$: C, 60.23; H, 6.12; N, 7.39. Found: C, 58.55; H, 6.09; N, 7.30.

N-[2-(2-Chlorophenethyl)]-N′-[2-(4-Methylphenethyl)]-thiourea (12). Yield: 90%; mp 107–108°C; UV ($CHCl_3$) λ_{max}: 256 nm; IR (KBr) ν 3403, 3264, 3058, 3018, 2927, 2863, 1552, 1515, 1475, 1442, 1382, 1346, 1282, 1184, 1120, 1053, 810, 754, 698, 487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.04 (m, 8H), 6.01 (s, 2H), 3.60 (q, 4H), 2.98–2.93 (t, 2H), 2.83–2.79 (t, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.4, 136.1, 135.8, 135.0, 133.7, 130.9, 129.4, 129.3, 128.4, 128.1, 127.0, 45.4, 43.6, 34.6, 32.8, 20.9; MALDI-TOF found: 334.0 (M+1), calcd.: 332.9; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SCl$: C, 64.95; H, 6.36; N, 8.42. Found: C, 64.72; H, 6.25; N, 8.33.

N-[2-(3-Chlorophenethyl)]-N′-[2-(4-Bromophenethyl)]-thiourea (13). Yield: 90%; mp 79–80°C; UV ($CHCl_3$) λ_{max}: 253 nm; IR (KBr) ν 3399, 3247, 3060, 2931, 2863, 1596, 1548, 1488, 1432, 1384, 1346, 1292, 1243, 1203, 1072, 1010, 885, 810, 781, 684, 486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.01 (m, 8H), 6.14 (s, 2H), 3.60 (q, 4H), 2.83–2.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.4, 140.2, 137.1, 134.2, 131.6, 130.3, 129.8, 128.6, 126.8, 126.7, 120.3, 45.0, 34.6, 34.4; MALDI-TOF found: 398.5 (M+1), calcd.: 397.8; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SBrCl$: C, 51.33; H, 4.56; N, 7.04. Found: C, 51.56; H, 4.48; N, 6.99.

N-[2-(3-Chlorophenethyl)]-N′-[2-(3-Chlorophenethyl)]-thiourea (14). Yield: 74%; mp 75–76°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3407, 3257, 3062, 2865, 1683, 1598, 1548, 1475, 1430, 1384, 1346, 1294, 1080, 1008, 908, 868, 823, 783, 732, 684, 557, 441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.03 (m, 8H), 6.16 (s, 1H), 6.13 (s, 1H), 3.60 (q, 4H), 2.85–2.80 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.5, 140.2, 134.2, 129.9, 128.6, 126.8, 126.7, 45.0, 34.6; MALDI-TOF found: 353.1, calcd.: 353.3; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SCl_2$: C, 57.79; H, 5.13; N, 7.93. Found: C, 57.37; H, 5.02; N, 7.77.

N-[2-(3-Chlorophenethyl)]-N′-[2-(2-Fluorophenethyl)]-thiourea (15). Yield: 75%; mp 70–71°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3409, 3257, 3062, 2933, 2865, 1664, 1556, 1492, 1348, 1290, 1230, 1189, 1103, 1080, 999, 869, 827, 756, 684, 553 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.99 (m, 8H), 6.09 (s, 1H), 6.02 (s, 1H), 3.64–3.63 (q, 4H), 2.92–2.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 162.6, 159.4, 140.3, 134.3, 131.04, 130.98, 129.9, 128.7, 128.6, 128.5, 126.9, 126.8, 124.9, 124.3, 115.4, 115.2, 45.1, 44.1, 34.7, 28.6; ^{19}F NMR ($CDCl_3$) δ −42.81, −42.76; MALDI-TOF found: 337.5 (M+1), calcd.: 336.9; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}N_2SClF$: C, 60.62; H, 5.39; N, 8.32. Found: C, 60.66; H, 5.37; N, 8.51.

N-[2-(3-Chlorophenethyl)]-N′-[2-(4-Hydroxyphenethyl)]-thiourea (16). Yield: 60%; mp 101–102°C; UV ($CHCl_3$) λ_{max}: 254, 277, and 286 nm; IR (KBr) ν 3266, 3064, 3016, 2933, 2863, 1612, 1596, 1556, 1513, 1475, 1438, 1346, 1220, 1172, 1103, 1080, 999, 827, 784, 752, 684, 644, 592, 545, 503, 439 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.74 (m, 8H), 6.16 (s, 1H), 5.91 (s, 1H), 5.79 (s, 1H), 3.60–3.51 (q, 4H), 2.82–2.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 154.6, 140.3, 134.3, 130.0, 129.7, 128.8, 126.9, 115.8, 45.4, 34.7, 34.0; MALDI-TOF found: 335.7 (M+1), calcd.: 334.9; HPLC: Rt: 2.1 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{19}N_2SOCl$: C, 60.98; H, 5.72; N, 8.37. Found: C, 60.74; H, 5.75; N, 8.41.

N-[2-(3-Chlorophenethyl)]-N′-[2-(2-Methoxyphenethyl)]-thiourea (17). Yield: 30%, (gel); UV ($CHCl_3$) λ_{max}: 256 nm; IR (KBr) ν 3355, 3253, 3062, 3006, 2937, 2834, 1726, 1598, 1552, 1494, 1465, 1438, 1382, 1346, 1290, 1243, 1122, 1080, 1029, 869, 754, 684, 665, 543 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.83 (m, 7H), 6.49 (s, 1H), 6.17 (s, 2H), 3.74 (s, 3H), 3.69–3.46 (q, 4H), 2.90–2.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.1, 160.0, 140.5, 139.7, 134.1, 130.4, 129.7, 128.7, 128.0, 126.9, 126.6, 120.8, 110.3, 55.3, 45.4, 34.8, 29.7; MALDI-TOF found: 349.4 (M+1), calcd.: 348.9; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOCl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.52; H, 6.14; N, 7.92.

N-[2-(3-Chlorophenethyl)]-N′-[2-(3-Methoxyphenethyl)]-thiourea (18). Yield: 77%; mp 48–49°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3257, 3060, 2937, 2834, 1598, 1548, 1488, 1436, 1346, 1259, 1153, 1080, 1043, 910, 871, 783, 732, 696, 648, 555, 460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–6.72 (m, 8H), 6.13 (s, 2H), 3.75 (s, 3H), 3.60 (q, 4H), 2.83–2.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.3, 159.6, 140.2, 139.7, 134.1, 129.8, 129.6, 128.6, 126.8, 126.6, 120.8, 114.3, 111.8, 55.0, 45.1, 35.0, 34.6; MALDI-TOF found: 349.7 (M+1), calcd.: 348.9; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOCl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.72; H, 6.01; N, 7.93.

N-[2-(3-Chlorophenethyl)]-N′-[2-(2,5-Dimethoxyphenethyl)]-thiourea (19). Yield: 40%; (gel); UV ($CHCl_3$) λ_{max}: 253 and 294 nm; IR (KBr) ν 3345, 3251, 3060, 2998, 2937, 2833, 1596, 1552, 1500, 1465, 1430, 1346, 1282, 1224, 1047, 869, 800, 756, 692, 553 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.70 (m, 7H), 6.49 (s, 1H), 6.12 (s, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.46 (q, 4H), 2.91–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 153.6, 151.2, 140.5, 134.2, 129.8, 128.7, 126.9, 126.7, 116.7, 112.1, 111.4, 55.9, 55.6, 45.4, 34.8, 29.9; MALDI-TOF found: 380.3 (M+1), calcd.: 378.9; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{23}N_2SO_2Cl$: C, 60.23; H, 6.12; N, 7.39. Found: C, 60.04; H, 6.06; N, 7.42.

N-[2-(3-Chlorophenethyl)]-N′-[2-(3,4-Dimethoxyphenethyl)]-thiourea (20). Yield: 61%; mp 97–98°C; UV ($CHCl_3$) λ_{max}: 252 and 283 nm; IR (KBr) ν 3344, 3278, 2998, 2935, 2867, 2834, 1596, 1546, 1515, 1465, 1344, 1261, 1234, 1141, 1026, 910, 869, 784, 730, 684, 646, 441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.70 (m, 7H), 6.01 (s, 2H), 3.80 (s, 3H), 3.79 9 (s, 3H), 3.65 (q, 4H), 2.85–2.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 148.8, 147.5, 140.4, 134.2, 130.7, 129.8, 128.8, 128.6, 126.8, 126.7, 120.5, 111.6, 111.2, 55.7, 46.6, 45.3, 45.1, 40.2, 34.9, 34.7, 34.6; MALDI-TOF found: 379.9 (M+1), calcd.: 378.9; HPLC: Rt: 2.4 min, purity 98.1%; Anal. calcd. for $C_{19}H_{23}N_2SO_2Cl$: C, 60.23; H, 6.12; N, 7.39. Found: C, 59.10; H, 6.22; N, 7.75.

N-[2-(3-Chlorophenethyl)]-N′-[2-(4-Methylphenethyl)]-thiourea (21). Yield: 92%; mp 74–75°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3403, 3251, 3054, 3020, 2925, 2861, 1598, 1550, 1515, 1475, 1430, 1384, 1346, 1292, 1203, 1095, 1022, 869, 810, 783, 684, 489 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–7.04 (m, 8H), 6.00 (s, 2H), 3.59 (q, 4H), 2.82–2.78 (t, 4H) 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.4, 140.3, 136.2, 134.9, 134.2, 129.8, 129.3, 128.7, 128.4, 126.8, 126.7, 45.3, 45.1, 34.7, 34.6, 21.0; MALDI-TOF found: 333.8 (M+1), calcd.: 332.9; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}ClN_2S$: C, 64.95; H, 6.36; N, 8.42. Found: C, 64.51; H, 6.17; N, 8.17.

N-[2-(4-Chlorophenethyl)]-N′-[2-(4-Bromophenethyl)]-thiourea (22). Yield: 62%; mp 131–132°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3264, 3062, 2937, 2856, 1645, 1548, 1488, 1405, 1348, 1124, 1107, 1012, 811, 759, 694, 665, 509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.03 (m, 8H), 5.75 (s, 2H), 3.60 (q, 4H), 2.85–2.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.8, 137.1, 136.6, 132.5, 131.8, 130.4, 130.0, 128.8, 45.2, 34.5, 34.4; MALDI-TOF found: 399.1 (M+1), calcd.: 397.8; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}BrClN_2S$: C, 51.33; H, 4.56; N, 7.04. Found: C, 51.23; H, 4.53; N, 7.03.

N-[2-(4-Chlorophenethyl)]-N′-[2-(2-Fluorophenethyl)]-thiourea (23). Yield: 87%; mp 81–82°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3411,

3276, 3064, 2933, 2865, 1704, 1662, 1552, 1492, 1456, 1348, 1290, 1228, 1188, 1091, 1016, 939, 811, 757, 661, 532 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28–7.00 (m, 8H), 5.98 (s, 1H), 5.89 (s, 1H), 3.63 (q, 4H), 2.92–2.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 162.7, 136.7, 132.4, 131.1, 131.0, 130.0, 128.7, 128.6, 128.5, 124.4, 115.5, 115.2, 45.2, 44.1, 34.4, 28.7; ^{19}F NMR ($CDCl_3$) δ −42.86, −42.82, −42.77; MALDI-TOF found: 337.2, calcd.: 336.9; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}FClN_2S$: C, 60.62; H, 5.39; N, 8.32. Found: C, 60.47; H, 5.38; N, 8.20.

N-[2-(4-Chlorophenethyl)]-N′-[2-(4-Hydroxyphenethyl)]-thiourea (24). Yield: 29%; mp 154–155°C; UV ($CHCl_3$) λ_{max}: 255 and 273 nm; IR (KBr) ν 3355, 2935, 2865, 1691, 1612, 1554, 1513, 1442, 1346, 1255, 1091, 1014, 819, 651, 511 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.39–8.37 (m, 1H), 7.33–6.76 (m, 8H), 6.57 (s, 2H), 3.69 (q, 4H), 2.86-2.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 182.2, 155.4, 137.5, 131.8, 130.1, 129.5, 128.3, 115.4, 43.4, 45.0, 40.1, 34.5, 34.2; MALDI-TOF found: 335.5 (M+1), calcd.: 334.9; HPLC: Rt: 2.1 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{19}ClN_2SO$: C, 60.98; H, 5.72; N, 8.37. Found: C, 60.01; H, 5.79; N, 8.18.

N-[2-(4-Chlorophenethyl)]-N′-[2-(2-Methoxyphenethyl)]-thiourea (25). Yield: 75%; mp 99–100°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3357, 3261, 3064, 3012, 2939, 2836, 1600, 1552, 1492, 1346, 1290, 1243, 1091, 1016, 892, 811, 754, 665, 532 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–6.83 (m, 8H), 6.42 (s, 1H), 6.06 (s, 1H), 3.74 (s, 3H), 3.66–3.45 (q, 4H), 2.91–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.1, 157.0, 136.9, 132.2, 130.5, 130.0, 128.6, 128.1, 120.9, 110.4, 55.3, 45.5, 34.5, 29.8; MALDI-TOF found: 349.1, calcd.: 348.9; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOCl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.73; H, 5.95; N, 7.98.

N-[2-(4-Chlorophenethyl)]-N′-[2-(3-Methoxyphenethyl)]-thiourea (26). Yield: 78%; mp 53–54°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3264, 3060, 2937, 2865, 2934, 1583, 1552, 1490, 1346, 1259, 1153, 1091, 1014, 811, 781, 696, 489 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27–6.73 (m, 8H), 5.91 (s, 2H), 3.78 (s, 3H), 3.61 (q, 4H), 2.85–2.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 159.7, 139.8, 136.7, 132.4, 130.0, 129.7, 128.7, 120.9, 114.4, 111.9, 55.2, 45.2, 35.1, 34.4; MALDI-TOF found: 349.6 (M+1), calcd.: 348.9; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOCl$: C, 61.97; H, 6.07; N, 8.03. Found: C, 61.09; H, 6.03; N, 8.44.

N-[2-(4-Chlorophenethyl)]-N′-[2-(2,5-Dimethoxyphenethyl)]-thiourea (27). Yield: 62%; mp 86–87°C; UV ($CHCl_3$) λ_{max}: 256 and 293 nm; IR (KBr) ν 3353, 3261, 3064, 3014, 2948, 2934, 1552, 1500, 1346, 1282, 1222, 1047,

1016, 810, 756, 667, 532 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.70 (m, 7H), 6.34 (s, 1H), 5.95 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.46 (q, 4H), 2.89–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.3, 153.7, 151.2, 136.9, 132.4, 130.1, 128.7, 116.8, 112.2, 111.5, 56.0, 55.7, 45.7, 34.6, 30.0; MALDI-TOF found: 379.5 (M+1), calcd.: 378.9; HPLC: Rt: 2.4 min, single peak with purity 100%. Anal. calcd. for $C_{19}H_{23}N_2SO_2Cl$: C, 60.23; H, 6.12; N, 7.39. Found: C, 60.82; H, 6.01; N, 7.34.

N-[2-(4-Chlorophenethyl)]-N′-[2-(3,4-Dimethoxyphenethyl)]-thiourea (28). Yield: 53%; mp 96–97°C; UV ($CHCl_3$) λ_{max}: 253 and 278 nm; IR (KBr) ν 3345, 3062, 3018, 2867, 2836, 1592, 1548, 1515, 1465, 1348, 1261, 1141, 1027, 810, 757, 665, 541 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.67 (m, 7H), 5.89 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.64 (q, 4H), 2.84–2.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 14839, 147.6, 136.7, 132.4, 130.7, 129.9, 128.7, 120.5, 111.6, 111.2, 55.8, 45.3, 34.6, 34.4; MALDI-TOF found: 379.5 (M+1), calcd.: 378.9; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{23}N_2SO_2Cl$: C, 60.23; H, 6.12; N, 7.39. Found: C, 60.14; H, 6.25; N, 7.48.

N-[2-(4-Chlorophenethyl)]-N′-[2-(4-Methylphenethyl)]-thiourea (29). Yield: 55%; mp 129–130°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3450, 3266, 3062, 2927, 2875, 1645, 1567, 1492, 1446, 1353, 1259, 1108, 1016, 813, 767, 663, 572, 487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.289–7.04 (m, 8H), 5.76 (s, 1H), 5.65 (s, 1H), 3.60 (q, 4H), 2.84–2.79 (t, 4H) 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.6, 136.7, 136.4, 134.9, 132.5, 130.0, 129.5, 128.8, 128.5, 45.3, 34.6, 34.4, 21.0; MALDI-TOF found: 334.2 (M+1), calcd.: 332.9; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}ClN_2S$: C, 64.95; H, 6.36; N, 8.42. Found: C, 63.81; H, 6.25; N, 8.50.

N-[2-(2-Fluorophenethyl)]-N′-[2-(4-Bromophenethyl)]-thiourea (30). Yield: 70%; mp 91–92°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3407, 3264, 3062, 2933, 2865, 1695, 1618, 1550, 1490, 1456, 1348, 1292, 1228, 1186, 1105, 1072, 1010, 939, 810, 757, 649, 505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.00 (m, 8H), 5.84 (s, 1H), 5.75 (s, 1H), 3.64–3.62 (q, 4H), 2.93–2.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 137.2, 131.8, 131.1, 13.4, 128.7, 128.6, 125.1, 124.4, 120.6, 115.5, 115.3, 45.2, 44.2, 34.5, 28.7; ^{19}F NMR ($CDCl_3$) δ −42.88, −42.85, −42.79; MALDI-TOF found: 382.8 (M+1), calcd.: 381.3; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}BrFN_2S$: C, 53.55; H, 4.76; N, 7.35. Found: C, 53.93; H, 4.74; N, 7.35.

N-[2-(2-Fluorophenethyl)]-N′-[2-(2-Fluorophenethyl)]-thiourea (31). Yield: 73%; mp 87–88°C; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3413, 3257, 3064, 2934, 2867, 1618, 1552, 1492, 1456, 1386, 1348, 1288, 1228,

1191, 1120, 1037, 1000, 939, 850, 827, 754, 665, 559, 462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–6.99 (m, 8H), 6.09 (s, 2H), 3.64 (q, 4H), 2.93–2.89 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 162.6, 159.4, 131.04, 130.98, 128.5, 128.4, 125.2, 125.0, 124.3, 115.4, 115.1, 44.1, 28.6; ^{19}F NMR ($CDCl_3$) δ −42.87, −42.81, −42.78; MALDI-TOF found: 321.2 (M+1), calcd.: 320.4; HPLC: Rt: 2.5 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{18}F_2N_2S$: C, 63.73; H, 5.66; N, 8.74. Found: C, 63.67; H, 5.61; N, 8.86.

N-[2-(2-Fluorophenethyl)]-N′-[2-(4-Hydroxyphenethyl)]-thiourea (32). Yield: 84%; mp 134–135°C; UV ($CHCl_3$) λ_{max}: 255 and 273 nm; IR (KBr) ν 3315, 3066, 2935, 2867, 1693, 1554, 1513, 1456, 1348, 1228, 1105, 1035, 1002, 960, 829, 759, 661, 559, 478 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–6.74 (m, 8H), 5.98 (s, 1H), 5.86 (s, 2H), 3.59 (q, 4H), 2.90–2.74 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 162.7, 159.4, 154.6, 131.1, 129.7, 128.7, 128.5, 124.9, 124.4, 115.7, 115.5, 115.2, 114.7, 45.4, 44.3, 34.0, 28.7; ^{19}F NMR ($CDCl_3$) δ −42.80, −42.75; MALDI-TOF found: 319.3 (M+1), calcd.: 318.4; HPLC: Rt: 2.0 min, single peak with purity 100%; Anal. calcd. for $C_{17}H_{19}FN_2SO$: C, 64.13; H, 6.01; N, 8.80. Found: C, 62.92; H, 6.01; N, 8.70.

N-[2-(2-Fluorophenethyl)]-N′-[2-(2-Methoxyphenethyl)]-thiourea (33). Yield: 68%; mp 78–79°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3357, 3264, 3064, 3004, 2937, 2836, 1708, 1552, 1230, 1116, 1031, 939, 850, 754, 665, 530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–6.84 (m, 8H), 6.34 (s, 1H), 6.03 (s, 1H), 3.77 (s, 3H), 3.70–3.47 (q, 4H), 2.93–2.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 157.1, 131.2, 130.5, 128.5, 128.4, 128.2, 124.3, 121.0, 115.4, 115.1, 110.4, 55.3, 44.4, 29.8, 28.8; ^{19}F NMR ($CDCl_3$) δ −42.89; MALDI-TOF found: 333.2 (M+1), calcd.: 332.4; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOF$: C, 65.03; H, 6.37; N, 8.43. Found: C, 64.84; H, 6.22; N, 8.39.

N-[2-(2-Fluorophenethyl)]-N′-[2-(3-Methoxyphenethyl)]-thiourea (34). Yield: 97%; mp 59–60°C; UV ($CHCl_3$) λ_{max}: 255 and 273 nm; IR (KBr) ν 3257, 3060, 2937, 2834, 1585, 1552, 1490, 1259, 1153, 1041, 910, 757, 696, 665, 570, 462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19–6.66 (m, 8H), 5.92 (s, 2H), 3.69 (s, 3H), 3.54 (q, 4H), 2.82–2.73 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.5, 162.6, 159.7, 159.4, 139.8, 131.02, 130.96, 129.6, 128.5, 128.4, 125.1, 124.9, 124.2, 120.9, 115.4, 115.1, 114.3, 111.9, 55.1, 45.2, 44.1, 35.1, 28.6; ^{19}F NMR ($CDCl_3$) δ −42.84, −42.81, −42.78; MALDI-TOF found: 332.4, calcd.: 332.4; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}N_2SOF$: C, 65.03; H, 6.37; N, 8.43. Found: C, 64.74; H, 6.26; N, 8.22.

N-[2-(2-Fluorophenethyl)]-N′-[2-(2,5-Dimethoxyphenethyl)]-thiourea (35). Yield: 73%; mp 71–72°C; UV ($CHCl_3$) λ_{max}: 256 and 292 nm; IR (KBr) ν

3345, 3257, 3064, 2998, 2937, 2833, 1556, 1494, 1456, 1224, 1047, 910, 804, 757, 732, 646, 553, 464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.71 (m, 7H), 6.51 (s, 1H), 6.21 (s, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.49–3.47 (q, 4H), 2.97–2.93 (t, 2H), 2.84–2.79 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.1, 162.6, 159.4, 153.6, 151.1, 131.1, 128.4, 128.3, 124.2, 116.6, 115.3, 115.0, 112.0, 111.3, 55.8, 55.6, 44.4, 29.9, 28.7; ^{19}F NMR ($CDCl_3$) δ -42.91; MALDI-TOF found: 364.1 (M + 2), calcd.: 362.5; HPLC: Rt: 2.3 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{23}N_2SO_2$ F: C, 62.96; H, 6.40; N, 7.73. Found: C, 62.72; H, 6.37; N, 7.63.

N-[2-(2-Fluorophenethyl)]-N′-[2-(3,4-Dimethoxyphenethyl)]-thiourea (36). Yield: 77%; mp 105–106°C; UV ($CHCl_3$) λ_{max}: 255 and 273 nm; IR (KBr) ν 3257, 3060, 2937, 2865, 2834, 1585, 1552, 1490, 1456, 1259, 1163, 1041, 850, 757, 696, 555, 462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.74 (m, 7H), 5.91 (s, 2H), 3.78 (s, 6H), 3.63 (q, 4H), 2.90–2.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 162.6, 159.8, 159.4, 139.8, 131.1, 131.0, 129.7, 128.6, 128.4, 125.2, 125.0, 124.3, 120.9, 115.4, 115.2, 114.4, 112.0, 55.1, 45.2, 44.2, 35.1, 28.6; ^{19}F NMR ($CDCl_3$) δ −42.85, −42.81, −42.79; MALDI-TOF found: 363.3 (M+1), calcd.: 362.5; HPLC: Rt: 2.2 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{23}N_2SO_2$ F: C, 62.96; H, 6.40; N, 7.73. Found: C, 62.70; H, 6.42; N, 7.82.

N-[2-(2-Fluorophenethyl)]-N′-[2-(4-Methylphenethyl)]-thiourea (37). Yield: 70%; mp 76–77°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3272, 3222, 3050, 2933, 2856, 1695, 1548, 1492, 1456, 1351, 1261, 1228, 1197, 1110, 1027, 939, 811, 757, 707, 665, 561, 497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–6.99 (m, 8H), 5.88 (s, 2H), 3.60 (q, 4H), 2.90–2.80 (m, 4H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.5, 162.6, 159.4, 136.2, 135.0, 131.1, 131.0, 129.4, 128.5, 125.2, 125.0, 124.3, 115.4, 115.2, 45.4, 44.2, 34.6, 28.6, 21.0; ^{19}F NMR ($CDCl_3$) δ −42.85, −42.82, −42.76; MALDI-TOF found: 317.4 (M+1), calcd.: 316.4; HPLC: Rt: 2.4 min, single peak with purity 100%; Anal. calcd. for $C_{18}H_{21}FN_2S$: C, 68.32; H, 6.69; N, 8.85. Found: C, 68.13; H, 6.60; N, 8.87.

N-[2-(2-Chlorophenethyl)]-N′-[2-(1-Cyclohexenyl)ethyl]-thiourea (38). Yield: 45%; mp 62–63°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3396, 3249, 3060, 2927, 2856, 2833, 1510, 1475, 1384, 1344, 1284, 1243, 1188, 1153, 1053, 1002, 918, 771, 752, 675, 486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–7.08 (m, 4H), 6.14 (s, 1H), 5.95 (s, 1H), 3.63 (m, 2H), 3.35 (m, 2H), 2.99–2.95 (t, 2H), 2.13–2.09 (t, 2H), 1.90–1.42 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 181.2, 135.9, 133.9, 133.7, 130.9, 129.4, 128.0, 126.9, 124.0, 60.3, 43.7, 41.7, 36.7, 32.8, 27.7, 25.1, 22.6, 22.1, 20.9, 14.0; MALDI-TOF found: 324.0 (M+1), calcd.: 322.9; HPLC: Rt: 2.5 min, purity 99.9%; Anal. calcd. for $C_{17}H_{23}ClN_2S$: C, 63.24; H, 7.18; N, 8.68. Found: C, 62.65; H, 7.15; N, 8.68.

N-[2-(2-Chlorophenethyl)]-N′-[2-(3-Indole)ethyl]-thiourea (39). Yield: 38% (gel); UV ($CHCl_3$) λ_{max}: 249, 255, 261, 281, 291 nm; IR (KBr) ν 3471, 3399, 3361, 3278, 3060, 3016, 2941, 2873, 1726, 1548, 1475, 1442, 1375, 1342, 1249, 1216, 1095, 1053, 1010, 931, 752, 667, 609, 582, 462, 424 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (s, 1H), 7.44–6.81 (m, 8H), 5.94 (s, 2H), 3.55–3.44 (q, 4H), 2.86–2.73 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 171.2, 136.1, 135.8, 133.7, 130.8, 129.3, 128.0, 126.9, 122.3, 122.0, 119.3, 118.3, 111.8, 111.3, 60.3, 44.3, 43.7, 32.7, 24.7; MALDI-TOF found: 359.2 (M+1), calcd.: 357.9; HPLC purity 98.0%; Anal. calcd. for $C_{19}H_{20}ClN_3S$: C, 63.76; H, 5.63; N, 11.74. Found: C, 62.65; H, 6.08; N, 10.24.

N-[2-(3-Chlorophenethyl)]-N′-[2-(1-Cyclohexenyl)ethyl]-thiourea (40). Yield: 81%; mp 70–71°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3421, 3266, 3020, 2937, 2860, 2836, 1598, 1542, 1492, 1436, 1342, 1215, 1080, 1010, 921, 756, 669, 441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–7.09 (m, 5H), 5.92 (s, 2H), 3.72 (m, 2H), 3.36 (m, 2H), 2.93–2.88 (t, 2H), 2.21–2.16 (t, 2H), 2.00–1.53 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 181.2, 140.4, 1134.3, 133.9, 129.9, 128.7, 126.9, 126.8, 124.3, 45.2, 41.5, 36.7, 34.8, 27.7, 25.1, 22.6, 22.2; MALDI-TOF found: 323.5 (M+1), calcd.: 322.9; HPLC: Rt: 2.6 min, purity 99.8%; Anal. calcd. for $C_{17}H_{23}ClN_2S$: C, 63.24; H, 7.18; N, 8.68. Found: C, 62.78; H, 7.15; N, 8.64.

N-[2-(3-Chlorophenethyl)]-N′-[2-(3-Indole)ethyl]-thiourea (41). Yield: 51%; mp 127–128°C; UV ($CHCl_3$) λ_{max}: 246, 254, 283, and 291 nm; IR (KBr) ν 3405, 3357, 3259, 3054, 2925, 2852, 1596, 1548, 1496, 1456, 1390, 1342, 1292, 1228, 1093, 1080, 1010, 867, 786, 746, 684, 482 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.56–6.95 (m, 8H), 5.85 (s, 1H), 5.61 (s, 1H), 3.62–3.47 (q, 4H), 2.99–2.95 (t, 2H), 2.68–2.63 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.4, 140.3, 136.3, 134.2, 129.9, 128.7, 126.9, 126.8, 122.5, 122.4, 119.6, 118.4, 111.4, 45.2, 34.6, 24.8; MALDI-TOF found: 358.7 (M+1), calcd.: 357.9; HPLC: Rt: 2.2 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{20}ClN_3S$: C, 63.76; H, 5.63; N, 11.74. Found: C, 63.76; H, 5.63; N, 11.78.

N-[2-(4-Chlorophenethyl)]-N′-[2-(1-Cyclohexenyl)ethyl]-thiourea (42). Yield: 62%; mp 137–138°C; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3266, 3060, 2935, 2856, 2836, 1668, 1537, 1438, 1348, 1270, 1130, 1095, 1014, 918, 811, 767, 707, 551, 514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.13 (m, 5H), 5.77 (s, 2H), 3.70 (m, 2H), 3.34 (m, 2H), 2.92–2.88 (t, 2H), 2.20–2.16 (t, 2H), 1.99–1.51 (m 8H); ^{13}C NMR ($CDCl_3$) δ 181.3, 157.9, 136.7, 132.5, 130.0, 128.8, 124.4, 45.4, 41.5, 36.7, 34.5, 27.7, 25.2, 22.7, 22.2; MALDI-TOF found: 323.6 (M+1), calcd.: 322.9; HPLC: Rt: 2.5 min, purity 97.7%; Anal. calcd. for $C_{17}H_{23}ClN_2S$: C, 63.24; H, 7.18; N, 8.68. Found: C, 63.33; H, 7.18; N, 8.60.

N-[2-(4-Chlorophenethyl)]-N′-[2-(3-Indole)ethyl]-thiourea (43). Yield: 30%; mp 152–153°C; UV ($CHCl_3$) λ_{max}: 254 and 291 nm; IR (KBr) ν 3396, 3058, 2933, 1619, 1548, 1490, 1456, 1340, 1290, 1228, 1091, 1014, 810, 744, 503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.57–6.98 (m, 9H), 5.84 (s, 1H), 5.59 (s, 1H), 3.63 (m, 2H), 3.49 (m, 2H), 3.01–2.96 (t, 2H), 2.69–2.64 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.5, 136.7, 136.3, 132.4, 130.0, 128.7, 126.9, 122.7, 119.7, 118.4, 112.1, 111.4, 45.2, 44.3, 34.3, 24.8; MALDI-TOF found: 359.7 (M + 2), calcd.: 357.9; HPLC: Rt: 2.2 min, purity 97.8%; Anal. calcd. for $C_{19}H_{20}ClN_3S$: C, 63.76; H, 5.63; N, 11.74. Found: C, 62.83; H, 5.33; N, 11.67.

N-[2-(2-Fluorophenethyl)]-N′-[2-(1-Cyclohexenyl)ethyl]-thiourea (44). Yield: 40%, mp 53–54°C; UV ($CHCl_3$) λ_{max}: 253 nm; IR (KBr) ν 3415, 3251, 3062, 2929, 2858, 2834, 1618, 1552, 1492, 1456, 1382, 1348, 1261, 1230, 1195, 1103, 1037, 1014, 910, 800, 757, 732, 646, 553, 472 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–6.91 (m, 5H), 6.12 (s, 1H), 5.95 (s, 1H), 3.60 (m, 2H), 3.33 (m, 2H), 2.89–2.85 (t, 2H), 2.13–2.09 (t, 2H), 1.90–1.42 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 181.1, 162.5, 159.3, 133.8, 131.0, 130.9, 128.4, 128.3, 125.2, 125.0, 124.1, 115.3, 115.0, 44.1, 41.7, 36.7, 28.6, 27.6, 25.0, 22.6, 22.1; ^{19}F NMR ($CDCl_3$) δ −42.89, −42.87, −42.84, −42.81; MALDI-TOF found: 307.7 (M+1), calcd.: 306.4; HPLC: Rt: 2.5 min, purity 95.6%; Anal. calcd. for $C_{17}H_{23}FN_2S$: C, 66.63; H, 7.56; N, 9.14. Found: C, 65.61; H, 7.56; N, 8.72.

N-[2-(2-Fluorophenethyl)]-N′-[2-(3-Indole)ethyl]-thiourea (45). Yield: 86%; mp 113–114°C; UV ($CHCl_3$) λ_{max}: 256, 284, and 291 nm; IR (KBr) ν 3403, 3353, 3280, 3056, 2935, 2865, 1695, 1618, 1550, 1492, 1456, 1342, 1228, 1188, 1103, 1010, 939, 825, 746, 649, 584, 478, 426 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.57–6.96 (m, 9H), 5.84 (s, 1H), 5.70 (s, 1H), 3.65–3.52 (q, 4H), 3.01–2.97 (t, 2H), 2.80–2.75 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.4, 162.6, 159.4, 136.3, 131.1, 131.0, 128.5, 128.4, 126.9, 124.3, 122.3, 119.6, 118.4, 115.4, 115.2, 112.1, 111.4, 44.3, 28.5, 24.8; ^{19}F NMR ($CDCl_3$) δ −42.81, −42.76; MALDI-TOF found: 342.2 (M+1), calcd.: 341.5; HPLC: Rt: 2.2 min, single peak with purity 100%; Anal. calcd. for $C_{19}H_{20}FN_3S$: C, 66.84;H, 5.90; N, 12.31. Found: C, 66.00; H, 5.85; N, 12.15

CONCLUSIONS

Substituted phenylethyl thioureas were synthesized as Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI) candidates. Synthesis of these derivatives was accomplished in two steps utilizing thiocarbonyldiimidazole instead of isothiocyanates with typical yields of approximately 70%.

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