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Anti-HIV Activity of Aromatic and Heterocyclic Thiazolyl Thiourea Compounds

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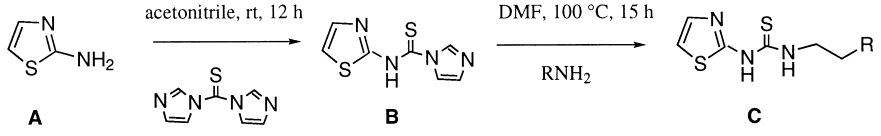
Abstract—Several thiazolyl thiourea derivatives were designed and synthesized as non-nucleoside inhibitors (NNRTI) of HIV-1 reverse transcriptase. Six lead compounds were identified that showed subnanomolar IC_{50} values for the inhibition of HIV replication, were minimally toxic to human peripheral blood mononuclear cells (PBMC) with CC_{50} values ranging from 28 to >100 μM, and showed remarkably high selectivity indices ranging from 28,000 to >100,000. The most promising compound was *N*-[1-(1-furoylmethyl)]-*N*′-[2-(thiazolyl)]thiourea (compound **6**), which showed potency against two NNRTI-resistant HIV-1 isolates (A17 and A17 variant) at nanomolar to low micromolar concentrations, exhibited much greater potency against both wild-type as well as NNRTI-resistant HIV-1 than nevirapine, delavirdine, HI-443, and HI-244, was minimally toxic to PBMC, and had a selectivity index of >100,000. The potency and minimal cytotoxicity of these aromatic/heterocyclic thiourea compounds suggest that they may be potentially useful as anti-AIDS drugs. © 2001 Published by Elsevier Science Ltd.

One of the main molecular targets in contemporary drug discovery efforts against human immunodeficiency virus (HIV-1) is reverse transcriptase (RT), a vital enzyme that is responsible for the reverse transcription of the retroviral RNA to proviral DNA.[1–3] The three categories of antiretroviral agents in use are nucleoside analogues (such as AZT), protease inhibitors (such as nelfinavir), and the recently introduced non-nucleoside inhibitors (NNRTIs) such as nevirapine, delavirdine, and efavirenz. Unlike nucleoside analogues, NNRTIs bind to an allosteric site of HIV-1 RT,[4–10] which is approximately 10 Å away from the catalytic site. NNRTI binding induces the rotamer conformation changes of some residues (Y181 and Y188) and renders the 'thumb' region more rigid, thereby altering the substrate binding mode and leading to a noncompetitive inhibition of the enzyme.[5–10] In a systematic search for derivatives of thiourea compounds[11–15] as useful anti-AIDS drugs, we have identified several structurally distinct thiourea compounds as potent NNRTIs of HIV-1 RT.[16–25] We have previously reported and established SARs for a series of 5-bromopyridyl thiourea compounds.[16–24] Our modeling studies have indicated that the 5-bromopyridyl group would tightly bind to the Wing 1 region of the binding pocket.[14,26–28] Similarly, the thiazolyl group is expected to favorably bind to the same region in the Wing 1 region of the binding pocket. Here, we now report the synthesis and anti-HIV activity of 13 novel aromatic/heterocyclic thiazolyl thiourea compounds.

For the synthesis of the thiazolyl thiourea compounds,[12] we followed the general procedure shown in Scheme 1. In brief, thiocarbonyldimidazole and 2-aminothiazole



Scheme 1.

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(**A**) were added to 100 mL of dry acetonitrile under nitrogen atmosphere and stirred at room temperature for 12–15 h. The precipitate was filtered, washed with cold acetonitrile, and dried thoroughly under vacuum to yield the thiocarbonyl (**B**) intermediate. In the subsequent step, this compound was taken up in a dry flask under nitrogen, 20 mL of anhydrous dimethylformamide was added to **B** and the contents were stirred for 30 min at room temperature. To this solution, we added the appropriate amine dissolved in 10 mL of dry dimethylformamide and heated the reaction mixture to 100 °C over an oil bath for 15 h. The reaction mixture was cooled and poured into ice water and the contents were stirred for an additional hour until a precipitate appeared. The precipitate (**C**) was filtered, washed with cold water several times and dried under vacuum. This precipitate was taken up in ethyl acetate and washed with water and brine and finally the separated ethyl acetate layer was dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent gave the desired thiourea compounds (**C**) which were further purified using silica gel column chromatography. The physicochemical properties of the compounds were determined using standard analytical methods[29] and the X-ray crystal structures of four compounds are shown in Figure 1.

We examined these thiazolyl thiourea compounds for anti-HIV activity by determining their ability to inhibit the replication of the HIV-1 strain $HTLV_{IIIB}$ in human peripheral blood mononuclear cells (PBMC) from healthy individuals. Of the 13 compounds, four (viz., compounds **9**, **10**, **11**, and **12**) were inactive with IC_{50} values ranging from 1 to >100 μM (Table 1). Three compounds (**2**, **4**, and **13**) showed moderate activity and inhibited HIV-1 replication at nanomolar concentrations. The remaining six lead compounds (**1**, **3**, and **5**–**8**) inhibited HIV-1 replication with subnanomolar IC_{50} values. These compounds were minimally toxic to PBMC with CC_{50} values ranging from 28 μM to >100 μM and their selectivity indices were remarkably high ranging from 28,000 to >100,000 (Table 1). The six

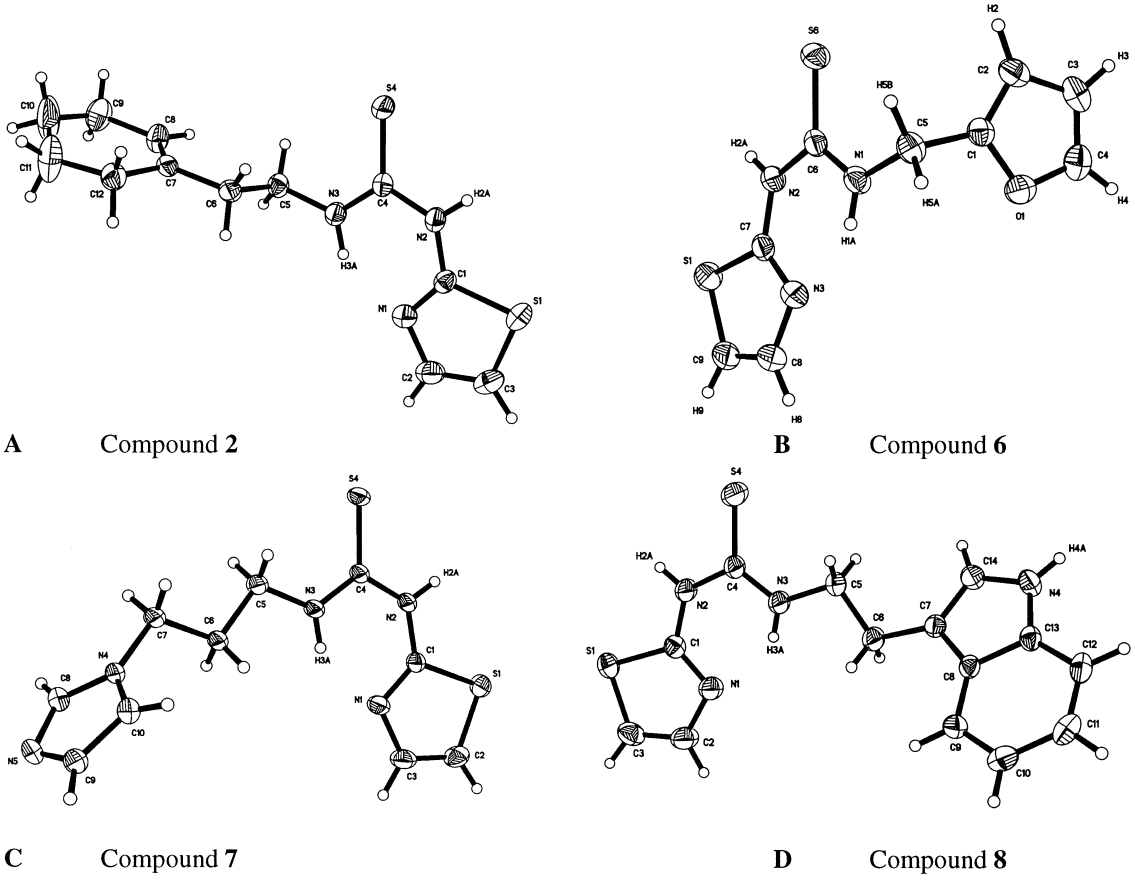
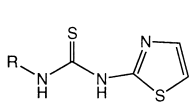
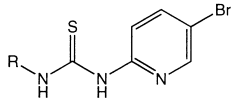


Figure 1. X-ray crystal structures of compounds **2**, **6**, **7**, and **8**. 30% probability ellipsoids, λ = 0.71073 Å. (**A**) Compound **2**, $T = 22$ °C, space group Pbca, unit cell: $a = 14.8206(11)$ Å, $b = 8.2577(6)$ Å, $c = 22.1026(16)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, volume = 2705.0(3) Å^3, $Z = 8$, θ range for data collection = 1.84–28.28°, total reflections collected = 15,621, independent reflections = 3208 ($R_{int} = 0.051$), data:restraints:parameters = 3208:0:162, R1 ($I > 2\sigma(I)$) = 0.060, wR2 = 0.13, Goodness of Fit on $F^2 = 1.013$. (**B**) Compound **6**, $T = 25$ °C, space group P-1, unit cell: $a = 4.3794(2)$ Å, $b = 10.0075(5)$ Å, $c = 12.3539(6)$ Å, $\alpha = 92.2930(10)°$, $\beta = 90.4950(10)°$, $\gamma = 97.7950(10)°$, volume = 535.95(4) Å^3, $Z = 2$, θ range for data collection = 1.65–27.11°, total reflections collected = 5978, independent reflections = 2344 ($R_{int} = 0.020$), data:restraints:parameters = 2344:0:145, R1 ($I > 2\sigma(I)$) = 0.030, wR2 = 0.084, Goodness of Fit on $F^2 = 1.069$. (**C**) Compound **7**, $T = 23$ °C, space group P-1, unit cell: $a = 5.2849(3)$ Å, $b = 10.3435(7)$ Å, $c = 11.8578(7)$ Å, $\alpha = 77.1380(10)°$, $\beta = 83.6470(10)°$, $\gamma = 85.3720(10)°$, volume = 627.00(7) Å^3, $Z = 2$, θ range for data collection = 1.77–26.04°, total reflections collected = 3528, independent reflections = 2413 ($R_{int} = 0.013$), data:restraints:parameters = 2413:0:163, R1 ($I > 2\sigma(I)$) = 0.032, wR2 = 0.094, Goodness of Fit on $F^2 = 1.056$. (**D**) Compound **8**, $T = 26$ °C, space group $P2_1/n$, unit cell: $a = 8.3723(7)$ Å, $b = 5.5107(4)$ Å, $c = 30.946(3)$ Å, $\alpha = 90°$, $\beta = 94.798(2)°$, $\gamma = 90°$, volume = 1422.8(2) Å^3, $Z = 4$, θ range for data collection = 1.32° to 27.67°, total reflections collected = 8193, independent reflections = 3172 ($R_{int} = 0.018$), data:restraints:parameters = 3172:0:193, R1 ($I > 2\sigma(I)$) = 0.042, wR2 = 0.12, Goodness of Fit on $F^2 = 1.090$.

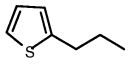
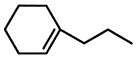
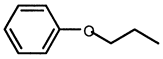
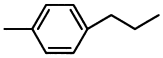
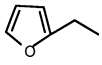
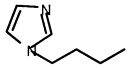
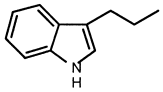
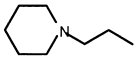
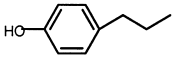
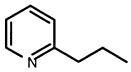
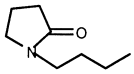
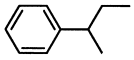
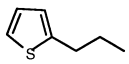
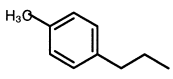
Table 1. Anti-HIV activity of thiazolyl thiourea compounds[a]



1–13



HI-244 and **HI-443**

Compound	R	Potency and selectivity			Activity against NNRTI-resistant HIV IC_{50} (μM)	
		IC_{50} $HTLV_{IIIB}$ (μM)	CC_{50} (μM)	SI	A17	A17 variant
1		< 0.001	71	71,000	>100	ND
2		0.007	4	571	0.9	>100
3		< 0.001	>100	>100,000	4.4	>100
4		0.07	>100	1429	3.9	>100
5		< 0.001	40	40,000	0.6	1.3
6		< 0.001	>100	>100,000	2.0	0.6
7		< 0.001	35	35,000	>100	>100
8		< 0.001	28	28,000	2.2	3.7
9		>100	N.D	N.D	ND	ND
10		>100	ND	ND	ND	ND
11		1	100	100	ND	ND
12		9	18	2	ND	ND
13		0.009	10	1111	2.1	1.5
Nevirapine	N.A.	0.034	ND	ND	>100	>100
Delavirdine	N.A.	0.009	ND	ND	50	>100
HI-443		0.030	>100	ND	0.048	3.3
HI-244		0.007	>100	ND	0.070	>100

[a]Normal human peripheral blood mononuclear cells (PBMNC) from HIV-negative donors were cultured 72 h in RPMI 1640 supplemented with 20% (v/v) heat-inactivated fetal bovine serum (FBS), 3% interleukin-2, 2 mM L-glutamine, 25 mM HEPES, 2 g/L $NaHCO_3$, 50 μg/mL gentamicin, and 4 μg/mL phytohemagglutinin prior to exposure to the HIV-1 strain $HTLV_{IIIB}$ at a multiplicity of infection (MOI) of 0.1 during a 1-h adsorption period at 37 °C in a humidified 5% CO_2 atm. Subsequently, cells were cultured in 96-well microtiter plates (100 μL/well; 2×10^6 cells/mL) in the presence of various concentrations of analogues and aliquots of culture supernatants were removed from the wells on the 7th day after infection for p24 antigen assays, as previously described.[31,21] The applied p24 enzyme immunoassay (EIA) was the unmodified kinetic assay commercially available from Coulter Corporation/Immunotech, Inc. (Westbrooke, ME), which utilizes a murine mAb to HIV core protein coated onto microwell strips to which the antigen present in the test culture supernatant samples binds. Percent viral inhibition was calculated by comparing the p24 values from the test substance-treated infected cells with p24 values from untreated infected cells (i.e., virus controls). The effects of various treatments on cell viability were also examined and the results were expressed as the cytotoxic concentration $(CC)_{50}$ values.[31,32] The selectivity indices (SI) were calculated using the formula: $SI = CC_{50}/IC_{50}$.

lead compounds (**1**, **3**, and **5**–**8**) were 9–34 times more potent than the standard NNRTI nevirapine and delavirdine and 7–30 times more potent than our previously reported NNRTIs HI-443 and HI-244 (Table 1). We also examined the activity of compounds **1**–**8** and compound **13** against NNRTI-resistant HIV-1 strains A17 with a Y181C mutation in RT and A17 variant with a Y181C plus K103N mutations in RT. Both A17 and A17 variant are resistant to nevirapine as well as delavirdine (Table 1). Even though compounds **1** and **7** inhibited wild-type HIV-1 at subnanomolar concentrations, they were ineffective against A17. By comparison, compounds **2**–**6**, **8**, and **13** inhibited A17 at nanomolar concentrations with IC_{50} values ranging from 0.6 μM to 4.4 μM, which are approximately 1 log better than the IC_{50} values of HI-443 or HI-244 and 1–2 logs better than the IC_{50} values of nevirapine or delavirdine against the same NNRTI-resistant HIV-1 strain (Table 1). Compounds **2**–**4** and **7** were ineffective against A17 variant. By comparison, compounds **5**, **6**, **8**, and **13** were very effective against A17 variant with IC_{50} values ranging from 0.6 μM to 3.7 μM, which are similar to the IC_{50} value of HI-443 and almost 2 logs better than the IC_{50} values of nevirapine, delavirdine, or compound HI-244 against the same NNRTI-resistant HIV-1 strain (Table 1). The most promising compounds were **5**, **6**, **8**, and **13**. These four compounds were effective against both NNRTI-resistant HIV-1 isolates at nanomolar to low micromolar concentrations and exhibited much greater potency against both wild-type as well as NNRTI-resistant HIV-1 than nevirapine, delavirdine, HI-443, and HI-244 (Table 1). Among these four compounds, the most promising was the novel compound **6** since it was minimally toxic to PBMC and had a selectivity index of >100,000 (Table 1).

The X-ray structures of compounds **2** and **6**–**8** confirmed that the essential binding components for the NNRTI binding pocket[19–25] are present in these new compounds. These components include a butterfly shape for the molecule, an intramolecular hydrogen bond, and one amide hydrogen bond donor. The crystal structures of **2** and **6**–**8** show that each molecule contains an intramolecular hydrogen bond between a thiourea NH and a thiazolyl nitrogen atom (Fig. 1). The more compact molecular conformation resulting from this hydrogen bond allows the molecule to more easily fit into the non-nucleoside binding site of HIV RT and is consistent with molecular modeling studies evaluating how NNRTI compounds can bind to HIV RT.[17–19] The crystal structures of the four compounds and the docking studies also indicate that conformations of these thiazolyl thiourea compounds could be adjusted (using a different rotamer conformation) to fit the binding pocket, and the individual interactions between the compound and the binding pocket determine the binding affinity. The 4-hydroxyl group of compound **10** was predicted to interact unfavorably with W229 and would have a low binding affinity with RT as revealed previously by a similar 5-bromopyridyl thiourea compound.[19,22] Compound **9** is inactive probably because of the entropy loss (flexibility) which offsets an otherwise strong binding affinity in modeling predictions. Compounds **1**, **2**, and **4** have geometric features similar to the previously published 5-bromopyridyl thiourea compounds[18,30] containing an ethyl linker and similarly demonstrated potent activity against wild-type RT. Compounds **3**, **7**, and **12** all have a three-atom linker group longer than in other compounds, suggesting a tight contact with the Wing 2 region of the binding pocket without steric clash. The potencies of compounds **5**, **8**, and **13** are consistent with our previously proposed working hypothesis that a larger group that can favorably interact with the Wing 2 region of the binding site is a desirable feature for inhibition of these mutants because Y181C and Y188C mutations result in a larger binding pocket.[18] A larger group that binds to the Wing 2 region of the binding site combined with a smaller thiazolyl group appears to deliver more potency against the mutant strains. The outstanding activity of compound **6** is however not anticipated and appears to reverse the trend that we have proposed before. Compared with compound **1**, it has a shorter linker group and a smaller Wing 2 group yet demonstrates better inhibition against both mutant strains, suggesting perhaps a novel binding mode.

A number of thiazolyl thioureas were designed and synthesized as non-nucleoside inhibitors (NNRTIs) of human immunodeficiency virus (HIV-1) reverse transcriptase (RT). Among the thiazolyl substituted derivatives, both the heterocyclic as well as alicyclic compounds elicited anti-HIV-1 activities at nanomolar levels. Compounds **5**, **8**, and **13** were potent against wild-type HIV as well as A17 and A17 variant mutant strains, consistent with our previous prediction that a larger Wing 2 group is advantageous for inhibition of these mutant strains. The most promising compound, **6**, which showed potency against two NNRTI-resistant HIV-1 isolates (A17 and A17 variant) at nanomolar to low micromolar concentrations, exhibited much greater potency against both wild-type as well as NNRTI-resistant HIV-1 than nevirapine, delavirdine, HI-443, and HI-244, was minimally toxic to PBMC, and had a selectivity index of >100,000. Because of their potency and minimal cytotoxicity, these aromatic/heterocyclic thiourea compounds may potentially be useful as anti-AIDS drugs.

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29. Physicochemical characteristics of thiazolyl compounds: ***N*-[2-(2-Thiophenylethyl)]-*N*-[2-(thiazolyl)]thiourea** (**1**): yield 36%, mp 193–194 °C; UV (MeOH) λ_{max} 207, 212, 215, 232, 236, 255, 289 nm; IR ν 3219, 3151, 3087, 3003, 2935, 1595, 1552, 1531, 1471, 1298, 1263, 1211, 1188, 1134, 1076, 846, 812, 686 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.66 (br s,1H), 9.69 (br s, 1H), 7.34 (d, 2H, $J=3.3$ Hz), 7.08 (d, 1H, $J=3.6$ Hz), 6.97–6.93 (m, 2H), 3.78 (q, 2H), 3.12 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.3, 161.9, 141.1, 136.5, 127.1, 125.6, 124.4, 112.1, 45.9, 28.6; MALDI-TOF 270.7 (M + 1). ***N*-[2-(1-Cyclohexenylethyl)]-*N'*-[2-(thiazolyl)]thiourea** (**2**): yield 38%, mp 153–154 °C; UV (MeOH) λ_{max} 209, 258, 288 nm; IR ν 3170, 2993, 2922, 2833, 1565, 1514, 1489, 1379, 1307, 1257, 1238, 1180, 11330, 1093, 1084, 1059, 920, 829, 730, 707 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.58 (br s, 1H), 9.69 (br s, 1H), 7.34 (d, 1H, $J=3.6$ Hz), 7.08 (d, 1H, $J=3.6$ Hz), 5.45 (s, 1H), 3.60 (q, 2H, $J=5.7$ Hz), 2.18 (t, 2H), 1.91 (d, 4H), 1.57–1.46 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 177.6, 161.7, 136.8, 134.3, 123.2, 112.2, 42.9, 36.5, 27.7, 25.0, 22.7, 22.2; MALDI-TOF 270.2 (M + 2). ***N*-[2-(Phenoxyethyl)]-*N'*-[2-(thiazolyl)]thiourea** (**3**): yield 48%, mp 168–169 °C; UV (MeOH) λ_{max} 204, 259, 286 nm; IR ν 3610, 3556, 3180, 3039, 2935, 2875, 1566, 1511, 1460, 1284, 1248, 1184, 1112, 1082, 1053, 756, 690, 605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.70 (s, 1H), 9.88 (s, 1H), 7.39 (s, 1H), 7.31–7.26 (t, 2H, $J=7.2$ Hz), 7.11 (s, 1H), 6.98–6.91 (m, 3H), 4.16 (t, 2H), 3.93 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 160.7, 158.2, 129.6, 120.9, 114.6, 112.3, 65.6, 43.8; MALDI-TOF 280.8 (M + 2). ***N*-[2-(4-Methylphenyl)ethyl]-*N'*-[2-(thiazolyl)]thiourea** (**4**): yield 40%, mp 166–167 °C; UV (MeOH) λ_{max} 208, 212, 259, 290 nm; IR ν 3170, 3047, 2997, 2943, 2920, 2850, 1562, 1514, 1449, 1348, 1323, 1279, 1217, 1196, 1159, 1097, 1053, 1020, 952, 868, 804, 760, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.58 (s, 1H), 9.66 (s, 1H), 7.34–7.32 (dd, 1H, $J=3.9$ Hz), 7.15–7.07 (q, 5H), 3.76–3.69 (q, 2H), 2.85–2.80 (t, 2H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 178.6, 162.4, 136.4, 135.9, 129.6, 129.2, 112.7, 46.6, 34.5, 31.5, 21.5; MS (MALDI-TOF) 279.3 (M + 1). ***N*-[1-(1-Adamantyl)methyl]-*N'*-[2-(thiazolyl)]thiourea** (**5**): yield 43%, mp 196–198 °C; UV (MeOH) λ_{max} 204, 208, 259, 289 nm; IR ν 3166, 3041, 2898, 2844, 1569, 1510, 1197, 1180, 779, 744, 678 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.96 (s, 1H), 10.66 (s, 1H), 7.34 (d, 1H, $J=3.9$ Hz), 6.84 (d, 1H, $J=3.6$ Hz), 6.84 (d, 2H, $J=5.1$ Hz), 2.18 (s, 3H), 2.02 (s, 2H), 1.77–1.63 (m, 10H); ^{13}C NMR (DMSO-d_6) δ 177.4, 161.9, 137.6, 110.9, 57.8, 40.5, 36.9, 33.9, 31.0, 28.3; MALDI-TOF 309 (M + 2). ***N*-[1-(1-Furoylmethyl)]-*N'*-[2-(thiazolyl)]thiourea** (**6**): yield 40%; mp 119–121 °C; UV (MeOH) λ_{max} 204, 214, 257, 292 nm; IR ν 3170, 3071, 3030, 1565, 1509, 125, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.10 (s, 2H), 7.39 (q, 1H), 7.30 (d, 1H, $J=3.6$ Hz), 6.82 (d, 1H, $J=3.9$ Hz), 6.38–6.33 (m, 2H), 4.93 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 177.8, 161.9, 150.1, 142.6, 137.9, 111.6, 110.7, 108.5, 42.65; MALDI-TOF 241.9. ***N*-[3-(2-Imidazole)propyl]-*N'*-[2-(thiazolyl)]thiourea** (**7**): yield 44%; mp 176–177 °C; UV (MeOH) λ_{max} 213, 258, 289 nm; IR ν 3190, 3051, 2932, 1565, 1514, 1225 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.39 (s, 1H), 9.98 (s, 1H), 7.53 (s, 1H), 7.25 (d, 1H, $J=3.9$ Hz), 7.02 (s, 1H), 6.88 (s, 1H), 6.85 (d, 1H, $J=3.6$ Hz), 3.54 (q, 2H), 3.01 (t, 2H), 2.12–2.03 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 178.9, 162.4, 137.5, 137.3, 129.2, 119.5, 111.9, 102.8, 44.6, 30.5; MALDI-TOF 269.7. ***N*-[2-(2-Indole)ethyl]-*N'*-[2-(thiazolyl)]thiourea** (**8**): yield 51%; mp 212–213 °C; UV (MeOH) λ_{max} 204, 207, 221, 285 nm; IR ν 3386, 3164, 3076, 3035, 1560, 1514, 1184, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.56 (s, 1H), 10.86 (s, 1H), 9.73 (s, 1H), 7.62 (d, 1H, $J=7.5$ Hz), 7.35 (s, 1H), 7.31 (t, 1H), 7.20 (s, 1H), 7.07 (d, 1H, $J=6.9$ Hz), 7.03 (s, 1H), 6.96 (t, 1H), 3.81 (q, 2H), 3.00 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.4, 162.3, 136.9, 127.7, 123.8, 121.7, 119.1, 118.9, 112.7, 112.1, 111.8, 102.8, 45.9, 24.9;

MALDI-TOF 304.2. ***N*-[2-(2-Piperdine)ethyl]-*N′*-[2-(thiazolyl)]thiourea** (**9**): yield 50%; mp 163–164 °C; UV (MeOH) λ_{max} 204, 207, 211, 258, 290 nm; IR ν 3169, 3019, 2931, 1556, 1512, 1181 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.75 (s, 2H), 7.33 (d, 1H, $J = 3.3$ Hz), 6.82 (d, 1H, $J = 3.6$ Hz), 3.78 (t, 2H), 2.59 (t, 2H), 2.45 (s, 5H), 1.60 (t, 3H), 1.45 (d, 3H); ^{13}C NMR (DMSO-d_6) δ 177.1, 161.9, 137.8, 111.4, 107.5, 56.4, 54.5, 43.2, 26.5, 24.8; MALDI-TOF 272.1. ***N*-[2-(4-Hydroxyphenyl)ethyl]-*N′*-[2-(thiazolyl)]thiourea** (**10**): yield 47%; mp 160–161 °C; UV (MeOH) λ_{max} 209, 219, 225, 260, 289 nm; IR ν 3437, 3050, 1581, 1556, 1518 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.57 (s, 1H), 9.66 (s, 1H), 9.22 (s, 1H), 7.33 (d, 1H, $J = 3.6$ Hz), 7.06 (t, 3H), 6.68 (d, 2H, $J = 8.1$ Hz), 3.68 (q, 2H), 2.76 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.5, 162.3, 156.4, 137.3, 130.3, 129.5, 115.9, 112.7, 46.9, 34.1; MALDI-TOF 280.6. ***N*-[2-Pyridylethyl]-*N′*-[2-(thiazolyl)]thiourea** (**11**): yield 60%; mp 140–141 °C; UV(MeOH) λ_{max} 209, 262, 269, 288 nm; IR ν 3176, 3047, 3002, 2937, 1581, 1558, 1514, 1475, 1433, 1342, 1304, 1246, 1167, 1147, 1068, 1020, 989, 869, 789, 752, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.59 (bs, 1), 9.77 (bs, 1H), 8.51–8.49 (d, 1H), 7.72–7.67 (m, 1H), 7.31–7.26 (m, 2H), 7.23–7.19 (m, 1H), 7.06–7.05 (m, 1H), 3.95–3.89 (m, 2H), 3.07–3.02 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 178.1, 161.8, 158.7, 149.2, 136.7, 129.4, 123.5, 121.8, 112.2, 43.9, 36.2; MALDI-TOF: 266.3 (M + 2). ***N*-[3-(Pyrrolidinone)propyl]-*N′*-[2-(thiazolyl)]thiourea** (**12**): yield 56%; mp 123.5–126 °C; UV (MeOH) λ_{max} 205, 256, 290 nm; IR ν 3199, 3054, 2964, 2863, 1660, 1550, 1508, 1315, 1166, 692 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.61 (s, 1H), 9.56 (s, 1H), 7.37 (d, 1H, $J = 3.6$ Hz), 7.08 (d, 1H, $J = 3.6$ Hz), 3.48 (q, 2H), 3.21 (t, 4H), 2.19 (t, 2H), 1.90 (t, 2H), 1.75 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 173.9, 161.9, 136.4, 122.8, 112.0, 102.7, 46.4, 41.9, 30.7, 26.3, 17.8; MALDI-TOF: 282.6. ***N*-[α-Ethylbenzyl]-*N′*-[2-(thiazolyl)]thiourea** (**13**): yield 44%; mp 149–151 °C; UV (MeOH) λ_{max} 210, 258, 291 nm; IR ν 3166, 3022, 2931, 1576, 1511, 1189, 1054, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.18 (s, 2H), 7.36–7.31 (m, 6H), 6.80 (d, 1H, $J = 3.6$ Hz), 5.52–5.45 (m, 1H), 2.10–1.92 (m, 2H), 0.97 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 177.0, 162.3, 141.3, 137.8, 128.8, 127.5, 111.5, 61.0, 29.9, 10.9; MALDI-TOF: 279.5.

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