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Regiospecific synthesis, X-ray crystal structure and biological activities of 5-bromothiophenethyl thioureas

Taracad K. Venkatachalam, Elise A. Sudbeck and Fatih M. Uckun*

Departments of Chemistry, Structural Biology and Virology, Parker Hughes Institute, 2665 Long Lake Road, Roseville, MN 55113, USA

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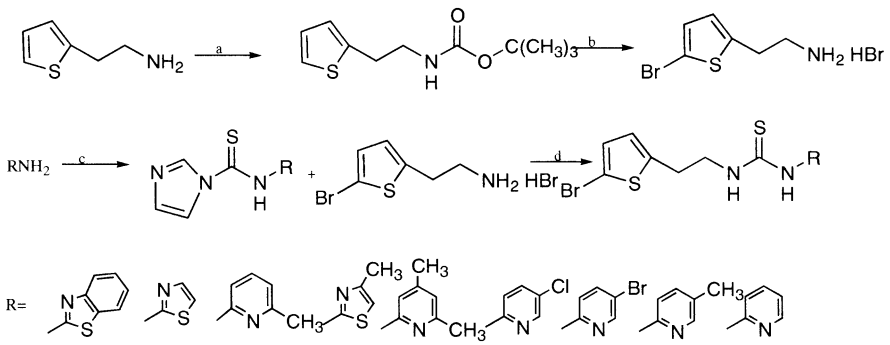
Abstract—The regiospecific synthesis of 5-bromothiophenethyl thioureas was accomplished in four steps with an overall yield of 40–60%. The requisite regioselectivity for bromination of the thiophene ring was achieved using bromine in acetic acid at low temperatures. The resulting 5-bromothiophenethylamine hydrobromide is an important precursor for the preparation of substituted thioureas. The X-ray crystal structure demonstrates that the bromine atom is indeed located at the 5-position of the thiophene ring.

The potent anti-HIV activities displayed by several thiourea derivatives has led to comprehensive efforts in preparing and evaluating the biological activities of many other substituted thioureas. Since the first class of phenethyl thiazolyl thioureas was reported in 1995,[1,2] several new derivatives have been synthesized and proven to be effective anti-HIV agents.[3–6] We have previously reported[7] that thiophene-substituted thioureas inhibit both wild-type and multidrug-resistant strains of HIV. To explore the structure–activity relationships of thiophene-substituted thioureas, the effects of substituents on the thiophene ring on the anti-HIV activities of the thioureas must be examined. The lack of commercially available precursors requires the development of new synthetic approaches for functionalizing the thiophene ring, however. We describe here a method for regioselectively brominating the thiophene ring.

Commercially available 2-thiophenethylamine was protected using a tboc group. Subsequent reaction with bromine in acetic acid at 0°C yielded 5-bromothiophenethylamine hydrobromide in a regiospecific fashion (Scheme 1). Alternatively, we can use the hydrochloride or bromide salt of thiophenethylamine as starting material. Condensation with a thiocarbaimidazole derivative of a pyridyl-substituted amine generated the final product (Scheme 1). Purification was achieved by column chromatography and recrystallization from ethanol.



Scheme 1. Synthesis of 5-bromothiophenethyl thioureas. (a) $CHCl_3$, $(BOC)_2O$, reflux, 6 h; (b) AcOH, 0°C, Br_2/AcOH, rt, overnight; (c) 1,1′-thiocarbonyldiimidazole, ACN, rt, 12 h; (d) K_2CO_3, DMF, 100°C, 15 h.

Keywords: HIV; reverse transcriptase; non-nucleoside inhibitor; thiophene thiourea.

* Corresponding author. Tel.: (651) 697-9228; fax: (651) 697-1042; e-mail: fatih_uckun@ih.org

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Electrophilic substitution on thiophene generally occurs at the 2- and 5-positions since the allylic cation intermediate can be stabilized by charge delocalization. Substitution at the 3- or 4-position would lead to a much less stable intermediate. Accordingly, bromination of thiophene yields 2-bromothiophene and 2,5-dibromothiophene as the major products.[8–10] Thus, the regioselective bromination of 2-ethylaminothiophene at the 5-position was expected since the 2-position is already occupied.

The regioselectivity of the reaction was confirmed by X-ray crystallography. Crystals of DDE 935 (*N*-[2-(5-bromo-2-thienyl)ethyl]-*N*′-[2-(pyridyl)]thiourea) were grown from dichloromethane by slow evaporation at room temperature. A crystal was mounted on a glass fiber using epoxy and X-ray diffraction data for a 0.25×0.25×0.02 mm crystal were collected at room temperature using a SMART 1K CCD X-ray detector (Bruker Analytical X-ray Systems, Madison, WI). Structure solution and refinement was performed using the SHELXTL suite of programs.[11] X-Ray crystal structure data and refinement statistics for DDE 935 are listed in Table 2. The refined small molecule X-ray crystal structure of DDE 935 is shown in Fig. 1 and atomic coordinates are listed in Table 3. All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were placed at ideal positions and refined as riding atoms with relative isotropic displacement parameters except for H1 and H3 (Fig. 1), which were located in the electron density difference map and refined isotropically. The crystal structure clearly indicated the presence of a bromine atom on the C5 carbon of the thiophene ring. No evidence for a bromine atom on the C3 or C4 carbons of the thiophene ring was observed in the crystal structure.

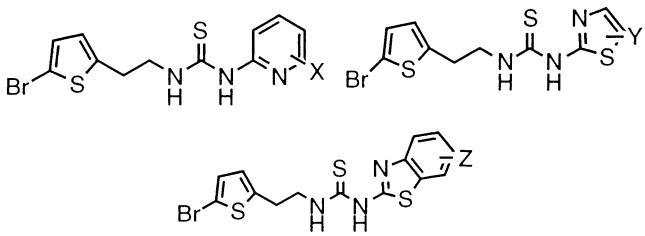
Of the eleven 5-bromothiophenethyl thioureas studied, six exhibited significant anti-HIV activity (nanomolar to micromolar IC_{50} values against recombinant reverse transcriptase; Table 1). Two of the compounds were

Table 2. X-Ray crystal structure data and refinement statistics for DDE935. Data collected at room temperature ($\lambda = 0.71073$ Å), refined using full-matrix least-squares refinement on F^2, and corrected for absorption using multiscan data (see text)

Unit cell	
a (Å)	8.3549(4)
b (Å)	8.7416(4)
c (Å)	10.9337(5)
α (°)	78.7300(10)
β (°)	86.0410(10)
γ (°)	61.9620(10)
Space group	$P\bar{1}$
Unit cell volume (Å^3)	690.99(6)
Z	2
θ Range for data collection (°)	1.90–28.27
Limiting indices (°)	$-11 \le h \le 10$
	$-11 \le k \le 11$
	$-14 \le l \le 13$
Reflections collected	8240
Independent reflections	3209 ($R_{int} = 0.031$)
Data/restraints/parameters	3209/0/171
Goodness-of-fit on F^2	1.046
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.038$, $wR_2 = 0.10$
R indices (all data)	$R_1 = 0.052$, $wR_2 = 0.11$
Absorption coefficient (mm^{-1})	3.261
Max. and min. transmission	0.9376, 0.4961
Largest difference peaks (e Å^{-3})	1.01, −0.53

$R_{int} = \Sigma|F_o^2 - \langle F_o^2 \rangle| / \Sigma|F_o^2|$, $R_1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$.
$wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$.
GooF $= S = \{\Sigma[w(F_o^2 - F_c^2)^2] / (n-p)\}^{1/2}$, where n = reflections and p = parameters.

Table 1. Anti-HIV activity of nine 5-bromothiophenethyl thioureas



Compound no.	X	Y	Z	IC_{50} rRT (μM)	IC_{50} $HTLV_{IIIB}$ (μM)
DDE 933	5-Me	NA	NA	0.60	0.16
DDE 934	Cl	NA	NA	0.10	0.012
DDE 935	H	NA	NA	1.24	0.015
DDE 946	Br	NA	NA	0.92	0.05
DDE 949	6-Me	NA	NA	12.5	0.24
DDE 950	4,6-Me	NA	NA	>100	ND
DDE 951	NA	H	NA	10.0	0.31
DDE 954	NA	NA	H	>100	ND
DDE 1009	NA	Me	NA	4.3	ND
Delavirdine	NA	NA	NA	NA	0.01
Nevirapine	NA	NA	NA	NA	0.04

NA, not applicable; ND, not determined.

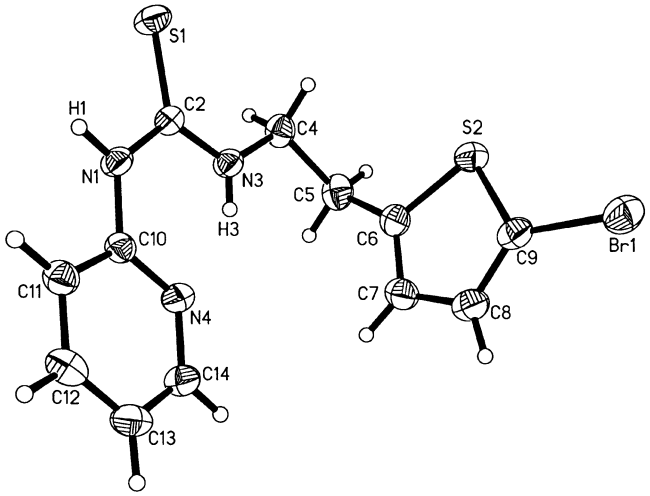


Figure 1. X-Ray crystal structure of DDE 935, which clearly shows the bromine atom present at the C5-position of the thiophene ring (30% ellipsoids, room temperature data).

Table 3. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å} \times 10^3$) for DDE 935 based on the X-ray crystal structure at room temperature. U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor

Atom	x	Y	z	U(eq)
Br1	440(1)	1514(1)	1039(1)	64(1)
S1	2057(1)	9142(1)	−3614(1)	54(1)
S2	2882(1)	3268(1)	41(1)	52(1)
C10	1839(4)	5780(4)	−5527(2)	40(1)
N3	3594(3)	5663(3)	−3304(2)	43(1)
C12	800(4)	4731(5)	−6969(3)	56(1)
N4	2963(3)	4143(3)	−4963(2)	46(1)
N1	1752(3)	7193(3)	−5058(2)	44(1)
C2	2520(4)	7198(3)	−3993(2)	39(1)
C14	2994(5)	2804(4)	−5413(3)	54(1)
C6	4319(4)	2693(4)	−1193(3)	48(1)
C4	4534(4)	5457(4)	−2171(3)	48(1)
C5	5524(4)	3511(4)	−1583(3)	55(1)
C13	1941(5)	3029(5)	−6389(3)	57(1)
C8	2864(5)	949(4)	−1056(3)	56(1)
C9	2077(4)	1832(4)	−114(3)	49(1)
C7	4133(5)	1467(4)	−1670(3)	56(1)
C11	745(4)	6128(4)	−6546(3)	49(1)
H1	970(50)	8240(50)	−5430(30)	60(10)
H3	3760(40)	4840(40)	−3580(30)	40(8)
H12	70	4928	−7647	67
H14	3783	1658	−5033	65
H4A	3670	6114	−1592	58
H4B	5396	5915	−2362	58
H5A	6376	2875	−2175	67
H5B	6218	3377	−858	67
H13	1985	2065	−6659	68
H8	2606	110	−1274	67
H7	4785	1001	−2347	68
H11	−7	7282	−6934	59

inactive. Six of the 5-bromothiophenethyl thioureas inhibit replication of the HIV-1 strain $HTLV_{IIIB}$ in the 12–300 nM range in human peripheral blood mononuclear cells (PBMC). Among the derivatives examined, DDE 934 was the most potent anti-HIV agent. In addition, DDE934 was three times more potent than Nevirapine (Table 1).

In summary, 5-bromothiophenethyl thioureas were synthesized from the commercially available 2-thiophenethylamine in four simple steps with an overall yield of 50%. Regioselective bromination at the 5-position of the thiophene ring was accomplished using acetic acid and bromine at low temperatures and was verified by X-ray crystallography. The intermediate 5-bromothiophenethylamine hydrobromide may be a useful building block in the preparation of a variety of biologically active compounds. The presence of a halogen atom may also facilitate the synthesis of thiophenethyl thioureas substituted with other functional groups.

Physical constants:

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(5-methylpyridyl)]-thiourea (DDE 933)**. Mp 159–160°C; ^{1}H NMR (DMSO-d_6) δ 11.70 (t, 1H), 10.53 (s, 1H), 7.90 (s, 1H), 7.57 (d, 1H, J=8.1 Hz), 7.06 (s, 1H), 7.03 (s, 1H), 6.79 (d, 1H, J=3.0 Hz), 3.82 (q, 2H), 3.10 (t, 2H), 2.18 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.4, 151.7, 144.6, 143.7, 139.7, 130.2, 126.8, 126.7, 112.2, 108.8, 45.9, 29.1, 17.5; IR ν 3563, 3220, 3035, 2935, 1608, 1565, 1535, 1488, 1330, 1188 cm^{-1}; MALDI-TOF m/z 357.5 ($C_{13}H_{14}BrN_3S_2$+2H$^+$); HPLC R_t: 12.42 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(5-chloropyridyl)]-thiourea (DDE 934)**. Mp 115–116°C; ^{1}H NMR (DMSO-d_6) δ 11.29 (t, 1H), 10.77 (s, 1H), 8.11 (t, 1H), 7.85 (dd, 1H, J=3.0, 9.3 Hz), 7.17 (d, 2H, J=8.7 Hz), 7.07 (d, 1H, J=3.6 Hz), 6.80 (d, 1H, J=3.0 Hz), 3.81 (q, 2H), 3.11 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.3, 152.0, 143.5, 138.9, 130.2, 126.7, 123.8, 114.1, 108.8, 46.0, 28.9; IR ν 3490, 3212, 3039, 2923, 1592, 1554, 1531, 1473, 1226 cm^{-1}; MALDI-TOF m/z 378.3 ($C_{12}H_{11}BrClN_3S_2$+2H$^+$); HPLC R_t: 14.04 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(pyridyl)]thiourea (DDE 935)**. Mp 156–157°C; ^{1}H NMR (DMSO-d_6) δ 11.78 (s, 1H), 10.61 (s, 1H), 8.08 (d, 1H, J=3.0 Hz), 7.74 (t, 1H), 7.13 (d, 1H, J=8.4 Hz), 7.06 (t, 1H), 7.01 (t, 1H), 6.81 (d, 1H, J=3.0 Hz), 3.83 (q, 2H), 3.12 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.6, 153.6, 145.3, 143.7, 138.9, 130.2, 126.7, 117.9, 112.6, 108.8, 45.9, 29.1; IR ν 3452, 3220, 3050, 2931, 1600, 1562, 1535, 1477, 1199, 775 cm^{-1}; MALDI-TOF m/z 343.8 ($C_{12}H_{12}BrN_3S_2$+3H$^+$); HPLC R_t: 9.29 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(5-bromopyridyl)]-thiourea (DDE 946)**. Mp 163–164°C; ^{1}H NMR (DMSO-d_6) δ 11.29 (t, 1H), 10.73 (s, 1H), 8.17 (d, 1H, J=2.4 Hz), 7.93 (dd, 1H, J=3.0, 9.0 Hz), 7.10 (d, 1H, J=9.0 Hz), 7.04 (d, 1H, J=3.9 Hz), 6.79 (d, 1H, J=3.6 Hz), 3.81 (q, 2H), 3.10 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.4, 152.4, 145.9, 143.7, 141.6, 130.3, 126.9, 114.7,

112.2, 108.9, 46.2, 29.0; IR ν 3506, 3212, 3037, 2925, 1591, 1552, 1529, 1473, 1227, 796 cm^{-1}; MALDI-TOF m/z 423.3 ($C_{12}H_{11}Br_2N_3S_2$+2H$^+$); HPLC R_t: 15.18 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(6-methylpyridyl)]-thiourea (DDE 949)**. Mp 125–126°C; ^{1}H NMR (DMSO-d_6) δ 11.92 (t, 1H), 10.54 (s, 1H), 7.61 (t, 1H), 7.03 (d, 1H, J=3.6 Hz), 6.93 (d, 1H, J=8.4 Hz), 6.84 (d, 1H, J=7.8 Hz), 6.78 (d, 1H, J=3.6 Hz), 3.90 (q, 2H), 3.11 (t, 2H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.6, 154.4, 153.2, 143.9, 139.1, 130.2, 126.5, 116.9, 109.4, 108.8, 45.5, 29.2, 23.5; IR ν 3442, 3047, 2919, 1610, 1560, 1452, 1226, 1157, 783 cm^{-1}; MALDI-TOF m/z 357.0 ($C_{13}H_{14}BrN_3S_2$+2H$^+$); HPLC R_t: 12.41 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(4,6-dimethylpyridyl)]thiourea (DDE 950)**. Mp 167–168°C; ^{1}H NMR (DMSO-d_6) δ 11.99 (d, 1H, J=5.1 Hz), 10.45 (d, 1H, J=4.8 Hz), 7.03 (q, 1H), 6.77 (t, 1H), 6.81 (dd, 2H, J=3.6, 14.7 Hz), 3.88 (m, 2H), 3.09 (q, 2H), 2.19 (t, 6H); ^{13}C NMR (DMSO-d_6) δ 179.7, 153.9, 153.3, 149.8, 143.9, 130.2, 126.5, 118.2, 109.4, 108.7, 45.5, 29.2, 23.3, 20.9; IR ν 3444, 3052, 2917, 1616, 1540, 1446, 1213, 833 cm^{-1}; MALDI-TOF m/z 372.1 ($C_{14}H_{16}BrN_3S_2$+3H$^+$); HPLC R_t: 18.77 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(thiazolyl)]thiourea (DDE 951)**. Mp 146–147°C; ^{1}H NMR (DMSO-d_6) δ 11.66 (s, 1H), 9.64 (s, 1H), 7.34 (t, 1H), 7.08 (s, 1H), 7.04 (t, 1H), 6.77 (s, 1H), 3.75 (d, 2H), 3.07 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.3, 161.9, 143.4, 136.5, 130.2, 126.6, 112.1, 108.8, 45.4. 28.9; IR ν 3484, 3079, 2993, 1560, 1513, 1235, 1178 cm^{-1}; MALDI-TOF m/z 350.3 ($C_{10}H_{10}BrN_3S_3$+2H$^+$); HPLC R_t: 7.98 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(benzothiazolyl)]-thiourea (DDE 954)**. Mp 179–180°C; ^{1}H NMR (DMSO-d_6) δ 1.93 (s, 1H), 10.21 (s, 1H), 7.88 (d, 1H, J=7.2 Hz), 7.57 (br s, 1H), 7.39 (t, 1H), 7.25 (t, 1H), 7.06 (d, 1H, J=3.6 Hz), 6.83 (s, 1H), 3.12 (t, 2H), 2.48 (d, 2H, J=2.1 Hz); ^{13}C NMR (DMSO-d_6) δ 178.8, 161.1, 148.7, 143.4, 130.2, 126.7, 126.3, 123.7, 121.9, 119.7, 112.8, 112.0, 108.9, 45.7, 28.8; IR ν 3463, 3029, 1569, 1527, 1207, 754 cm^{-1}; MALDI-TOF m/z 400.0 ($C_{14}H_{12}BrN_3S_3$+3H$^+$); HPLC R_t: 16.04 min.

***N*-[2-(5-Bromo-2-thienyl)ethyl]-*N*′-[2-(4-methylthiazolyl)]thiourea (DDE 1009)**. Mp 151–152°C; ^{1}H NMR (DMSO-d_6) δ 11.60 (s, 1H), 9.90 (s, 1H), 7.05 (d, 1H, J=3.9 Hz), 6.79 (d. 1H, J=3.6 Hz), 6.62 (s, 1H), 3.78 (q, 2H), 3.07 (t, 2H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 178.4, 161.4, 143.5, 130.2, 126.6, 108.8, 106.1, 45.5, 28.9, 16.7; IR ν 3455, 3174, 3016, 1585, 1562, 1531, 1506, 1270, 1211 cm^{-1}; MALDI-TOF m/z 364.1 ($C_{11}H_{12}BrN_3S_3$+2H$^+$); HPLC R_t: 4.03 min.

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