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Synthesis of β-Fluorophenethyl Halopyridyl Thiourea Compounds as Non-nucleoside Inhibitors of HIV-1 Reverse Transcriptase

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Synthesis of β-Fluorophenethyl Halopyridyl Thiourea Compounds as Non-nucleoside Inhibitors of HIV-1 Reverse Transcriptase

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ABSTRACT

Synthesis of β-fluorophenethylamines was accomplished in three steps with an overall yield of 50%. Condensation of β-fluorophenethylamine hydrochloride with thiocarbonylimidazole derivative derived from halopyridyl amines in dimethylformamide furnished the desired thiourea compounds as crystalline solids. Several of the β-fluorophenethyl thiourea compounds inhibited HIV-1 reverse transcriptase (RT) at nanomolar to low micromolar concentrations.

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Key Words: β-Fluorophenethylamines; Thiourea; HIV-1; Reverse transcriptase.

INTRODUCTION

Several thiourea compounds has been found to inhibit HIV reverse transcriptase (RT).[1–6] In a systematic search for non-nucleoside inhibitors of HIV RT, we prepared 30 β-fluorophenethyl halopyridyl thiourea compounds.

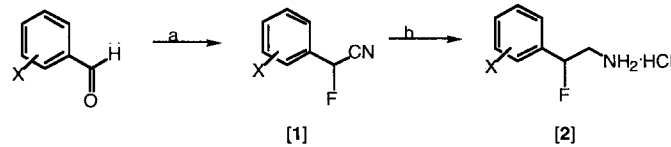
MATERIALS AND METHODS

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 nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were obtained on a 300 MHz Varian Mercury 300 instrument at ambient temperature in either $CDCl_3$ or DMSO-d_6. Chemical shifts are reported as δ values in parts per million downfield from tetramethylsilane ($\delta = 0.0$ ppm) as an internal standard in the case of $CDCl_3$ or from the residual dimethylsufloxide signal ($\delta = 2.49$ ppm for ^{1}H NMR or $\delta = 39.7$ ppm for ^{13}C NMR). ^{19}F NMR spectra were obtained using either of the above solvents and a capillary containing 0.1% trifluoroacetic acid in water which served as internal standard. Chemical shifts for fluorine NMR are based on the trifluoroacetic acid signal referenced at 0.0 ppm. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FT–IR spectra were recorded on a Nicolet Protege 460 spectrometer (KBr pellet). Mass spectra were performed on a Hewlett–Packard MALDI-TOF spectrometer (Model G2025A LD-TOF). Melting points were determined using a Melt John's apparatus and are uncorrected. HPLC was done using a Hewlett–Packard 1100 series instrument consisting of an automatic sampler, an electronic degasser, a thermostatic control unit, and a diode array detector in conjunction with Chemstation software. The column used was an analytical RP-18 Lichrospher column, 5u (4.6×150 mm) and the eluent was 35 : 65, H_2O (0.1% ACOH) : acetonitrile. 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 varied depending on the

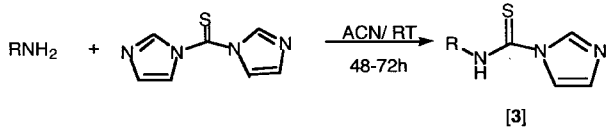
compound and included either one or a combination of the following: ethylacetate, methanol, chloroform, hexane, methylene chloride, tetrahydrofuran (THF), and ether.

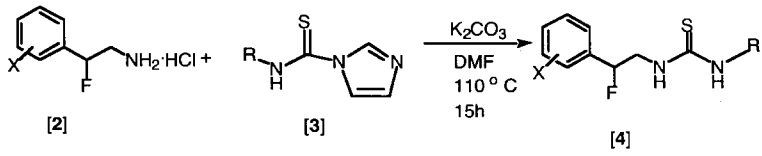
RESULTS AND DISCUSSION

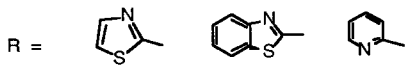
The thiourea compounds were prepared by condensing β-fluorophenethylamines and thiocarbonylimidazole derivatives of 5- or 6-substituted amino pyridines in anhydrous dimethylformamide (Sch. 1). Substituted β-fluorophenethylamines were synthesized using the procedure described here. The amines were used as hydrochloride salt. Thiazolyl- and benzothiazolyl-substituted thioureas were prepared in a similar fashion using thiocarbaimidazole derivatives derived from either substituted amino thiazoles or benzothiazoles, respectively.



Reagents: a) 1. ZnI_2, TMSCN, neat, 0 °C, 2. DAST, CH_2Cl_2, 0 °C; b) THF, 1.0 M BH_3THF, 0 °C







X = H, 3-F, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br

Scheme 1. Synthetic scheme.

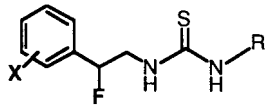
General Example for the Preparation of 2-Fluoro-Substituted Phenethylamines

Preparation of 2-fluoro-2-arylacetonitrile (1). Anhydrous ZnI_2 (40 mg) was placed in a 250 mL three-necked round-bottomed flask fitted with a 60 mL addition funnel under nitrogen atmosphere. Using a syringe, an aryl aldehyde (0.080 mol) was added and the contents were stirred at room temperature. In the case of solid aryl aldehydes, 5–10 mL of anhydrous methylene chloride was used to form a homogenous mixture. The mixture was cooled to 0°C using an ice bath and trimethylsilylcyanide (10.67 mL, 0.080 mol) was added to the vigorously stirred reaction mixture. After addition, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 18 hr. After the reaction, CH_2Cl_2 (100 mL) was added and the mixture cooled to 0°C. In the meantime, the additional funnel was charged with a solution of diethylamino sulfurtrifluoride (11.63 mL, 0.088 mol) in CH_2Cl_2 (40 mL). This solution was added dropwise to the stirring mixture. Upon completion of addition, the ice bath was removed and the reaction was allowed to warm to room temperature overnight, poured into ice water (500 mL), and the organic layer was separated from the aqueous layer. The organic layer was sequentially washed with water (250 mL), 0.5 N HCl (250 mL), water (250 mL), sat. $NaHCO_3$ (250 mL), and water (250 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotary evaporator to yield a viscous liquid. This product was further purified by column chromatography, using solvent mixture consisting of 7% ethylacetate and 93% hexane as eluent.

Preparation of 2-fluoro-2-arylethylamine hydrochloride (2). A round-bottomed flask was charged with one-equivalent of 2-fluoro-2-arylacetonitrile and anhydrous THF (50 mL) and cooled to 0°C. Using a dry syringe, two equivalents of 1.0 M borane–THF solution was added and the reaction was allowed to stir overnight. The reaction was quenched using ethanol and acidified with ethanolic HCl. Rotary evaporation of the solvent under vacuum furnished the required hydrochloride.

Preparation of β-fluorophenethyl thioureas (4). Based on previously published synthetic procedures[1,4,5] the synthesis of the thiourea compounds (Table 1) was accomplished as shown in the scheme using one equivalent of both the thiocabonylimidazole derivatives (**3**) derived from the respective amino heterocyles and β-fluorophenylethylamine hydrochloride salt in DMF. Anhydrous potassium carbonate (30–40 mg) was added to the mixture. The contents was sitrred and heated to 100°C over an oil bath for 15–20 hr. The solution was cooled and poured into ice water. The precipitated product was filtered, washed with water, and dried. The product was then redissolved in chloroform, transferred into a separatory funnel, and washed thoroughly

Table 1. Chemical properties of β-fluorophenylethyl thiourea derivatives.



Compound no.	X	R	Mp (°C)
565	H	5-Bromopyridyl	185–186
566	H	5-Chloropyridyl	183–184
1,054	3-F	4-Methylbenzothiazolyl	198–199
1,063	3-F	5-Methylpyridyl	142–144
1,072	3-F	Pyridyl	158–160
1,089	3-F	6-Chlorobenzothiazolyl	195–196
1,090	3-F	6-Methoxybenzothiazolyl	188–189
1,091	3-F	4-Methyleneethoxythiazolyl	126–128
1,092	3-F	Thiazolyl	159–160
1,093	3-F	6-Flurobenzothiazolyl	175–177
1,096	3-F	4,6-Dimethylpyridyl	156–157
1,122	4-Br	5-Bromopyridyl	148–150
1,123	4-Br	4-Methylenethoxythiazolyl	111–112
1,125	4-Br	Thiazolyl	137–138
1,126	4-Br	5,6-Dimethylbenzothiazolyl	172–173
1,127	4-Br	Pyridyl	149–150
1,128	H	3,4-Dimebenzothiazolyl	150–151
1,129	4-Br	6-Methoxybenzothiazolyl	165–166
1,174	2-Br	6-Methylpyridyl	171–172
1,175	3-F	5-Methylpyridyl	189–190
1,176	4-Cl	Benzothiazolyl	159–160
1,177	4-Cl	5-Methylpyridyl	185–186
1,178	2-Cl	Thiazolyl	144–145
1,179	3-Cl	Thiazolyl	141–142
1,180	3-Cl	5-Bromopyridyl	170–171
1,181	2-Cl	4-Methylbenzothiazolyl	191–192
1,182	3-Cl	5-Methylpyridyl	119–120
1,184	4-Br	5-Chloropyridyl	168–169
1,185	3-Cl	5-Chloropyridyl	143–145
1,188	H	Pyridyl	136–137

with brine and water. The organic layer was separated and dried over anhydrous $MgSO_4$. Filtration and rotary evaporation of the solvent under vacuum furnished a residue which was column chromatographed using slica gel and solvent mixture consisting of 20% THF and 80% hexane as eluent. The compounds were finally recrystallized from ethanol to give thioureas as cyrstalline solids. The purity of the compounds was determined using various analytical techniques.

Physical Constants of Selected Thiourea Derivatives

DDE 565. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 185–186°C, ^{1}H NMR ($CDCl_3$): 11.63 (bs, 1H), 8.76 (bs, 1H), 8.24–8.23 (m, 1H), 7.76–7.46 (m, 1H), 7.44–7.40 (m, 5H), 6.73–6.70 (m, 1H), 5.94–5.91 (m, 1/2H), 5.78–5.74 (m, 1/2H), 4.57–4.40 (m, 1H), 3.98–3.84 (m, 1H), ^{13}C NMR ($CDCl_3$): 179.9, 151.3, 146.7, 141.3, 137.1, 136.9, 128.8, 128.7, 128.5, 125.4, 125.3, 113.2, 113.1, 93.2, 90.9, 51.6, 51.3; IR ν: 3219, 3161, 3087, 3030, 2924, 1602, 1560, 1533, 1479, 1458, 1340, 1307, 1232, 1178, 1137, 1111, 1012, 916, 855, 868, 825, 758, 700 cm^{-1}; MALDI-TOF m/z: 356 (M + 2); Anal. calcd. for: $C_{14}H_{13}N_3SFBr$: C, 47.46; H, 3.67; N, 11.86. Found: C, 47.75; H, 3.66; N, 11.50.

DDE 566. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 183–184°C, ^{1}H NMR ($CDCl_3$): 11.63 (bs, 1H), 8.76 (bs, 1H), 8.24–8.23 (m, 1H), 7.76–7.46 (m, 1H), 7.44–7.40 (m, 5H), 6.73–6.70 (m, 1H), 5.94–5.91 (m, 1/2H), 5.78–5.74 (m, 1/2H), 4.57–4.39 (m, 1H), 3.98–3.84 (m, 1H); ^{13}C NMR ($CDCl_3$): 179.9, 151.5, 146.6, 141.3, 137.1, 136.9, 128.7, 128.5, 125.4, 125.3, 113.5, 113.0, 93.1, 90.8, 51.5, 51.1; IR ν: 3224, 3157, 3024, 2925, 2858, 2742, 1822, 1595, 1537, 1477, 1340, 1306, 1197, 1178, 1140, 1093, 1070, 1014, 918, 885, 823, 758, 700 cm^{-1}; UV (MeOH): 251, 267 nm, MALDI-TOF m/z: 311.8 (M + 2) Anal. calcd. for: $C_{14}H_{13}N_3SFCl$: C, 54.19; H, 4.19; N, 13.54. Found: C, 49.97; H, 4.58; N, 21.15.

DDE 1063. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 142–144°C; ^{1}H NMR (DMSO-d_6) δ 11.89 (t, 1H), 10.67 (s, 1H), 7.94 (s, 1H), 7.57 (dd, 1H, J = 2.1, 8.7 Hz), 7.47 (q, 1H), 7.28 (d, 1H, J = 8.4 Hz), 7.21 (t, 1H), 7.06 (d, 1H, J = 8.4 Hz), 5.99 (dd, 1/2H, J = 3.3, 7.2 Hz), 5.83 (dd, 1/2H, J = 3.0, 6.6 Hz), 4.21 (m, 1H), 7.03 (m, 1H), 2.18 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 180.1, 163.7, 160.5, 151.7, 144.7, 140.3, 140.1 (d), 139.8 (d), 130.7 (d), 127.1, 121.8 (t), 115.6 (d), 112.6 (m), 92.4, 90.1, 50.0, 49.7, 17.4; IR ν: 3222, 3174, 3020, 2935, 1592, 1556, 1492, 1446, 1342, 1234, 11914, 1029 cm^{-1}; MALDI-TOF m/z: 309.5 ($C_{15}H_{15}F_2N_3S + 2H^+$); HPLC R_t: 7.66 min. Single peak in HPLC (AUC) purity 99.5%. Anal. calcd. for: $C_{15}H_{15}N_3SF_2$: C, 58.62; H, 4.92; N, 13.67. Found: C, 58.73; H, 4.93; N, 13.61.

DDE 1072. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 158–160°C; ^{1}H NMR (DMSO-d_6) δ 11.96 (t, 1H), 10.76 (s, 1H), 8.11 (d, 1H, J = 5.1 Hz), 7.75 (m, 1H), 7.47 (q, 1H), 7.29 (d, 2H, J = 8.4 Hz), 7.22 (d, 1H, J = 9.0 Hz), 7.16 (d, 1H, J = 8.7 Hz), 7.01 (m, 1H), 6.01 (d, 1/2H, J = 5.7 Hz), 5.85 (d, 1/2H, J = 5.4 Hz), 4.26 (m, 1H), 4.03 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 180.3, 163.7, 160.5, 153.6, 145.4, 140.0 (q), 139.1, 130.8 (d), 121.8 (q), 118.1, 115.6 (d), 112.6 (q), 92.3, 90.0, 50.0 (d); ^{19}F NMR (DMSO-d_6) δ −36.5 (t), −105.9 (m); IR ν: 3455, 3239, 3110, 2987, 1604, 1560, 1537, 1481, 1269, 1186, 784 cm^{-1}; MALDI-TOF m/z 292.3

($C_{14}H_{13}F_2N_3S - H^+$); HPLC R_t: 6.01 min. Single peak in HPLC (AUC) purity 98.4%. Anal. calcd. for $C_{14}H_{13}N_3SF_2$: C, 57.33; H, 4.47; N, 14.33. Found: C, 57.43; H, 4.44; N, 14.32.

DDE 1092. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 159–160°C; ^{1}H NMR (DMSO-d_6) δ 11.79 (s, 1H), 9.94 (s, 1H), 7.47 (q, 1H), 7.38 (d, 1H, $J = 3.6$ Hz), 7.27 (d, 2H, $J = 7.8$ Hz), 7.21 (t, 1H), 7.10 (d, 1H, $J = 3.0$ Hz), 5.96 (dd, 1/2H, $J = 2.7$, 7.5 Hz), 5.79 (dd, 1/2H, $J = 3.0$, 7.5 Hz), 4.24–3.91 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 178.9, 163.7, 161.9, 160.5, 139.9 (dd), 136.4, 130.8 (d), 121.9 (dd), 115.6 (d), 112.7 (dd), 112.3, 92.4, 90.1, 49.5; IR ν: 3417, 3185, 3041, 2935, 1583, 1513, 1450, 1346, 1276, 1184, 1141, 1033, 688 cm^{-1}; HPLC R_t: 5.20 min. Single peak in HPLC (AUC) purity 99.2%. Anal. calcd. for $C_{12}H_{11}N_3S_2F_2$: C, 48.15; H, 3.70; N, 14.04. Found: C, 48.35; H, 3.81; N, 13.89.

DDE 1093. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 175–177°C; ^{1}H NMR (DMSO-d_6) δ 12.01 (s, 1H), 9.95 (s, 1H), 7.80 (d, 1H, $J = 9.0$ Hz), 7.57 (q, 2H), 7.47 (q, 1H), 7.29 (d, 2H, $J = 8.1$ Hz), 7.22 (d, 1H, $J = 8.7$ Hz), 5.99 (d, 1/2H, $J = 4.2$ Hz), 5.83 (d, 1/2H, $J = 4.2$ Hz), 4.09 (m, 2H); ^{13}C NMR (DMSO-d_6) δ; IR ν: 471, 3178, 3043, 2939, 1560, 1537, 1454, 1270, 1201, 1139, 865 cm^{-1}; HPLC R_t: 10.52 min. Main peak in HPLC (AUC) purity 90.1%, isomer shoulder peak (AUC) 8.0% Anal. calcd. for $C_{16}H_{12}N_3S_2F_3$: C, 52.31; H, 3.29; N, 11.44. Found: C, 52.69; H, 3.28; N, 11.42.

DDE 1122. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 148–150°C; ^{1}H NMR (DMSO-d_6) δ 11.44 (t, 1H), 10.89 (s, 1H), 8.23 (t, 1H), 7.97 (m, 1H), 7.62 (d, 2H, $J = 7.5$ Hz), 7.39 (d, 2H, $J = 8.1$ Hz), 7.13 (dd, 1H, $J = 0.9$, 9.0 Hz), 5.97 (dd, 1/2H, $J = 2.7$, 7.25 Hz), 5.81 (dd, 1/2H, $J = 2.4$, 7.2 Hz), 4.20 (m, 1H), 4.03 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 179.9, 152.2, 145.9, 141.6, 136.6 (d), 131.6, 127.8 m(d), 122.0, 114.7, 112.36, 92.4, 90.1, 50.1, 49.8; ^{19}F NMR (DMSO-d_6) δ -105.6 (7); IR ν: 3448, 3224, 3022, 2925, 1592, 1564, 1529, 1340, 1305, 1180 cm^{-1}; MALDI-TOF m/z 457.6 ($C_{14}H_{12}Br_2FN_3S + Na + H^+$); HPLC R_t: 14.37 min. Main peak in HPLC (AUC) purity 86.8%, isomer peak (AUC) 12.8%. Anal. calcd. for $C_{14}H_{12}N_3SFBr_2$: C, 38.82; H, 2.79; N, 9.70. Found: C, 38.21; H, 2.69; N, 10.23.

DDE 1127. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 149–150°C; ^{1}H NMR (DMSO-d_6) δ 11.95 (t, 1H), 10.76 (s, 1H), 8.13 (d, 1H, $J = 5.1$ Hz), 7.76 (m, 1H), 7.63 (d, 2H, $J = 8.4$ Hz), 7.41 (d, 2H, $J = 8.4$ Hz), 7.15 (d, 1H, $J = 8.1$ Hz), 7.03 (q, 1H), 5.98 (dd, 1/2H, $J = 3.0$, 6.9 Hz), 5.82 (dd, 1/2H, $J = 3.0$, 6.9 Hz), 4.22 (m, 1H), 4.02 (m, 1H); ^{13}CNMR (DMSO-d_6) δ 180.2, 153.6, 145.4, 139.1, 136.7 (d), 131.6, 127.9 (d), 122.0, 118.1, 112.7, 92.5, 90.2, 49.9 (d); ^{19}F NMR (DMSO-d_6) δ −105.4 (7); IR ν: 3423, 3234, 3010, 2929, 1604, 1538, 1479, 1319, 1180, 1031, 773 cm^{-1}; MALDI-TOF m/z 397.3 ($C_{14}H_{13}BrFN_3S + K + Na - H^+$); HPLC

R_t: 8.54 min. Single peak in HPLC (AUC) purity 98.8%. Anal. calcd. for $C_{14}H_{13}N_3SFBr$: C, 47.47; H, 3.70; N, 11.86. Found: C, 47.57; H, 3.77; N, 11.73.

DDE 1174. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 171–172°C; ^{1}H NMR(DMSO-d_6) δ 12.29 (m, 1H), 10.67 (s, 1H), 7.71 (m, 1H), 7.64–7.63 (m, 1H), 7.61–7.56 (m, 1H), 7.45 (t, 1H), 7.32 (t, 1H), 7.02–6.99 (d, 1H, $J = 9.0$ Hz), 6.95–6.87 (m, 1H), 6.10–6.07 (m, 1/2H), 5.94–5.91 (m, 1/2H), 4.34–4.08(m, 2H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 180.3, 176.7, 154.3, 153.2, 139.4, 136.1, 135.8, 132.9, 131.0, 128.2, 127.9, 127.8, 121.3, 117.2, 109.5, 92.2, 89.9, 48.2, 47.9, 23.8, 23.7; IR ν: 3227, 3198, 3048, 3029, 1613, 1595, 1561, 1538, 1471, 1449, 1380, 1334, 1311, 1227, 1198, 1162, 1153, 785, 755 cm^{-1}; UV (MeOH): 204, 248, 266, 301 nm; HPLC R_t: 9.32 min. Main peak in HPLC (AUC) purity 97.0%, isomer peak HPLC (AUC) purity 1.7%. Anal. calcd. for $C_{14}H_{12}N_3SFBr_2$: C, 48.92; H, 4.11; N, 11.41. Found: C, 53.79; H, 4.54; N, 11.50.

DDE 1177. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 185–186°C; ^{1}H NMR (DMSO-d_6) δ 11.88 (bs, 1H), 10.66 (bs, 1H), 7.95–7.94 (d, 1H, $J = 3.0$ Hz), 7.61–7.58 (dd, 1H, $J = 8.0$, 9.0 Hz), 7.57–7.47 (m, 4H), 7.08–7.05 (d, 1H, $J = 9.0$ Hz), 5.99–5.96 (m, 1/2H), 5.83–5.80 (m, 1/2H), 4.28–3.93 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 180.0, 151.7, 144.7, 139.9, 136.4, 136.2, 133.4, 128.7, 127.7, 127.6, 127.1, 112.3, 92.5, 90.2, 50.0, 49.7, 17.5; IR ν: 3229, 3176, 3019, 2939, 1611, 1596, 1550, 1533, 1341, 1309, 1255, 1235, 1186, 1178, 1092, 1029, 1014, 824 cm^{-1}; UV (MeOH): 203, 207, 247, 270 nm; HPLC R_t: 9.38 min. Single peak in HPLC (AUC) purity 97.8% Anal. calcd. for $C_{15}H_{15}N_3SFCl$: C, 55.64; H, 4.67; N, 12.98. Found: C, 55.77; H, 4.75; N, 12.92.

DDE 1180. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 170–171°C, ^{1}H NMR (DMSO-d_6) δ 11.44 (m, 1H), 10.88 (m, 1H) 8.23–8.19 (m, 1H), 7.98–7.91 (m, 2H), 7.48–7.39 (m, 3H), 7.15–7.10 (m, 1H), 6.01–5.98 (m, 1/2H), 5.85–5.82 (m, 1/2H), 4.27–3.98 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 180.1, 152.3, 145.9, 141.6, 139.9, 139.6, 133.0, 130.7, 128.8, 125.7, 125.6, 124.4, 124.3, 114.8, 112.4, 92.3, 89.9, 50.3, 49.9; IR ν: 3236, 3156, 3086, 3037, 2943, 1592, 1498, 1476, 1469, 1431, 1389, 1311, 1227, 1183, 1030, 827, 709 cm^{-1}; UV (MeOH): 205, 255, 276, 306 nm; MALDI-TOF m/z: 389.1 (M + 1); HPLC R_t: 11.6 min. Single peak in HPLC (AUC) purity 97.5% Anal. calcd. for $C_{14}H_{12}N_3SFBr$ Cl: C, 43.26; H, 3.11; N, 10.81. Found: C, 42.88; H, 3.07; N, 10.89.

DDE 1182. Column chromatography (hexane/THF, 80 : 20), Xst EtOH; mp. 119–120°C; ^{1}H NMR (DMSO-d_6) δ 11.88 (m, 1H), 10.65 (bs, 1H), 7.94 (s, 1H), 7.60–7.59 (d, 1H, $J = 3.0$ Hz), 7.49 (s, 1H), 7.45–7.42 (m, 3H), 7.07–7.04 (d, 1H, $J = 9.0$ Hz), 6.02–5.97 (m, 1/2H), 5.84–5.81 (m, 1/2H), 4.30–3.95 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 180.1, 151.7, 144.8, 139.7, 139.5, 133.4, 130.7, 128.8, 127.3, 125.7, 125.6, 124.5, 124.4,

112.4, 92.4, 90.2, 50.2, 49.9, 17.5; IR ν: 3424, 3287, 3172, 3099, 3033, 3013, 2966, 2933, 1613, 1592, 1563, 1534, 1491, 1431, 1345, 1314, 1238, 1223, 1185, 1028, 833, 776, 689, 678 cm^{-1}; UV (MeOH): 209, 246, 270, 299 nm; MALDI-TOF m/z: 325.9 (M + 2); HPLC R_t: 9.17 min. Single peak in HPLC (AUC) purity 98.0%. Anal. calcd. for $C_{15}H_{15}N_3SFCl$: C, 55.64; H, 4.67; N, 12.98. Found: C, 55.88; H, 4.63; N, 13.13.

CONCLUSIONS

Novel β-fluorophenethyl thiazolyl as well as halopyridyl thioureas were synthesized as NNRTI candidates. Synthesis of β-fluorophenethylamines was accomplished in three steps with an overall yield of 50%. Further condensation with thiocarbonylimidazole derivative derived from halopyridyl- or thiazolyl-substituted amines in dimethylformamide gave the desired thiourea compounds. The unsubstituted phenyl group compounds exhibited potent anti-HIV activity. Our lead compounds HI-565 (β-fluoro[2-phenethyl]-N'-[2-(5-bromopyridyl)]-thiourea and HI-566 (β-fluoro[2-phenethyl]-N′-[2-(5-chloropyridyl)]-thiourea were more potent inhibitors of HIV replication in peripheral blood mononuclear cells than several of the known compounds in the literature.

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