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**Abstract**

Thirteen kinds of N-monosubstituted thioureas have been synthesized from various primary amines through three different methods. The chemical structures of all the compounds have been characterized by the various spectral analyses. Four of them were evaluated for the anti-HIV-1 activity. The results showed that compound 1b, showing the IC₅₀ = 29.7 (μg/mL) to the strain of ROD of HIV-1, CC₅₀ > 50 (μg/mL), SI (selectivity index) > 2, was the best one among the test compounds. As for other compound 1a, 1c and 1d, the SI of them was less than 1, which means that these compounds might be toxic at the therapeutic level. Both the steric, electronic and topologic descriptors of the molecules were calculated to assist understanding the basic relationship between the structure and the biological activity. The docking result of 1c with HIV-1 reverse transcriptase (HIV-1 RT, PDB ID: 2HNZ) showed that there were still more unexploited rooms in the active site of the binding pocket of HIV-1 RT with compounds 1c.

**Keywords:** Mono-Substituted Thioureas; Anti-HIV Activity; Molecular Descriptors; SAR; CADD; DOCK.

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**Introduction**

As the important classes of compounds [76], thioureas could be used as the versatile reagents [56] and building blocks for constructing the S,N-containing heterocyclic compounds as well as the substrates for the further structural modification. Beside being oxidized into ureas [74] or alkylated into isothioureas [77], they were widely used to construct thiazole [5, 28, 61, 75, 87, 91, 92] 2-thiouracil [50], aminothiazole [25 28, 51, 62, 69, 75, 93, 95] aminobenzothiazoles [34, 90] iminothiazolines [2, 36, 54, 60] thiodihydantoin [38, 39] 1, 3, 5-triazines [14], 2-aminooxazolidines [26], thiazolidinediones [51, 53, 55], fused and spiro N/S-containing heterocycles [4]. The most interesting aspects of this type of compounds are the potent heterogeneous biological activities [58], such as anti-HIV activity [6], antituberculosis activity [35], cyto-kinin activity [8], promoting effect on wheat growth [94], reverses cross-links and restores biological activity in DNA, antimicrobial activity [13], anti-oxidant activity [1], anti-cancer activity [44, 73], tyrosinase inhibition [11, 84] and melanogenesis inhibition [83, 45]. The thiourea derivatives were also reported to be HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) for both the wild type [88], drug-resistant [49] and multidrug-resistant virus [86]. Among these active compounds, the anti-HIV agents have recently received much more attention than ever before, including the dual functional agents [12], PETTs [6, 64, 67, 80], ITUs [15, 48].

N-monosubstituted thioureas are biologically attractive for containing the primary NH₂ group, serving as a hydrogen bond donor [30] to interact with the amino acid residues in the binding pocket of target enzymes [84] especially the reverse transcriptase (RT) during the HIV-1 life cycle. Therefore, as part of our research program for the possible anti-HIV-1 RT agents [19, 46, 50, 52, 54, 96] we would like to report the synthesis and the anti-HIV RT evaluation of a series of N-monosubstituted thioureas. The target compounds were obtained from various substituted amines [4] mainly by the method shown in Scheme 1. This procedure usually required three steps from benzoyl chloride [2] and ammonium thiocyanate, via an intermediate of aroyl isothiocyanate [3] to afford primary amine [4] followed by the basic hydrolysis to give the target compounds (1a-1j) [66].

Although the above method was tedious in overall procedures, it might give the relatively high yield. Some other synthesis methods...
were also developed to obtain N-mono substituted thioureas efficiently. They might also involve using the toxic or special reagents, such as CS$_2$ [59], carbonothioic dichloride (thiophosgene) [42], hydrazine hydrate, [40] LiAlHSH [41] and TMS-Cl [9] via the harsh conditions, such as the high temperature, the long time and the tedious work-ups [40].

In some special circumstances, when above procedures described in the method A could not give the desired result; other alternative methods were used to achieve the target molecules such as Method B and Method C, which were illustrated in the following (Scheme 2-3), respectively.

It should be pointed out that the synthesis procedures have also been improved based on these traditionally reported methods. The chemical structures of all of these compounds have been characterized by the spectrum analysis as well as their physical data (Table 1).

The anti-HIV activities of N-monosubstituted thioureas were measured using the MTT method via comparing with four FDA-approved drugs (Nevirapine, Zidovudine, Dideoxycitidine and Dideoxyinosine). The cells were infected with HIV-1 wild-type virus (IIIb) strain cell line and HIV-2 strain (ROD). The results were reported as the half maximal (50%) inhibitory concentration (IC$_{50}$). Moreover, the cytotoxicity (CC$_{50}$) values of the compounds for each strain line were also determined. The selective index (SI=CC$_{50}$/IC$_{50}$) indicating the specificity of the antiviral effect, was given for both virus strains (Meng et al. 2003).

Due to the poor solubility of the molecules, only four compounds in the target molecules were tested for their anti-HIV activities. The result showed that compound 1b, showing the IC$_{50}$=29.7μg/mL to the strain of ROD of HIV-1, CC$_{50}$>50μg/mL, SI (selectivity index) > 2, was the best one among all the test compounds. The SI of other compound 1a, 1c and 1d were all less than 1, meaning these compounds might be toxic at the therapeutic level (Table 2).

The steric, electronic and topologic descriptors of the compounds have been calculated using Chem3D Ultra (Cambridge software package) to find some relationships between the biological activities and the chemical structure features (Table 3).

### Materials and Methods

#### Experimental Section

**General Methods and Materials:** All materials were obtained from the commercial suppliers and used as received. Melting points were taken on an X-4 digital melting point apparatus and were uncorrected. The elemental analyses were performed on a Carlo-Elba 1106 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were determined on a Bruker AM-400 (400 MHz) spectrometer with TMS as an internal standard. Chemical shifts were reported in δ. Mass spectra were measured on a HP5988A instrument by direct inlet at 70ev. All materials were obtained from the commercial suppliers and used as received.

1. **Synthesis**

**General procedures for synthesizing N-mono-substituted (1):** The N-mono-substituted thioureas were synthesized according to the following three methods (A, B, C) based on the different substituents on the aromatic ring. The general synthetic procedures were described as follows in details. The related descriptors of the desired thioureas obtained via calculating with Cambridge software package were also listed thereafter.

**Method A:** Benzoyl chloride (7.20 g, 50.0 mmol) was added dropwise to a solution of NH$_4$SCN (4.20 g, 51.0 mmol) in dry acetone (25.0 mL). The mixture was stirred under refluxing for 15 mins. Heating was removed and appropriate substituted anilines (50.0 mL) were added dropwise to the solution of ROD of HIV-1, CC$_{50}$>50μg/mL, SI (selectivity index) > 2, was the best one among all the test compounds. The SI of other compound 1a, 1c and 1d were all less than 1, meaning these compounds might be toxic at the therapeutic level (Table 2).

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| Entry | Chemical structure | No. | Mp (°C) | Form (Recrystallization solvent) | Yield (%) | Method |
|-------|-------------------|-----|---------|----------------------------------|-----------|--------|
| 1     | ![Chemical structure](image1) | 1a  | 178-179 | White crystal from anhydrous ethanol | 70.0      | Method A |
| 2     | ![Chemical structure](image2) | 1b  | 201-202 | White crystal from anhydrous ethanol | 60.0      | Method A |
| 3     | ![Chemical structure](image3) | 1c  | 190-192 | White crystal from anhydrous ethanol | 81.0      | Method A |
| 4     | ![Chemical structure](image4) | 1d  | 173-175 | White crystal from anhydrous ethanol | 57.9      | Method A |
| 5     | ![Chemical structure](image5) | 1e  | 198-200 | White crystal from anhydrous ethanol | 55.0      | Method A |
| 6     | ![Chemical structure](image6) | 1f  | 220-222 | White crystal from anhydrous ethanol | 67.0      | Method A |
| 7     | ![Chemical structure](image7) | 1g  | 212-214 | White needle like crystal from anhydrous ethanol | 40.0      | Method A |
| 8     | ![Chemical structure](image8) | 1h  | 163-164 | Yellow to white crystals from anhydrous ethanol | 99.3      | Method C |
| 9     | ![Chemical structure](image9) | 1i  | 236-238 | White needle like crystals from anhydrous ethanol | 85.7      | Method A |
| 10    | ![Chemical structure](image10) | 1j  | 104-105 | White crystals from anhydrous ethanol | 70.5      | Method A |
|       |                   |     |         |                                  | 49.2      | Method B |
| 11    | ![Chemical structure](image11) | 1k  | 193-195 | White crystals from anhydrous ethanol | 58.0      | Method A |
| 12    | ![Chemical structure](image12) | 1l  | 150-156 | White crystals from anhydrous ethanol | 31.9      | Method A |
| 13    | ![Chemical structure](image13) | 1m  | 122-124 | White crystals from anhydrous ethanol | 62.4      | Method A |
mmol) were added drop wise over a period of 15 mins. The reaction mixture was kept under refluxing for further 30 mins, and then cooled to room temperature before pouring into icy water (375 mL). The resulting precipitates were collected by filtration, washed with water or a cold mixture of water and methanol (1:1) [28]. The yellow solids (various substituted benzoyl thioureas), were added to a solution of sodium hydroxide (NaOH, 7.50 g, 65.0 mL water) and stirred at 80°C for 30 mins [61]. The mixture was adjusted to pH=7 with hydrochloric acid (HCl, 10.0 %). The appeared precipitates were filtered and washed with water, recrystallized with ethanol and then dried to give the pure products (1a-1g, 1i-1j) [66].

**Method B:** To a flask was added substituted aromatic amine (150 mmol) and aqueous hydrochloride (1.0 N, 16.0 mL) or HCl (conc. 36%, 15.2 g, 15.0 mmol), after slightly heated, the mixture was added ammonium thiocyanate (NH4 SCN, 12.6 g, 165 mmol), and then the temperature of the mixture was raised to 90°C for 2 hrs, and then stop heating to stay for 16~18 hrs, until there was a first portion of the yellow solid appeared from the solution. The solid was filtered and then the filtration was concentrated to give a second part of the yellow solids. The two parts were combined and heated to 100°C for 8 hrs. After being triturated and washed with

| No. | Chemical structure | Strain III B | Strain ROD |
|-----|-------------------|--------------|------------|
|     | IC50 (SD) | CC50 (SD) SI | IC50 (SD) | CC50 (SD) SI |
| 1c  | >50.00 | 1.70 | >50.00 | X1 | 29.70 | >50.00 | >2 |
| 1k  | >31.70 | ≥31.70 | < or X1 | >31.7 | ≥31.7 | < or X1 |
| 1l  | >19.38 | >19.38 (0.58) | 1 | 19.38 | >19.38 (0.58) | 1 |
| 1m  | >50.00 | >50.00 | X1 | >50.00 | X1 |
| C1  | 0.047 | 0.016 | >4 | >86 | >4 | >4 | <1 |
| C2  | 0.0015 | 0.0002 | >25 | >1640 | >25 | 0.0003 | >15408 |
| C3  | 0.29 | 0.05 | >20 | >69 | >20 | 0.10 | >20 | >67 |
| C4  | 2.89 | 0.43 | >50 | >17 | 4.59 | 0.81 | >50 | >11 |

CI-4: were the reference compounds (Nevirapine, Zidovudine, Dideoxycytidine and Dideoxyinosine) as the controlling group.

**Figure 1. The HOMO (Left) and LUMO (Right) of the compound 1c.**

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water (5.0 mL×3), the solid was obtained from filtration. Further recrystallization with a mixed solvent petroleum and ether (3:2), ethanol or THF (especially when 3,4-dichloroaniline was chosen as the material) [78] afforded the white crystal like products (I) [25].

Method C: A solution of aromatic amine (0.017 mol) in ethanol (15.0 mL) was stirred at room temperature while concentrated hydrochloric acid (37.4%, 2.14 mL) was added dropwise. The formed suspension was heated to reflux until being dissolved, to which was added with a solution of potassium thiocyanate (2.60 g, 25.5 mmol) in ethanol (5.00 mL). The reaction mixture was stirred at reflux for 18 h. The precipitate formed upon cooling was dried under vacuum and recrystallized from ethanol to yield the desired compounds (II) [27].

N-Phenythiourea (1a). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 70.0%, mp. 178-179°C, lit. 148-150°C [22]. 1H NMR (DMSO- d6, 400 MHz): δ 2.49 (br, 2H, -N H), 7.10 (d, 2H, Ar-H-2, 6), 7.31 (dd, 2H, Ar-H-3, 5), 7.45 (dd, 1H, Ar-H-4), 9.66 (br, 1H, NH); 13C NMR (DMSO-d6, 100 MHz): δ 123.01 (Ar-C-3), 124.38 (Ar-C-2, 6), 126.87 (Ar-C-3, 5), 139.06 (Ar-C-1), 180.99 (C=S).

N-(p-Toly) Ithiourea (1b). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 60.0%, mp. 201-202°C, lit. 181-183°C [27]. 1H NMR (DMSO-d6, 400 MHz): δ 2.25 (s, 3H, CH3), 2.49 (br, 1H, -NH2), 7.11 (d, 2H, Ar-H-2, 6), 7.23 (d, 2H, Ar-H-3, 5), 9.55 (br, 2H, NH); 13C NMR (DMSO-d6, 100 MHz): δ 20.47 (4-CH3), 123.33 (Ar-C-3, 5), 129.16 (Ar-C-2, 6), 133.70 (Ar-C-4), 136.40 (Ar-C-1), 180.94 (C=S).

N-(3-Chloro-2-methylphenyl) thiourea (1c). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 81.0%, mp. 190-192°C, lit. 153-154°C [60]. 1H NMR (DMSO-d6, 400 MHz): δ 2.20 (s, 3H, CH3), 3.32 (s, 2H, NH), 7.19 (m, 1H, Ar-H-5), 7.34 (d, 1H, Ar-H-6), 7.54 (d, 1H, Ar-H-6), 9.37 (br, 1H, NH); 13C NMR (DMSO-d6, 100 MHz): δ 15.05 (2-CH3), 126.97 (Ar-C-6), 127.09 (Ar-C-4), 127.34 (Ar-C-5), 133.18 (Ar-C-3), 138.87 (Ar-C-1), 138.79 (Ar-C-2), 181.86 (C=S).

N-(4-fluorophenyl) thiourea (1d). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 57.9%, mp. 173-175°C, lit. 164°C [16]. 1H NMR (DMSO-d6, 400 MHz): δ 3.34 (s, 2H, NH), 7.19 (d, 2H, Ar-H-2, 6), 7.49 (d, 2H, Ar-H-3, 5), 9.45 (br, 1H, NH).

N-(4-Bromophenyl) thiourea (1e). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 55.0%, mp. 198-200°C, lit. 171°C [23]. 1H NMR (DMSO-d6, 400 MHz): δ 3.34 (s, 2H, NH), 7.39 (d, 2H, Ar-H-2, 6), 7.47 (d, 2H, Ar-H-3, 5), 9.75 (br, 1H, NH).

N-(3,4-Dichlorophenyl) thiourea (1f). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White needle like crystals, Yield 67.0%, mp. 220-222°C, lit. 216-217°C [78], lit. 205-206°C [31]. 1H NMR (DMSO-d6, 400 MHz): δ 3.33 (s, 2H, NH), 7.19 (m, 1H, Ar-H-2), 7.34 (d, 1H, Ar-H-6), 7.54 (d, 1H, Ar-H-5), 9.86 (br, 1H, NH); MS (m/z): 220 (M+H+).

N-(p -Aminosulphonylphenyl) thiourea (Ig, also call as 4-thioureido-benzensulphonamide). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: Yellow to white needle like crystals, Yield 40.0%, mp. 212-214°C, lit. 206°C [79]. 1H NMR (DMSO-d6, 400 MHz): δ 3.33 (s, 2H, NH), 7.64 (d, 2H, Ar-H-2, 6), 7.72 (d, 2H, Ar-H-3, 5), 9.96 (br, 1H, NH).

N-(2-Trifluoromethylphenyl) thiourea (Ih). Synthesis method: Method C, Recrystallization solvent: Anhydrous ethanol, Form: Yellow to white crystals, Yield 99.3 %, mp. 163-164°C, lit. 170°C, [71, 82, 87]. 1H NMR (DMSO-d6, 400 MHz): 6.56 (s, 2H, NH), 7.01 (d, 1H, Ar-H-6), 7.10 (dd, 1H, Ar-H-4), 7.26 (dd, 1H, Ar-H-5), 7.53 (d, 1H, Ar-H-3), 8.91 (br, 1H, NH).

N-(p-Methoxyphenyl) thiourea (II). Synthesis method: Meth-
od A, Recrystallization solvent: Anhydrous ethanol, Form: White needle like crystals, Yield 85.7%. mp. 236-238°C, lit. 206-209°C [25], 212-214°C [65], 198-200°C [20], 210°C [85]. ^H NMR (DMSO- d 6, 400 MHz): 3.72 (s, 3H, OCH 3), 6.87 (d, 2H, ArH-2, 6), 7.13 (d, 2H, H-3, H-5), 7.29 (br, 2 H, NH 2), 9.02 (br, 1 H, NH).

N-(3-Trifluoromethylphenyl)thiourea (1j). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 70.5%. mp. 104-105°C, lit. Triclinic crystals [70]. ^H NMR (DMSO-d 6, 400 MHz): 6.09 (s, 2H, -NH 2), 6.45 (d, 1H, ArH-6), 7.01 (s, 1H, ArH-2), 7.09 (d, 1H, ArH-4), 7.16 (dd, 1H, ArH-5), 8.68 (br, 1H, NH).

N-(3-Chloro-4-fluorophenyl)thiourea (1k). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White crystals, Yield 58.0%. mp. 193-195°C, lit. 198-199°C [65], 212-214°C [65], 200°C [20]. ^H NMR (DMSO-d 6, 400 MHz): 6.06 (s, 2H, -NH 2), 6.96 (s, 2H, ArH-2, 6), 7.37 (s, 1H, ArH-4), 8.91 (br, 1H, NH).

N-(N',N'-Diethylaminoethylene) thiourea (1m). Synthesis method: Method A, Recrystallization solvent: Anhydrous ethanol, Form: White needle crystals, Yield 62.4%. mp. 122-124°C [24]. ^H NMR (DMSO-d 6, 400 MHz): 1.10 (t, 6H, CH 3 × 2), 2.79 (m, 4H, CH 2 × 2), 2.56 (t, 4H, CH 2 × 2), 2.95 (t, 4H, CH 2 × 2), 6.65 (s, 1H, ArH-2), 7.26 (d, 1H, ArH-5), 8.59 (br, 1H, NH).
ta-position of the phenyl group, showed the relative inhibitory activity against HIV-2 strain ROD (IC₅₀=29.70μg/mL, SI > 1). Other compounds exhibit almost no activity against both wild-type HIV-1 strain IIIB and HIV-2 strain ROD.

The most active molecule (1c) of the series was subjected to MM minimization, and then the HOMO and LUMO of compound 1c were calculated and shown in Figure 2. The properties of all the target molecules were calculated according the different kind of molecular descriptors listed as the following: steric descriptors including molecular weight (MW) and Connolly molecular area (CMA), etc. (Table 3).

As a summary, it was quite surprising that the compounds 1c show activity against HIV-2, although the rest tested compounds could not inhibit both the wild type and the HIV-2 strain line virus.

The molecular weight of 1c and other target molecule were much more less than that of the ligand of 2HNZ, in which the ligand is a PETT derivative with the name of 1-(2-(4-ethoxy-3-fluoropyridin-2-yl)ethyl)-3-(5-methylpyrindin-2-yl) thiourea (Ren et al. 2006). This might lead to the active binding pocket of HIV-1 RT was less sterically fulfilled when interacting with 1c (Both the left and right diagram, Figure 2). The phenyl ring of 1c was almost perpendicular to the aromatic phenyl ring of Tyr181 in the HIV-1 RT BP, which was not favorable for enhancing aromatic π-π stacking effect for steric reasons. (The right diagram, Figure 2).

Conclusion

To summarize, it should be cautious when trying to change the structure feature of PETT from di-substituted thiourea into the mono-substituted thiourea structures for achieving the possible potential anti-HIV-1 RT reagents. The simplification in the structural skeleton might decrease the biological activity for their poor solubility and less compatibility in the active binding pocket of HIV-1 RT.

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