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RESEARCH ARTICLE

Chemoselectivity of thiophene dicarboxylate towards hydrazine hydrate: Synthesis of some new bis heterocycles from thiophene monocarbohydrazide

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Chemoselectivity of C_5-carbethoxy function over that of C_3-carbethoxy function of the thiophene dicarboxylate towards the nucleophilic attack of hydrazine hydrate has been evidenced by exclusive formation of monocarbohydrazide *i.e.* ethyl 2-amino-5-(hydrazinocarbonyl)-4-methylthiophene-3-carboxylate and this monocarbohydrazide was reacted separately with acetylacetone, cyanogen bromide, acetonylacetone and CS_2 in ethanolic potassium hydroxide solution to furnish corresponding derivatives of 3,5-dimethylpyrazole, 5-aminooxadiazole, 2,5-dimethylpyrrole and 5-thiooxadiazole respectively. Thiophene monocarbohydrazide was converted to hydrazone derivatives by reacting with *p*-chlorobenzaldehyde and isatin. The monocarbohydrazide was also converted to thiosemicarbohydrazide derivatives, which was then cyclised with $POCl_3$ to afford corresponding thiadiazole derivatives. The structures of all the newly synthesized compounds were elucidated on the basis of their spectral and analytical data and the compounds were screened for their antituberculosis, antibacterial and antifungal activities.

Keywords: Chemoselectivity; Carbohydrazide; Bis heterocycles; Antitubercular activity; Antimicrobial activity

1. Introduction

Thiophene derivatives have attracted organic chemists and they are also continuously being investigated due to their significant contributions as therapeutic agents [1–5]. In general, the 2,5-dimethyl pyrrole derivatives have shown interesting antiulcer [6] and hypotensive [7] activities. The 1,3,4-oxadiazoles are endowed with muscle relaxant, antitubercular [8], antiviral [9], amoebicidal [10], antimicrobial [11] analgesic and anti-inflammatory [12] activities. The 1,3,4-thiadiazole derivatives have been shown to possess a wide range of biological properties [13–17]. The carbohydrazides [17, 18] are reported to have anticancer activity and their hydrazone derivatives [17] have also exhibited interesting biological activity. So we thought to prepare bis heterocycles by reacting thiophene monocarbohydrazide with various reagents.

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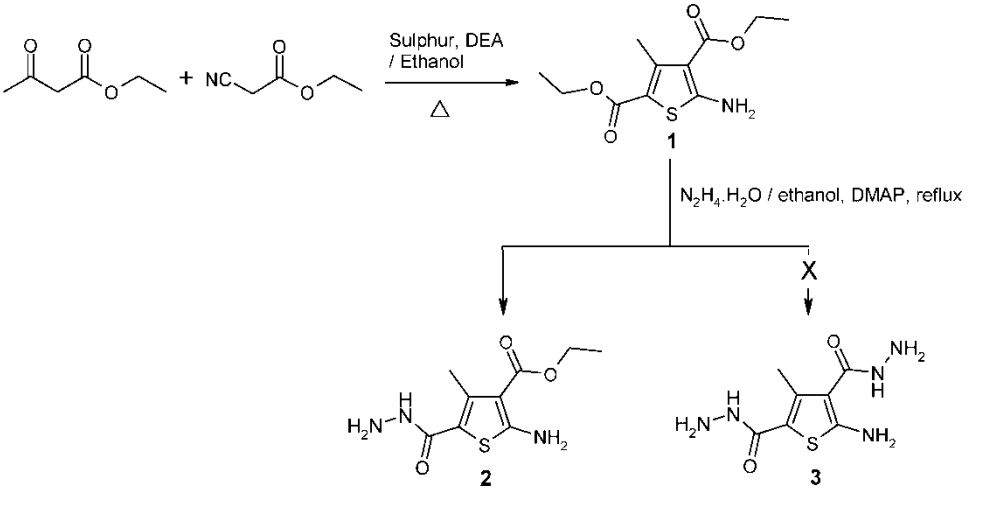
In recent years, much attention has been devoted to the synthesis of heterocycles as antitubercular and antimicrobial agents. The treatment of mycobacterial infections especially tuberculosis has become an important problem due to the emergence of monodrug and multidrug resistance [19]. It is reported that many heterocycles like oxadiazoles and thiadiazole derivatives have exhibited good activity against *Mycobacterium tuberculosis* [8, 16], which encouraged us to prepare some new bis heterocycles to study their antitubercular activity and other biological properties.

Diethyl 2-amino-4-methylthiophene-3,5-dicarboxylate **1** was prepared as per literature method [20]. Further, thiophene dicarboxylate **1** was reacted with excess of hydrazine hydrate in ethanol (at refluxing temperature) with a catalytic amount of dimethylaminopyridine (DMAP) for 40 hr, which yielded exclusively monocarbohydrazide *i.e.* ethyl 2-amino-5-(hydrazinocarbonyl)-4-methylthiophene-3-carboxylate **2**, but not the expected thiophene dicarbohydrazide **3** (scheme 1). The chemoselectivity of C_5-ester group of **1** towards the reaction with hydrazine hydrate to furnish the monocarbohydrazide **2** was established by the IR spectra of **1** and **2**. The IR spectrum of **1** showed C_3-carbethoxy carbonyl around 1661 cm^{-1} and that of C_5-carbethoxy function at 1683 cm^{-1}. Whereas after the reaction of **1** with hydrazine hydrate the band due to C_3-carbethoxy carbonyl (1659 cm^{-1}) remained unaffected, while the band due to C_5-carbethoxy carbonyl at 1683 cm^{-1} disappeared in the product **2**. The presence of another band at 1624 cm^{-1} due to $\nu_{C=O}$ of C_5-carbohydrazide established the formation of monocarbohydrazide **2**. The ^1H NMR spectrum of **2** displayed the presence of a characteristic quartet at δ 4.26 and triplet at δ 1.34 pattern due to the C_3-ethyl ester group. The singlet at δ 2.53 is attributed to C_4-methyl protons. Two D_2O exchangeable singlets at δ 8.52 and 7.46 are attributed to C_2-amino and NH_2 of C_5-carbohydrazide, while D_2O exchangeable singlet at δ 7.77 assigned to NH proton of C_5-carbohydrazide.

An attempt was made to synthesize dicarbohydrazide **3** by carrying out the reaction of thiophene dicarboxylate **1** with hydrazine hydrate in high boiling solvent (ethylene glycol) with catalytic amount of DMAP under refluxing temperature but we ended up with the same product, monocarbohydrazide **2.** However, the observation was the drastic reduction in reaction time with less yield (48%).

The observed resistance of C_3-carbethoxy group of **1a** towards the nucleophilic attack by hydrazine hydrate is due to canonical form of **1b** wherein the C_3-carbethoxy carbonyl



SCHEME 1

has reduced double bond character in addition to its intramolecular H-bonding with $-NH_2$ function (figure 1). Because of this reason the amino group is also resistant towards some of its typical reactions. Our present observation is in conformity with an earlier report [11] on chemoselectivity.

The monocarbohydrazide **2** was reacted with acetylacetone in boiling ethanol with catalytic amount of acetic acid to afford the desired 3,5-dimethylpyrazole derivative **4**. The thiophene carbohydrazide **2** was further treated with cyanogen bromide in dry ethanol. The hydrobromide salt separated was basified with aqueous sodium carbonate solution to afford 5-aminooxadiazole derivative **5**. The 2,5-dimethylpyrrole derivative **6** was prepared by reacting thiophene monocarbohydrazide **2** with acetonylacetone in absolute ethanol with catalytic amount of acetic acid. When the monocarbohydrazide **2** was reacted with carbon disulphide in ethanolic potassium hydroxide solution at reflux yielded the expected 5-thiooxadiazole derivative **7**. In another set of reactions, the carbohydrazide **2** was converted to its hydrazone derivative **8**/**9** on reaction with *p*-chlorobenzaldehyde/isatin in ethanol with catalytic amount of acetic acid (scheme2).

When the thiophene monocarbohydrazide **2** was reacted with ethyl/phenyl isothiocyanate yielded corresponding thiosemicarbazide derivatives **10a**,**b** which on cyclisation with phosphorous oxychloride resulted (scheme 2) in the formation of expected 1,3,4-thiadiazole derivatives **11a**,**b**.

The structures of all the newly synthesized compounds were elucidated by spectral techniques. All the compounds were also analyzed for their C, H and N compositions and are within the limits. Analytical and spectral data for all compounds is given in the experimental section.

All the newly synthesized compounds were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system [21,22]. Among the compounds tested, hydrazone derivative **8** showed 56% inhibition against *M. tuberculosis* at a low concentration of 6.25 μg/mL (MIC) in the preliminary screening test using Rifampin as a reference drug, while rest of the compounds were less active. They were also tested for their antibacterial activity [23, 24] against *Escherichia coli and Bacillus cirrhosis* and antifungal activity [25] against *Penicillium wortmannii and Aspergillus niger* by cup plate method. The oxadiazole derivatives **5**, **7** and the isatin condensed derivative **11** have exhibited good antibacterial activity at concentration of 25–100 μg/mL against *E. coli and B. cirrhosis* but not comparable to standard Norfloxacin. Thiosemicarbazide derivatives **10a,b** have shown moderate antibacterial activity against *E. coli*. The carbohydrazide **2** and 2-aminooxadiazole derivative **5** showed good antifungal activity at concentration 25–100 μg/mL against *P. wortmannii and A. niger* but not comparable to standard Greseofulvin.

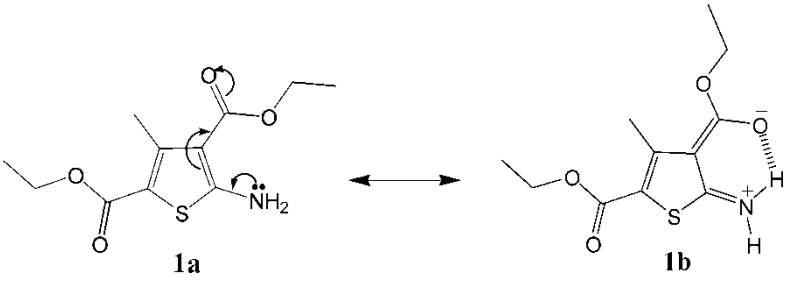
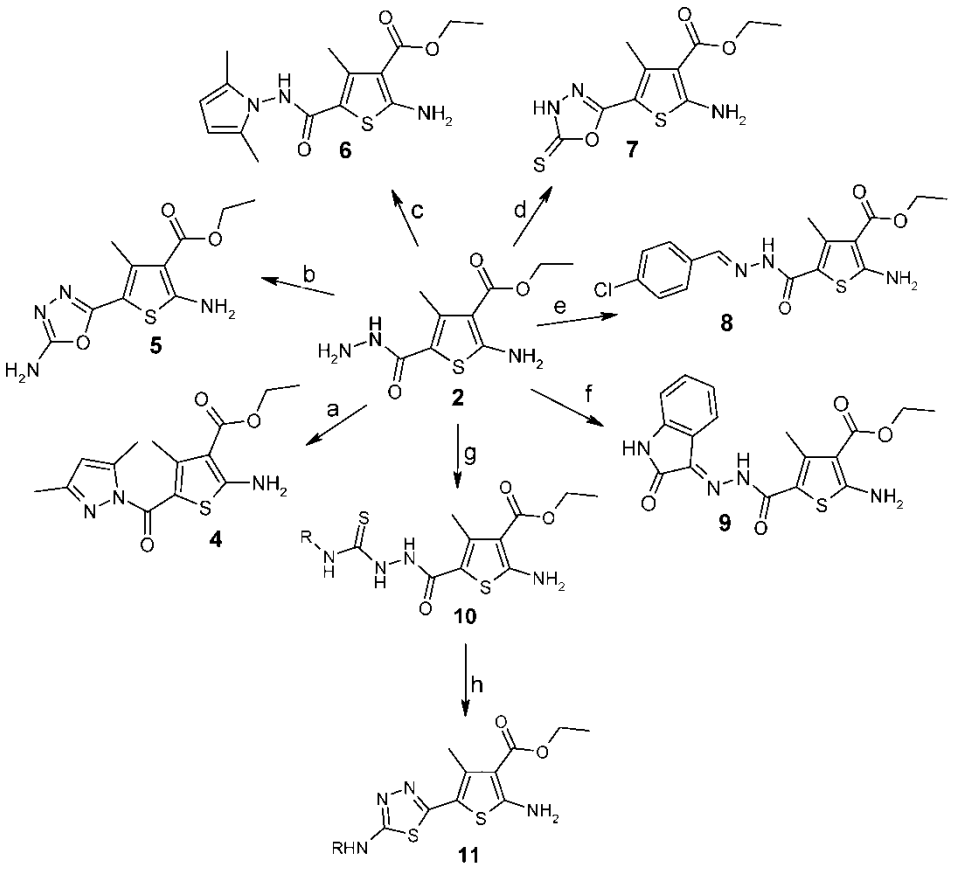


Figure 1.



a. Acetylacetone / ethanol, H^+, reflux.
b. i. CNBr / ethanol, reflux. ii. Na_2CO_3.
c. Acetonylacetone / ethanol, H^+, reflux.
d. i. CS_2, KOH / aq.ethanol, reflux. ii. dil. HCl.
e. *p*-Chlorobenzaldehyde/ ethanol, H^+, reflux.
f. Isatin / ethanol / H^+, reflux.
g. RNCS / ethanol, reflux.
h. i. $POCl_3$, reflux; ii. aq. KOH

SCHEME 2

2. Experimental

Melting points are uncorrected. TLC was carried out on aluminium silica gel 60 F_{254} (Merck) detected by UV light and iodine vapors. IR spectra were obtained from Nicolet Impact-410 FT-IR spectrophotometer, using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-300F 300 MHz, spectrometer in $CDCl_3$ and DMSO-d_6 using $SiMe_4$ as an internal standard. Electrospray ionization mass spectra (ESI-MS) were recorded on a Quattro LCZ (Walters-Micromass, Manchester) and elemental analysis was carried out using Heraus CHN rapid analyzer.

2.1 *Diethyl 2-amino-4-methylthiophene-3,5-dicarboxylate (1)*

To a well stirred mixture of ethyl acetoacetate (13.0 g, 0.1 mol) and ethyl cyanoacetate (11.3 g, 0.1 mol) in ethanol (50 mL) was added elemental sulfur (3.36 g, 0.105 mol). To the cooled (10 °C) reaction mixture was added (under stirring) diethylamine (10 mL) over the period

of 2 min. The dark red colored reaction mixture was stirred at 45 °C for 1 hr. The separated solid was filtered, washed with ethanol till colorless and recrystallized from ethanol to afford colorless needles. Yield 36%, m.p. 108–110 °C (lit. 109 °C); IR (KBr) ν: 3404, 3284, 2989, 1683, 1661, 1585, 1530, 1230 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.35 (m, 6H, CH_3 of C_3 and C_5- ethyl carboxylate), 2.70 (s, 3H, CH_3), 4.28 (m, 4H, CH_2 of C_3 and C_5- ethyl carboxylate), 6.49 (br s, 2H, NH_2, D_2O exchangeable).

2.2 *Ethyl 2-amino-5-(hydrazinocarbonyl)-4-methylthiophene-3-carboxylate (2)*

A mixture of thiophene dicarboxylate **1** (12.9 g, 0.05 mol), excess of hydrazine hydrate (10 mL) and catalytic amount of dimethylaminopyridine (DMAP) in ethanol (60 mL) was refluxed for 40 hr. Colorless solid that separated was filtered, washed with hot ethanol and recrystallized from ethanol-dioxane mixture to afford colorless crystals. Yield 64%, m.p. 226–228 °C; IR (KBr) ν: 3390, 3300, 3218, 3109, 2982, 1659, 1624, 1590, 1537, 1478, 1272 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.34 (t, $J = 7.2$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.58 (s, 3H, CH_3), 4.26 (q, $J = 7.2$ Hz, 2H, $CO\underline{CH_2}CH_3$), 7.46 (br s, 2H, NH_2, D_2O exchangeable), 7.77 (s, 1H, NH, D_2O exchangeable), 8.52 (s, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_9H_{13}N_3O_3S$: C, 44.43; H, 5.39; N, 17.27. Found: C, 44.62; H, 5.45; N, 17.16%.

2.3 *Ethyl 2-amino-5-[(3,5-dimethyl-1H-pyrazol-1-yl)carbonyl]-4-methylthiophene-3-carboxylate (4)*

A mixture of monocarbohydrazide **1** (0.50 g, 0.002 mol), acetylacetone (0.40 g, 0.004 mol) and catalytic amount of glacial acetic acid in ethanol (15 mL) was heated under reflux for 4 hr. The solid that separated was filtered, washed and recrystallized from ethanol to afford light pink colored granules. Yield 81%, m.p. 146–148 °C; IR (KBr) ν: 3390, 3276, 2934, 1658, 1644, 1588, 1542, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, $J = 7.0$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.27 (s, 3H, C_3-methyl, pyrazole), 2.59 (s, 3H, C_5-methyl, pyrazole), 2.80 (s, 3H, C_4-methyl, thiophene), 4.32 (q, $J = 6.9$ Hz, 2H, $CO\underline{CH_2}CH_3$), 5.99 (s, 1H, C_4-H, pyrazole), 6.60 (br s, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.57; N, 13.67. Found: C, 54.78; H, 5.60; N, 13.64%.

2.4 *Ethyl 2-amino-5-(5-amino-1,3,4-oxadiazol-2-yl)-4-methylthiophene-3-carboxylate (5)*

A mixture of monocarbohydrazide **2** (0.250 g, 0.001 mol) and cyanogen bromide (0.127 g, 0.0012 mol) in dry ethanol (10 mL) was heated under reflux for 2 hr. The hydrobromide salt separated was filtered, washed with cold ethanol and basified with aq. sodium carbonate solution. The free base was filtered, washed with water and recrystallized from ethanol-dioxane mixture to secure colorless granules. Yield 76%, m.p. 218–220 °C; IR (KBr) ν: 3456, 3385, 3289, 3169, 2980, 2929, 1655, 1601, 1568, 1273 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.29 (t, $J = 6.9$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.53 (s, 3H, CH_3), 4.23 (q, $J = 7.0$ Hz, 3H, $CO\underline{CH_2}CH_3$), 7.10 (s, 2H, NH_2, D_2O exchangeable), 7.78 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.3, 16.0, 59.3, 100.5, 105.1, 138.1, 154.1, 162.4, 164.7 and 165.0; MS (ESI): 269.07 (M+H), 291.05 (M+Na), 599.11 (2M+Na). Anal. Calcd for $C_{10}H_{12}N_4O_3S$: C, 44.77; H, 4.51; N, 20.88. Found: C, 44.68; H, 4.59 N, 20.95%.

2.5 *2-Amino-5-{[(2,5-dimethyl-1H-pyrrol-1-yl)amino]carbonyl}-4-methylthiophene-3-carboxylate (6)*

A mixture of monocarbohydrazide **2** (0.250 g, 0.001 mol) and acetonylacetone (0.200 g, 0.002 mol) in presence of catalytic amount of glacial acetic acid in ethanol (8 mL) was heated under reflux for 4 hr. The solid that separated was filtered, washed with cold ethanol, dried and recrystallized with aqueous ethanol to afford light gray colored granules. Yield 72%, m.p. 192–194 °C; IR (KBr) ν: 3366, 3278, 3234, 3158, 2978, 2918, 1677, 1639, 1590, 1519, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, $J = 7.0$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.14 (s, 6H, C_2, C_5-methyl, pyrrole), 2.71 (s, 3H, C_4-methyl, thiophene), 4.34 (q, 2H, $J = 6.9$ Hz, $CO\underline{CH_2}CH_3$), 5.84 (s, 2H, pyrrole), 6.54 (br s, 2H, NH_2, D_2O exchangeable), 7.70 (br s, 1H, NH, D_2O exchangeable); MS (ESI): 322.12 (M+H), 344.10 (M+Na), 665.21 (2M+Na). Anal. Calcd for $C_{15}H_{19}N_3O_3S$: C, 56.06; H, 5.96; N, 13.07. Found: C, 56.23; H, 6.02; N, 13.01%.

2.6 *Ethyl 2-amino-4-methyl-5-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiophene-3-carboxylate (7)*

A mixture of thiophene monocarbohydrazide **2** (0.250 g, 0.001 mol) in ethanol (20 mL), potassium hydroxide (0.16 g, 0.003 mol) dissolved in water (3 mL) and carbon disulphide (0.34 g, 0.0045 mol) was heated under reflux until the evolution of H_2S ceased (20 hr). The reaction mixture was cooled to room temperature and poured into ice cold water (100 mL). It was then neutralized with dilute hydrochloric acid. The precipitated solid was filtered, washed with water and dried. The crude product was recrystallized from ethanol-dioxane mixture as pale yellow granules. Yield 66%, m.p. 192–194 °C; IR (KBr) ν: 3378, 3252, 3144, 2932, 1659, 1592, 1548, 1168 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.28 (t, $J = 6.9$ Hz, 3H, $CO\underline{CH_2}CH_3$), 2.53 (s, 3H, CH_3), 4.23 (q, $J = 6.9$ Hz, 2H, $CO\underline{CH_2}CH_3$), 8.00 (s, 1H, NH_2, D_2O exchangeable), 14.61 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_{11}N_3O_3S_2$: C, 42.09, H, 3.89; N, 14.73. Found: C, 41.91, H, 3.96; N, 14.85%.

2.7 *Ethyl 2-amino-5-{[2-(4-chlorobenzylidene)hydrazino]carbonyl}-4-methylthiophene-3-carboxylate (8)*

A mixture of monocarbohydrazide **2** (0.250 g, 0.001 mol) and *p*-chlorobenzaldehyde (0.141 g, 0.001 mol) in ethanol (10 mL) with catalytic amount of glacial acetic acid, was heated under reflux for 5 hr. Yellow solid that separated was filtered, washed with hot ethanol and recrystallized from ethanol-dioxane mixture to afford pale yellow granules. Yield 77%, m.p. 208–210 °C; IR (KBr) ν: 3386, 3334, 1252, 1659, 1628, 1556, 1528 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.28 (t, $J = 7.2$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.56 (s, 3H, CH_3), 4.21 (q, $J = 7.0$ Hz, 2H, $CO\underline{CH_2}CH_3$), 7.40 (d, $J = 8.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.80 (s, 2H, NH_2, D_2O exchangeable), 7.90 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl), 8.06 (br s, 1H, N = CH), 11.23 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{16}H_{16}ClN_3O_3S$: C, 52.53; H, 4.41; N, 11.49. Found: C, 52.44; H, 4.48; N, 11.62%.

2.8 *Ethyl 2-amino-4-methyl-5-{[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazino]carbonyl}thiophene-3-carboxylate (9)*

A mixture of monocarbohydrazide **2** (0.250 g, 0.001 mol) and isatin (0.133 g, 0.001 mol) in ethanol (8 mL) with catalytic amount of glacial acetic acid was heated under reflux for 6 hr. Bright orange-yellow solid that separated was filtered, washed with aqueous ethanol and

recrystallized from ethanol-dioxane mixture to secure the bright yellow solid. Yield 64%, m.p. 272–274 °C; IR (KBr) ν: 3387, 3245, 3063, 2935, 2865, 1705, 1648, 1626, 1587, 1532, 1218 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.29 (t, $J = 3.3$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.67 (s, 3H, CH_3), 4.25 (q, $J = 3.5$ Hz, 2H, $CO\underline{CH_2}CH_3$), 6.96 (t, $J = 6.3$ Hz, 1H, C_5-H, indole), 7.10 (t, $J = 6.2$ Hz, 1H, C_6-H, indole), 7.37 (d, $J = 6.6$ Hz, 1H, C_4-H, indole), 7.57 (d, $J = 6.5$ Hz, 1H, C_7-H, indole). 7.98 (s, 2H, NH_2, D_2O exchangeable), 11.25 (s, 1H, NH, D_2O exchangeable), 13.10 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{17}H_{16}N_4O_4S$: C, 54.83; H, 4.33; N, 15.04. Found: C, 54.61; H, 4.40; N, 14.96%.

2.9 *Preparation of thiosemicarbazide derivatives (10a,b)*

2.9.1 General procedure. A mixture of monocarbohydrazide **2** (0.002 mol) and ethyl/*p*-chlorophenyl isothiocyanate (0.0021 mol) in ethanol (20 mL) was heated under reflux for 4 hr. Colorless solid that separated from the clear solution was filtered hot and washed with hot ethanol and crystallized from ethanol-dioxane mixture to afford colorless needles.

2.9.2 Ethyl 2-amino-5-({2-[(ethylamino)carbonothioyl]hydrazino}carbonyl)-4-methyl thiophene-3-carboxylate (10a). Colorless needles (ethanol + dioxane), yield 82%, m.p. 212–214 °C; IR (KBr) ν: 3371, 3283, 3163, 2979, 2932, 1672, 1651, 1618, 1591, 1558, 1526, 1219 cm^{-1}; Anal. Calcd for $C_{12}H_{18}N_4O_3S_2$: C, 43.62; H, 5.49; N, 16.96. Found: C, 43.48; H, 5.50; N, 17.04%.

2.9.3 Ethyl 2-amino-5-[(2-{[(4-chlorophenyl)amino]carbonothioyl}hydrazino)carbonyl] -4-methylthiophene-3- carboxylate (10b). Colorless needles (ethanol + dioxane), yield 75%, m.p. 228–230 °C; IR (KBr) ν: 3374, 3277, 3044, 2969, 1674, 1652, 1614, 1596, 1555, 1216 cm^{-1}. Anal. Calcd for $C_{16}H_{17}ClN_4O_3S_2$: C, 46.54; H, 4.15; N, 13.57. Found: C, 46.38; H, 4.20; N, 13.66%.

2.10 *Preparation of thiadiazole derivatives (11a,b)*

2.10.1 General procedure. Thiosemicarbazide derivative **8** (0.001 mol) in $POCl_3$ (4 mL) was heated under reflux for 1 hr. The reaction mixture was cooled in ice bath and quenched with water (12 mL). The reaction mixture was digested on water bath for 1 hr and filtered. Filtrate was basified with aqueous potassium hydroxide solution. Orange-yellow solid separated was filtered, washed with water, ethanol and recrystallized from ethanol-dioxane mixture.

2.10.2 Ethyl 2-amino-5-[5-(ethylamino)-1,3,4-thiadiazol-2-yl]-4-methylthiophene-3-carboxylate 11a. Pale yellow granules, yield: 46%, m.p. 246–248 °C; IR (KBr) ν: 3453, 3385, 3284, 3175, 2979, 2938, 2854, 1655, 1589, 1546, 1218 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.32–1.40 (m, 6H, $COCH_2\underline{CH_3}$, $NCH_2\underline{CH_3}$), 2.56 (s, 3H, CH_3), 3.38 (q, $J = 6.3$ Hz, 2H, NCH_2CH_3), 4.28 (q, $J = 7.2$ Hz, 2H, $CO\underline{CH_2}CH_3$), 7.77 (s, 2H, NH_2, D_2O exchangeable), 8.52 (br s, 1H, NH, D_2O exchangeable); MS (ESI): 313.48 (M + H), 325.44 (M + Na), 647.83 (2M + Na). Anal. Calcd for $C_{12}H_{16}N_4O_2S_2$: C, 46.13; H, 5.16; N, 17.93. Found: C, 46.25; H, 5.22; N, 17.78%.

2.10.3 Ethyl 2-amino-5-5-[(4-chlorophenyl)amino]-1,3,4-thiadiazol-2-yl-4-methylthiophene-3-carboxylate 11b. Yellow granules, yield 40%, m.p. 262–264 °C; IR (KBr) ν: 3442,

3379, 3284, 3182, 3038, 2954, 1657, 1594, 1548, 1223 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.34 (t, $J = 6.3$ Hz, 3H, $COCH_2\underline{CH_3}$), 2.57 (s, 3H, CH_3), 4.35 (q, $J = 6.1$ Hz, 2H, $CO\underline{CH_2}CH_3$), 7.26 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl), 7.63 (d, $J = 7.6$ Hz, 2H, C_3, C_5-H, phenyl), 7.87 (s, 2H, NH_2, D_2O exchangeable), 8.72 (br s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{16}H_{15}ClN_4O_2S_2$: C, 48.66; H, 3.83; N, 14.19. Found: C, 48.57; H, 3.91; N, 14.14%.

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