S. Afr. J. Chem., 2012, **65**, 223–227,
<http://journals.sabinet.co.za/sajchem/>.

Synthesis of Novel Thieno[3,2-*b*]quinolines and Thieno[3,2-*d*][1,3]thiazoles

Yazid Datoussaid[a,b,*], Gilbert Kirsch[b], Adil A. Othman[a] and Ismail Abdillahi[b]

[a]*Laboratory of Bimolecular and Organic Synthesis, Chemistry Department, Faculty of Science, University of Sciences and Technology-Mohamed Boudiaf-Oran-USTO,MB-, P.O.B. 1505 El-M'naouer, 31000, Oran Algeria.*

[b]*Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Institut Jean Barriol, FR CNRS 2843, 1 Boulevard Arago, 57070 METZ, France.*

Received 20 April 2012, revised 13 August 2012, accepted 16 August 2012.

ABSTRACT

New heterocyclic 2-Aryl-9-chloro-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline derivatives [Aryl-CTTQ] (2a–e) and 5-aryl-thieno[3,2-*d*][1,3]thiazol-2-amine derivatives[Aryl-TZA] (6a–e)were achieved in good yields starting from 5-aryl-3-aminothiophene-2-carboxylic acid (1a–c).

KEYWORDS

5-Aryl-3-aminothiophene-2-carboxylic acid, thieno[3,2-*b*]quinoline, thiourea, thieno [3,2-*d*][1,3]thiazole.

1. Introduction

Thiophene, thiazole, and quinoline are well-known examples of heteroaromaticorganic compounds found naturally in plants and animal cell constituents. They are also found in artificial compounds,[1] such as agrochemicals,[2] pharmaceuticals,[3] dyes,[4] plastics, solvents, photographic chemicals, electronics, corrosion inhibitors,[5] preservatives and polymers.[6] At the same time, condensed heterocyclic derivatives of thiophene are of interest as biologically active substances and technical materials. A variety of such sulfur-containing heterocycles have been described. In addition to this, the introduction of sulfur-containing rings into the structure of compounds often modulates their pharmacological properties,[7–9] reduces the side-effects of drugs[10] or improves the technical characteristics of materials.[11,12]

Very little is known concerning the thieno[3,2-*b*]quinoline skeleton,[13,14] as for instance, found in 2-aryl-9-chloro-5,6,7,8-tetrahydrothieno[3,2-*b*] quinolines A and thieno[3,2-*d*][1,3] thiazoles B,[15] shown in Fig. 1.

In terms of biological relevance, benzothiazoles such as the medicinal compound riluzole, which is a benzothiazole with and additional amine group, have been noted to demonstrate anticancer activity and has used to treat amyotrophic lateral sclerosis.[15,16]

In this present work we report the synthesis and characterization of a series of thieno[3,2-*b*] quinoline derivatives (**2a–e**), as well as a set of thieno[3,2-*d*][1,3]thiazole derivatives (**6a–e**) which are related to **A** and **B**, respectively, and are anticipated to have biological activity.

2. Results and Discussion

2.1. Synthesis and Characterization of Thieno[3,2-*b*]quinoline Derivatives

The synthesis of the 2-aryl-9-chloro-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline derivatives(**2a–e**) was achieved by the direct condensation of acids (**1a–e**) and cyclohexanone in $POCl_3$ without the isolation of dehydrated adducts (see Scheme 1 and Table 1). It should be noted that this work is an extension of the research published earlier by one of us.[15] The successful construction of the 5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline ring systems was proved by ^1H,^{13}C NMR spectroscopy, CHN analysis and mass spectrometry.

Figure 1 Structural skeletons of thieno[3,2-*b*]quinoline (**A**) and thieno[3,2-*d*][1,3] thiazole (**B**).

The successful one-pot reactions were thought to proceed *via* a rapid dehydration, followed by cyclization and chloro substitution *in situ* in the presence of the chlorinating agent, as shown by the proposed mechanism illustrated Scheme 2.

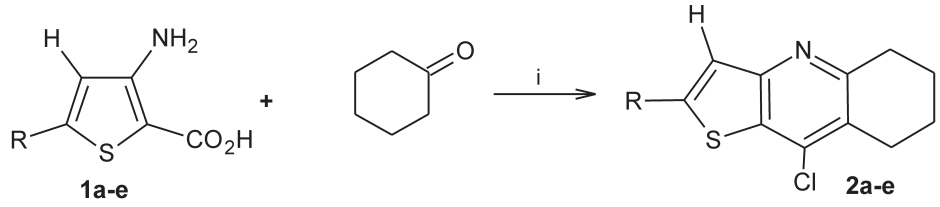
2.2. Synthesis and Characterization of Thieno[3,2-*b*]quinoline Derivatives

In continuation tofour previous work[17–20], the synthesis of thieno[3,2-*d*][1,3]thiazole derivatives **6a–e** was performed successfully *via* a multi-step synthesis from 3-amino-5-aryl-thiophene-2-carboxylic acids **1a–e**, as described in Scheme 3. Details concerning the decarboxylation of the aromatic β-amino acids **1a–e**[17–19] to the corresponding amines **3a–e** has already been published[15,19–22] 3-Isothiocyanato thiophenes **4a-e** were next isolated in good yields (58–80 %) by treatment of the amines **3a–e** with thiophosgene. The isothiocyanates **4a–e** were subsequently treated with *p*-anisidine at room temperature after which the thiourea adducts **5a–e** were collected in excellent yields (83–96 %), except for compound **5a** which was obtained in 40 % yield. Treatment of the thiourea derivatives **5a–e** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for a short time then afforded the 5-arylo-thieno [3,2-*d*][1,3]thiazoles (**6a–e**). The structural details, percentages of yields, and important ^1H and ^{13}C-NMR spectroscopic data are summarized in Table 2.

3. Conclusions

We have accomplished the synthesis of an expanded set of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolines **2a–e** and a

* To whom correspondence should be addressed. E-mail:datou_yazid@yahoo.fr



R: a = -C_6H_5; **b** = p-MeC_6H_4-; **c** = p-OMe-C_6H_4-; **d** = p-Cl-C_6H_4-; **e** = p-F-C_6H_4-

Scheme 1
Synthesis of substituted tetrahydrothieno[3,2-*b*]quinoline. (i) $POCl_3$, reflux, 5 h (for yields see Table 1).

small library of thieno[3,2-*d*][1,3]thiazol-2-amine analogues **6a–e** from the same starting materials **1a–e**, in one and four steps, respectively. All compounds, mostly new, were unambiguously identified by thorough spectroscopic analyses. In all cases, angular cyclization took place, which was established from the ^{1}H NMR spectroscopic data . Moreover, we hope that the synthesized compounds will be biologically tested in due course.

4. Experimental

4.1. General

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on an AC Bruker 250 MHz spectrometer in $CDCl_3$ or DMSO-d6. Mass Spectra were recorded on a MicroTof-Q 98. The homogeneity of all compounds synthesized was checked by TLC on 2.0 cm × 6.0 cm aluminium sheets recoated with silica gel 60 containing a fluorescent indicator, to a thickness of 0.25.

The preparation of 3-amino-5-phenylthiophene-2-carboxylic acid **1a–e** and thiophenamines **3a–e** has already been described by us.[15,19–21]

4.2. Synthesis of 9-Chloro-5,6,7,8-tetrahydrothieno[3,2-*b*] quinoline 2a–e. General Procedure

To a mixture of **1** (10 mmol) and cyclohexanone (20 mL) was carefully added 30 mL of $POCl_3$ in an ice bath. The mixture was heated under reflux for 5 h, then cooled at room temperature, and concentrated to give a slurry. The residue was diluted with EtOAc, neutralized with aqueous K_2CO_3, and washed with brine. The organic layer was dried over anhydrous K_2CO_3 and concentrated under vacuum.

4.2.1. *9-Chloro-2-phenyl-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline* **2a**

Yield: 55 %; brown solid; mp 172 °C. δ_H ($CDCl_3$, 250 MHz) 1.89 (s, 4H, $2CH_2$); 2.89 (s, 2H, CH_2); 3.01 (s, 2H, CH_2); 7.57–7.62 (m, 3H, 3CH); 7.90–7.93 (m, 3H, 3CH; δ_C ($CDCl_3$, 62.5 MHz) 23.2; 23.6; 24.7; 29.7; 124.1; 126.3; 128.1; 128.9; 129.3; 136.4; 138.2; 139.1; 144.4; 148.8; 161.9. HRMS (APCI): *m/z* [$C_{17}H_{14}ClNS$ + H]$^+$ calcd.: 300.8250; found: 300.8247.

4.2.2. *9-Chloro-2-(4-methylphenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*] quinoline* **2b**

Yield: 69 %; pale-brown solid; mp 185 °C. δ_H ($CDCl_3$, 250 MHz) 1.85 (s, 4H, $2CH_2$); 2.88 (s, 3H, CH_3); 2.96 (s, 2H, CH_2); 3.12 (s, 2H, CH_2); 7.67 (d, J = 8.55 Hz, 2H, 2CH); 7.91 (d, J = 8.55 Hz, 2H, 2CH); 8.00 (s, 1H, CH); δ_C ($CDCl_3$, 62.5 MHz) 21.2; 22.3; 22.7; 30.1; 118.4; 120.1; 124.0; 126.9; 127.5; 135.3; 137.6; 139.1; 139.4; 141.8; 144.1; 161.9. HRMS (APCI): *m/z* [$C_{18}H_{16}ClNS$ + H]$^+$calcd.: 314.8517; found: 314.8517.

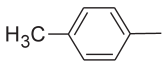
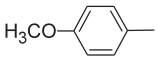
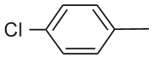
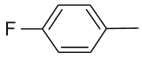
4.2.3. *9-Chloro-2-(4-methoxyphenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*] quinoline* **2c**

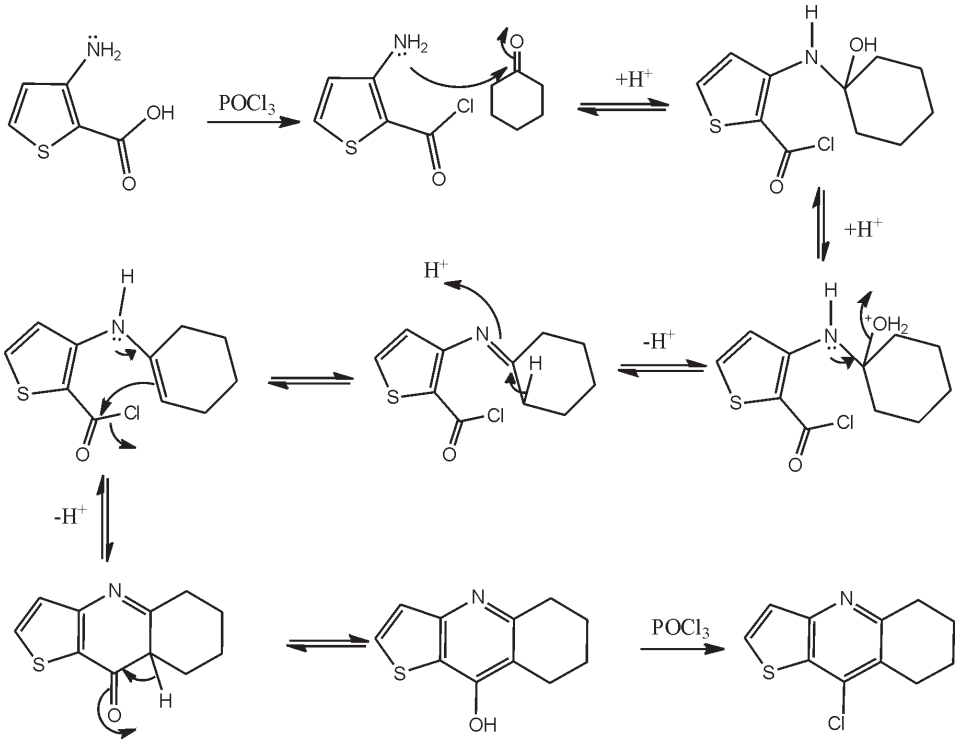
Yield: 71 %; brown solid; mp 155 °C. δ_H ($CDCl_3$, 250 MHz) 1.85 (s, 4H, $2CH_2$); 2.90 (s, 2H, CH_2); 3.03 (s, 2H, CH_2); 3.88(s, 3H, OCH_3); 7.57 (d, J = 8.55 Hz, 2H, 2CH); 7.85 (s, 1H, CH); 7.91 (d, J = 8.55 Hz, 2H, 2CH); δ_C ($CDCl_3$, 62.5 MHz) 38.4; 38.8; 40.1; 40.4; 55.2; 112.9; 113.6; 114.4; 121.3; 126.2; 129.1; 132.1; 138.2; 139.3; 156.6; 179.3.HRMS (APCI): *m/z* [$C_{18}H_{16}ClNOS$ + H]$^+$ calcd.: 330.8511; found: 330.8515.

4.2.4. *9-Chloro-2-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*] quinoline* **2d**

Yield: 56 %; Gris solid; mp 146 °C. δ_H ($CDCl_3$, 250 MHz) 1.87 (s,

Table 1 Starting materials **1a–e**, products **2a–e**, percentages of yields and key ^{1}H and ^{13}C NMR spectroscopic data.

Compound	R	Product	Yield/%	^{1}H NMR, ppm^{13}C				
				C2	C5	C7	C8	C9
1a		**2a**	55	7.57 124.1	3.01 29.7	1.89 24.7	1.89 23.6	2.88 23.2
1b		**2b**	69	8.00 124.0	2.88 30.1	1.85 22.7	1.85 22.3	2.96 21.2
1c		**2c**	71	7.85 112.9	3.03 40.4	1.85 40.1	1.85 38.8	2.90 38.4
1d		**2d**	56	8.04 121.5	3.03 41.4	1.87 41.0	1.87 39.2	2.90 22.1
1e		**2e**	61	8.06 121.1	3.01 41.4	1.85 40.5	1.85 39.7	2.90 21.6



Scheme 2
Proposed mechanism for intramolecular cyclization of thieno[3,2-*b*]quinolone

4H, $2CH_2$); 2.90 (s, 2H, CH_2); 3.03 (s, 2H, CH_2); 7.57 (d, J = 8.55 Hz, 2H, 2CH); 7.91 (d, J = 8.55 Hz, 2H, 2CH); 8.04 (s, 1H, CH) ; δ_C($CDCl_3$, 62.5 MHz) 21.9; 22.1; 39.2; 41.0; 41.4; 121.5; 126.2; 127.7; 127.8; 129.3; 131.5;134.0; 136.0; 145.3; 157.5. HRMS (APCI): m/z[$C_{17}H_{13}Cl_2NS$ + H]$^+$calcd.: 335.2702; found: 335.2707.

4.2.5. *9-Chloro-2-(4-fluorophenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*] quinoline* **2e**

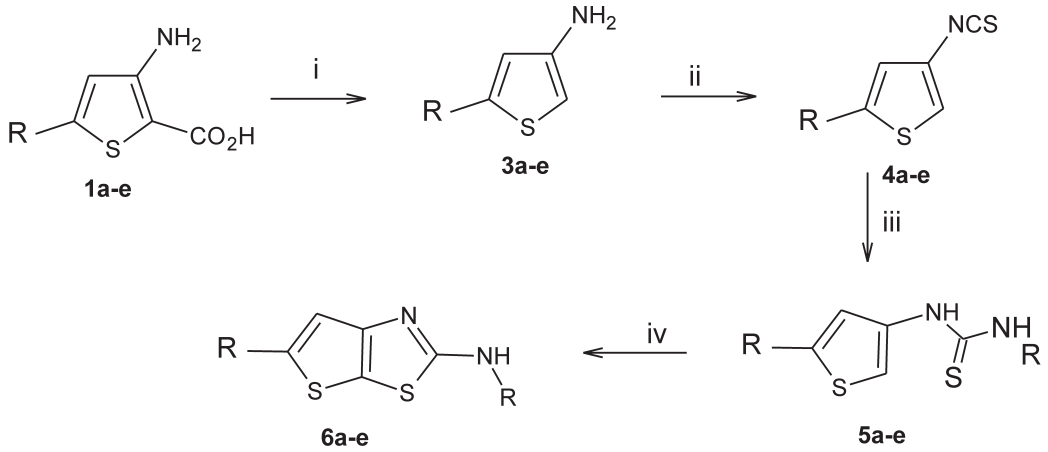
Yield: 61 %; brown solid; mp 117 °C. δ_H ($CDCl_3$, 250 MHz) 1.85 (s, 4H, $2CH_2$); 2.90 (s, 2H, CH_2); 3.01 (s, 2H, CH_2); 7.57 (d, J = 8.55 Hz, 2H, 2CH); 7.89 (d, J = 8.55 Hz, 2H, 2CH); 8.06 (s, 1H, CH) ; δ_C($CDCl_3$, 62.5 MHz) 21.1; 21.6; 39.7; 40.5; 41.4; 121.1; 124.4; 127.7; 127.8; 129.3; 130.5; 134.7; 136.0; 141.3; 157.2 .HRMS (APCI): *m/z* [$C_{17}H_{13}$ ClFNS + H]$^+$ calcd.: 318.8156; found: 318.8150.

4.3. Synthesis of 3-Isothiocyanatothiophene 4a–e; General Procedure

To a stirred suspension of chloroform (21 mL), water (15 mL), sodium hydrogencarbonate (25.0 mmole) andthiophosgene (12.5 mmol), a solution of thiophenamine **3a–e** (25.0 mmol) (**3a–e**) in chloroform (10 mL) was dropwise added during 10 min. The mixture was stirred at room temperature for an additional 2 h, and then it was repeatedly extracted with chloroform (5 × 25 mL). The pooled organics were washed with water, dried over anhydrous sodium sulfate, filtered and rotary evaporated under vacuum.

4.3.1. *4-Isothiocyanato-2-phenylthiophene* **4a**

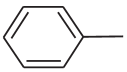
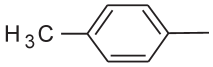
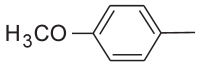
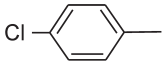
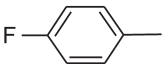
Yield: 78 %; pale-brown solid; mp 98 °C. υ_{max}: 1670 (N=C=S)



R : a = -C_6H_5; **b** = p-MeC_6H_4-; **c** = p-OMe-C_6H_4-; **d** = p-Cl-C_6H_4-; **e** = p-F-C_6H_4-

Scheme 3
Synthesis of substituted thieno[3,2-*d*][1,3]thiazoles. (i) oxalic acid, propanol, 40 °C (ii) $CSCl_2$, $CHCl_3$, 2h ; (iii) *p*-anisidine, CH_2Cl_2, r.t , 16 h; (iv) DDQ, CH_2Cl_2, rt, 1 h.

Table 2 Starting materials **1a–e**, products **6a–e**, percentages of yields and key ^{1}H and ^{13}C NMR spectroscopic data.

Compound	R	Product	Yield/%	^{1}H NMR , ppm ^{13}C		
				C2	C5	C6
1a		**6a**	87	– 166.0	– 141.2	1.89 116.8
1b		**6b**	73	– 166.0	– 154.2	1.85 129.2
1c		**6c**	75	– 162.0	– 138.1	1.85 124.7
1d		**6d**	95	– 181.2	– 138.1	1.87 123.1
1e		**6e**	93	– 159.2	– 138.1	1.85 121.6

cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 7.09 (s, 1H, CH); 7.17 (s, 1H, CH); 7.33–7.43 (m, 3H, 3CH); 7.53–7.57 (m, 3H, 3CH); δ_C ($CDCl_3$, 62.5 MHz) 97.2; 117.5; 124.7; 127.2; 129.0; 134.1; 141.3; 147.1; 161.3.

4.3.2. *4-Isothiocyanato-2-(4-methylphenyl)thiophene* **4b**

Yield: 58 %; brown solid; mp: 56 °C. $\tilde{\upsilon}_{max}$: 1690 (N=C=S) cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 2.30 (s, 3H, CH_3); 7.20 (d, J = 7,5 Hz, 2H, 2CH); 7.50 (s, 1H, CH); 7.54–7.56 (d, J = 7,5 Hz, 2H, CH_2); δ_C($CDCl_3$, 62.5 MHz) 20.6; 120.5; 121.0; 123.2; 125.1; 126.3; 129.7; 132.9; 138.0; 143.0.

4.3.3. *4-Isothiocyanato-2-(4-methoxyphenyl)thiophene* **4c**

Yield: 80 %; pale-brown solid; mp 97 °C. $\tilde{\upsilon}_{max}$: 1560 (N=C=S) cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 3.88 (s, 3H, OCH_3); 6. 90 (s, 1H, CH); 6.94 (s, 1H, CH); 7.04 (d, J =7.5 Hz, 2H, 2CH); 7.45 (d, J = 7.5 Hz, 2H, 2CH); δ_C ($CDCl_3$, 62.5 MHz) 55.4; 114.5; 118.0; 119.4; 125.9; 127.0; 127.6; 131.1; 144.6; 159.9; 143.2.

4.3.4. *2-(4-Chlorophenyl)-4-isothiocyanatothiophene* **4d**

Yield: 84 %; pale-brown solid; mp 80 °C. $\tilde{\upsilon}_{max}$: 1630 (N=C=S) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.02 (s, 1H, CH); 7.06 (s, 1H, CH); 7.31 (d, J =7.5 Hz, 2H, 2CH); 7.40 (d, J = 7.5 Hz, 2H, 2CH); δ_C ($CDCl_3$, 62.5 MHz) 119.2; 120.8; 126.9; 128.0; 129.3; 129.6; 131.6; 134.4; 143.2.

4.3.5. *2-(4-Fluorophenyl)-4-isothiocyanatothiophene* **4e**

Yield: 78 %; pale-brown solid; mp 87 °C. $\tilde{\upsilon}_{max}$: 1730 (N=C=S) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) δ = 7.09 (s, 1H, CH); 7.17 (s, 1H, CH); 7.33–7.43 (m, 3H, 3CH); 7.53–7.57 (m, 3H, CH); δ_C($CDCl_3$, 62.5 MHz) 97.5; 118.1; 126.3; 129.0; 131.6; 132.3; 139.8; 147.4; 161.2.

4.4. Synthesis of 1-(3-Thienyl)thiourea 5a–e; General Procedure

p-Anisidine (5 mmol) was added to a solution of isothiocyanato **4a–e** (1.53 g, 2 eq. mol) dissolved in chloroform (30 mL). The solid was stirred for about 16 h at room temperature and concentrated under reduced pressure. The mixture was filtered, washed with water and anhydrous dicholoromethane, and dried under vacuum to produce the corresponding thiourea **5** at high purity and in high yield. This compound was used directly without further purification.

4.4.1. *1-(4-Methoxyphenyl)-3-(5-phenyl-3-thienyl)thiourea* **5a**

Yield: 83 %; pale-brown solid; mp 160 °C. $\tilde{\upsilon}_{max}$: 3240 (NH), 1170 (C=S) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.73 (s, 3H, CH_3); 6.88 (d, J = 8.8 Hz, 2H, 2CH); 7.30 (m, 3H, 3CH); 7. 38 (m, 2H, 2CH); 7.52 (s, 1H, CH); 7.58 (d, J = 8.8 Hz, 2H, 2CH); 9.62(s, 1H, NH); 9.86 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 55.7; 89.2; 104.6; 114.5; 126.3; 127.2; 129.6;130.6; 130.9; 135.7; 140.1; 156.9; 179.5.HRMS (APCI): *m/z* $[C_{18}H_{16}N_2OS_2 + H]^+$ calcd.: 341.4698; found: 341.4697.

4.4.2. *1-(4-Methoxyphenyl-3-[5-(4-methylphenyl)-3-thiényl] thiourea* **5b**

Yield: 40 %; beige solid; mp: 152 °C. $\tilde{\upsilon}_{max}$: 3160 (NH), 1230 (C=S) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 2.30 (s, 3H, CH_3); 3.60 (s, 3H, OCH_3); 6.85 (d, J = 7.5Hz, 2H, 2CH); 7.22 (d, J = 7.5 Hz, 2H, 2CH); 7.31 (d, J = 7.5 Hz, 2H, 2CH,); 7.46 (s, 1H, CH); 7.48 (d, J = 7.5 Hz, 2H, 2CH); 7.60 (s, 1H, CH); δ_C ($CDCl_3$, 62.5 MHz) 20.7; 55.2; 111.7; 113.6; 114.5; 120.0; 124.9; 126.1; 129.6;130.8; 132.0; 137.2; 138.0; 141.0; 156.5; 179.2. HRMS (APCI): *m/z* $[C_{19}H_{18}N_2O_1S_2 + Na]^+$ calcd.: 377.4782 found: 377.4779.

4.4.3. *1-(4-Methoxyphenyl)-3-[5-(4-methoxyphenyl)-3-thienyl] thiourea* **5c**

Yield: 96 %; pale-brown solid; mp 162 °C. $\tilde{\upsilon}_{max}$: 3050 (NH), 1130 (C=S) cm^{-1}; δ_H($CDCl_3$, 250 MHz) 3.73 (s, 3H, CH_3); 3.77(s, 3H, CH_3); 6.88 (d, J = 7.5 Hz, 2H, 2CH); 6.95 (d, J = 7.5 Hz, 2H, 2CH); 7.29 (s, 1H, CH); 7. 38 (s, 1H, CH); 7.52 (d, J = 7.5 Hz, 2H, 2CH); 9.54 (s, 1H, NH); 9.78(s, 1H, NH); δ_C($CDCl_3$, 62.5 MHz) 53.7; 53.9; 92.1; 103.1; 114.5; 116.0; 127.6; 128.7; 129.2; 130.5; 134.2; 138.1; 159.1; 160.2; 179.1. HRMS (APCI): *m/z* $[C_{19}H_{19}N_2O_2S_2 + H]^+$calcd.: 371.4958 found: 371.4952.

4.4.4. *1-[5-(4-Chlorophenyl)-3-thienyl]-3-(4-methoxyphenyl)thiourea* **5d**

Yield: 95 %; pale-brown solid; mp 168 °C. $\tilde{\upsilon}_{max}$: 3260 (NH), 1270 (C=S) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.88 (s, 3H, CH_3); 6.88 (d, J = 7.5 Hz, 2H, 2CH); 7.29 (d, J = 7.5 Hz, 2H, 2CH); 7.44 (d, J = 7.5 Hz, 2H, 2CH); 7.6 (d, J = 7.5 Hz, 2H, 2CH); 7. 55 (s, 1H, CH); 7.56 (s,

1H, CH); 7.60 (d, J = 7.5 Hz, 2H, 2CH); 9.64 (s, 1H, NH); 9.86 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 55.8; 88.2; 102.1; 114.6; 127.4; 128.8; 129.5; 131.5; 133.2; 133.8; 135.1; 140.3; 157.4; 179.4. HRMS (APCI): *m/z* $[C_{18}H_{15}C_lN_2OS_2 + Na]^+$ calcd.: 397.8967; found: 397.8967.

4.4.5. *1-[5-(4-Fluorophenyl)-3-thienyl]-3-(4-methoxyphenyl) thiourea* **5e**

Yield: 89 %; pale-brown solid; mp 139 °C. $\tilde{\upsilon}_{max}$: 3040 (NH), 1150 (C=S) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.88 (s, 3H, CH_3); 6.88 (d, J = 8.87 Hz, 2H, 2CH); 7.25 (d, J = 8.87 Hz, 2H, 2CH); 7.30 (m, 2H, 2CH); 7.48 (s, 1H, CH); 7.60 (m, 1H, CH); 7.60 (m, 2H, 2CH); 9.65 (s, 1H, NH); 9.89 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 55.3; 88.9; 104.4; 114.6; 117.4; 127.8; 129.5; 131.5; 133.8; 135.1; 139.3; 156.9; 162.3; 179.5. HRMS (APCI): *m/z* $[C_{18}H_{15}FN_2OS_2 + Na]^+$ calcd.: 381.4421; found: 381.4425.

4.5. Synthesis of Thieno[3,2-*d*][1,3]thiazole 6a–e; General Procedure

DDQ (5.5 mmol) was added to a stirred solution of primary thiourea 5a–e (5.0 mmol) in CH_2Cl_2 at room temperature. The progress of the reaction was monitored by TLC. After an hour the precipitate was collected by filtration and thoroughly washed with anhydrous dichloromethane.

4.5.1. *N-(4-Methoxyphenyl)-5-phenylthieno[3,2-*d*][1,3] thiazol-2-amine* **6a**

Yield: 87 %; brown solid; mp 230 °C. $\tilde{\upsilon}_{max}$: 3060 (NH) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.72 (s, 3H, OCH_3); 6.60 (d, J = 8.95 Hz, 2H, 2CH); 6.73 (d, J = 8.95 Hz, 2H, 2CH); 7.1 (s, 1H, CH); 7.22 (m, 3H, 3CH); 7. 40 (m, 2H, 2CH); 9.86 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 56.1; 86.2; 105.9; 116.8; 118.1;119.8; 126.7; 129.9; 135.5; 136.3; 139.0; 141.2; 153.9; 159.5; 166.0. HRMS (APCI): *m/z* $[C_{18}H_{14}N_2O_1S_2 + H]^+$calcd.: 339.4539; found: 339.4534.

4.5.2. *N-(4-Methoxyphenyl)-5(4-methylphenyl)thieno[3,2-*d*][1,3] thiazol-2-amine* **6b**

Yield: 73 %; Gris solid; mp: 264–266 °C. $\tilde{\upsilon}_{max}$: 2950 (NH) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 2.30 (s, 3H, CH_3); 3.72 (s, 3H, OCH_3); 6.92 (d, J = 8.5 Hz, 2H, 2CH); 7.21 (d, J = 8 Hz, 2H, 2CH); 7.52 (d, J = 8 Hz,2H, 2CH,); 7.53 (d, 2H, 2CH, J = 8.5 Hz); 7.6 (s, 1H, CH); 10.16 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 20.7; 55.2; 113.9; 114.2; 118.0;118.8; 124.7; 129.2; 131.5; 134.2; 137.0; 144.0; 154.2; 157.0; 166.0.HRMS (APCI): *m/z* $[C_{19}H_{16}N_2O_1S_2 + H]^+$ calcd.: 353.4805; found: 353.4799.

4.5.3. *N,5-Bis(4-methoxyphenyl)thieno[3,2-*d*][1,3]thiazol-2-amine* **6c**

Yield: 95 %; pale-brown solid; mp 160 °C. $\tilde{\upsilon}_{max}$: 3160 (NH) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.72 (s, 3H, CH_3); 3.77(s, 3H, OCH_3); 6.88 (d, J = 7.5 Hz, 2H, 2CH); 6.95 (d, J = 7.5 Hz, 2H, 2CH); 7.53 (s, 1H, CH); 7.59 (d, J = 7.5 Hz, 2H, 2CH,); 10.15 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 53.7; 53.9; 103.1; 113.8; 116.0; 119.8; 124.7; 129.2; 131.5; 134.2; 138.1; 139.8; 151.2; 159.2; 162.0. HRMS (APCI): *m/z* $[C_{19}H_{16}N_2O_2S_2 + H]^+$ calcd.: 369.4799; found: 369.4796

4.5.4. *5-(4-Chlorophenyl)-N-(4-methoxyphenyl)thieno[3,2-*d*] [1,3]thiazol-2-amine* **6d**

Yield: 75 %; pale-brown solid; mp 224 °C. $\tilde{\upsilon}_{max}$: 2960 (NH) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.15 (s, 3H, OCH_3); 6.90 (d, J = 7.5 Hz, 2H, 2CH); 7.14 (d, J = 7.5 Hz, 2H, 2CH); 7.56 (d, J = 7.5 Hz, 2H, 2CH,); 7.66 (d, J = 7.5 Hz, 2H, 2CH); 7.73 (s, 1H, CH); 10.18 (s, 1H, NH); δ_C ($CDCl_3$, 62.5 MHz) 56.3; 108.2; 115.1; 116.6; 117.4; 123.1; 129.5; 133.5; 137.2; 138.1; 139.1; 149.8; 159.2; 181.2. HRMS (APCI): *m/z* $[C_{18}H_{13}Cl_1N_2O_1S_2 + H]^+$ calcd.: 373.8990; found: 373.8990

4.5.5. *5-(4-Fluorophenyl)-N-(4-methoxyphenyl)thieno[3,2-*d*][1,3] thiazol-2-amine* **6e**

Yield: 93 %; brown solid; mp 90 °C. $\tilde{\upsilon}_{max}$: 2990 (NH) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 3.76 (s, 3H, OCH_3); 6.90 (d, J = 8.8 Hz, 2H, 2CH); 7.21 (m, 2H, 2CH); 7.66 (m, 2H, 2CH); 7.72 (s, 1H, CH); 10.15 (s, 1H, NH); δ_C($CDCl_3$, 62.5 MHz) 55.1; 107.1; 115.1; 117.4; 121.6; 124.7; 129.2; 131.5; 134.2; 138.1; 139.1; 139.8; 151.2; 159.2. HRMS (APCI): *m/z* $[C_{18}H_{13}FN_2O_1S_2 + H]^+$ calcd.: 357.4444; found: 357.4449.

References

1 S.L. Gould, G. Kodis, P.A. Liddell, R.E Palacios, A. Brune, D. Gust, T.A. Moore and A.L. Moore, *Tetrahedron,* 2006, **62**, 2074–2096.
2 Y. Higashio and T. Shoji, *Appl. Catal.,* 2004, **260**, 251–259.
3 I.G. Monterrey, P. Lama, T. Campiglia, P. La Colla, M.V. Diurno, P. Grieco, and E. Novellino, *Arkivoc,* 2004, **5**, 85–96.
4 Y. Ooyama, T. Mamura and K. Yoshida, *Tetrahedron Lett.,* 2007, **48**, 5791–5793.
5 M. Rohwerder and A. Michalik, *Electrochim. Acta,* 2007, **53**, 1300–1313.
6 T.A. Stroganova, A.V. Butin, J.N. Sorotskaya and V.G. Kulńevich, *Arkivoc,* 2000, **4**, 641–659.
7 D. Yue and R.C. Larock, *J. Org. Chem.,* 2002, **67**, 1905–1909.
8 F.E. McDonald, S.A. Burova and L.G. Huffman, *Synthesis,* 2000, 970–974.
9 T.G. Tolstikova, V.A. Davydova, E.E. Shul'ts, G.F. Vafina, G.M. Safarova, F.A. Zarudii, D.N. Lazareva and G.A. Tolstikov, *Khim.-Farm. Zh.,* 1990, **24**, 27–31.
10 Y. Kita, M.Kirihara, J. Sekihachi, R. Okunaka, M Sasho, Sh. Mohri, T. Honda, Sh. Akai, Y. Tamura and K. Shimooka, *Chem. Pharm. Bull.,* 1990, **38**, 1836–1840.
11 Y. Ohba, Y. Murakami, T. Sone and H. Awano, *J. Heterocycl. Chem.,* 1997, **34**, 787.
12 X. Deng and L.S. Liebeskind, *J. Am. Chem. Soc.,* 2001, **123**, 7703–7704.
13 C.A. Boateng, S.V.K. Eyunni, X.Y. Zhu, J.R. Etukala, B.A. Bricker, M.K. Ashfaq, M.R. Jacob, S.I., Khan, L.A. Walker and S.Y. Ablordeppey, *Bioorg. Med. Chem.,* 2011, **19**, 458–470.
14 M.M. Ghorab, S.G. Abdel-Hamid and A.F. Hala, *Drug Res.,* 2001, **58**,175–184.
15 G. Revelant, S, Hesse and G. Kirsch,*Tetrahedron.,* 2011, **67**, 9352–9357.
16 H.L.K. Stanton, R. Gambari, C.H. Chui, M.C.W. Yuen, E. Lin, R.S.M. Wong, F.Y. Lau, G.Y.M. Cheng, W.S. Lam, S.H. Chan, K.H. Lam, C.H. Cheng, P.B.S. Lai, M.W.Y. Yu, F. Cheung, J.C.O. Tang and A.S.C.Chan, *Bioorg. Med. Chem.,* 2008, **16**, 3626–3631.
17 D. Subhas Bose and I. Mohd, *Tetrahedron Lett.,* 2007, **48**, 669–672.
18 E. Migianu and G. Kirsch, *Synthesis,* 2007, 1096–1102.
19 D. Thomae, G. Kirsch and P. Seck, *Synthesis,* 2007, 1027–1032.
20 D. Thomae, G. Kirsch and P. Seck, *Synthesis,* 2007, 2153–2156.
21 I. Abdillahi, G. Revelant, Y. Datoussaid and G. Kirsch, *Synthesis,* 2010, 2543–2546.