Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 06 May 2010.

To cite this article: A. M. Khalil , M. A. Berghot , Ghada E. Abd El-Ghani & M. A. Gouda (2010): Synthesis and Antimicrobial Evaluation of Some New Thiophene Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:11, 1658-1669

To link to this article: http://dx.doi.org/10.1080/00397910903161652

Synthetic Communications®, 40: 1658–1669, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903161652

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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW THIOPHENE DERIVATIVES

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2-(2-Cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide(3) was used as starting material for synthesis of 4-thiazolidinone, thiazolidine, and thiophene derivatives 6, 7a, b, and 8a, b, respectively. Thiocarbomyl derivative 5, 4-thizolidinone 9, and thioxothiazolidine 10 were obtained from reaction of 3 with thioglycolic acid and phenyl isothiocyanatelsulfur, respectively. Condensation of 3 with selected cyclic ketones and aromatic aldehydes yielded the arylidine derivatives 11a, b and 13, respectively. Refluxing of 11a, b with sulfur and morpholine yielded the thiophene derivatives 12a, b, respectively. Diazocoupling of compound 3 with p-tolyl diazonium chloride yielded the hydrazone derivative 14. The newly synthesized compounds were characterized by infrared, ^{1}H NMR, and mass spectral studies. Representative compounds of the synthesized product were tested and evaluated as antimicrobial agents. Compound 12b gives very high antimicrobial activity against Ampicillin.

Keywords: Ampicillin; antimicrobial evaluation; thiazolidine; thiazolidinone; thiophene; thiophene derivatives

INTRODUCTION

Substituted 2-aminothiophene are important intermediates, extensively studied because of their biological activities,[1] that have recently found application in the syntheses of compounds such as allosteric enhancers of adenosine A_1 receptor,[2] antibacterial compounds,[3] GABAB allosteric enhancers for treating central nervous system disorders,[4] kinase inhibitors,[5] and more recently as antitubercular drugs against *Mycobacterium* tuberculosis H37RV[6] and as anti-Alzheimer drugs.[7] In view of these findings and in continuation of our efforts to design new, potent, selective, and antimicrobial compounds, we report here the synthesis of some new heterocyclic systems incorporated with the thiophene moiety, starting from 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**3**),[8] in order to investigate their antimicrobial activity.

Received February 10, 2009.

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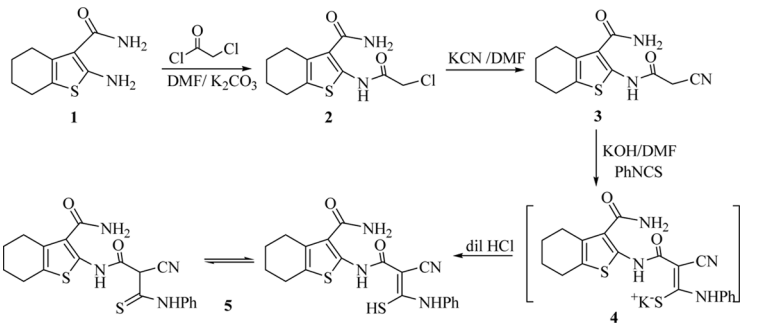
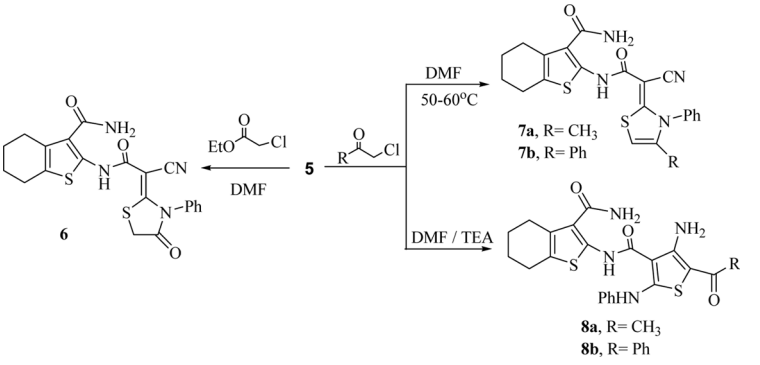
RESULTS AND DISCUSSION

Chemistry

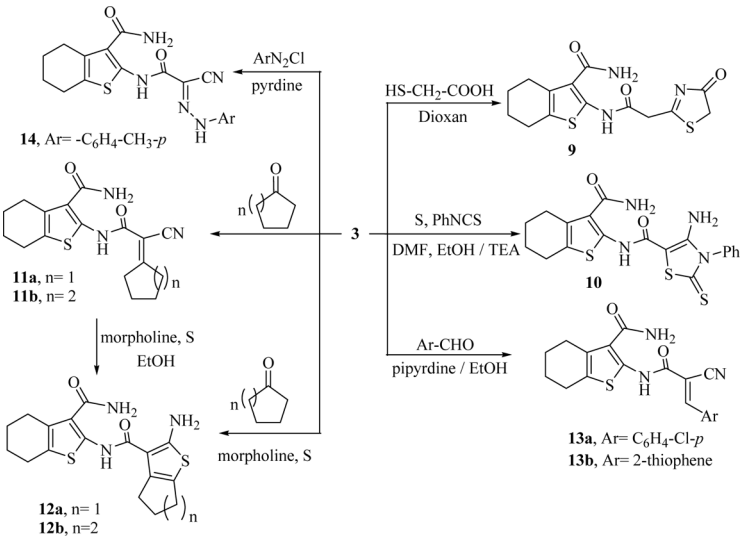
The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1–3. The starting compound 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide **(3)**[8] was obtained by treatment of **1** with chloroacetyl chloride[9] and subsequent treatment with potassium cyanide in dimethylformamide (DMF). The structure of compound **3** was established by spectral data. The infrared (IR) spectrum showed a characteristic absorption band at 2242 cm^{-1} due to the CN group. The ^1H NMR spectrum revealed the presence of a singlet signal, equivalent to two protons at δ 4.14 ppm, which represents the methylene protons of the cyanoacetamide group. Moreover, the mass spectrum exhibited the molecular ion peak at m/z 263, which is in agreement with the molecular formula $C_{12}H_{13}N_3O_2S$. In view of the synthetic importance of thiocarbomyl derivatives[10–20] and the biological results of compounds that contain thiazolidinone,[20,21] thiazolidine,[21,22] and thiophene[23] moieties, our attention was directed to incorporating the benzo[b]thiophene nucleus into these ring systems. Thus, the base-catalyzed reaction of compound **3** with phenyl isothiocyanate yielded the nonisolable potassium



Scheme 1.



Scheme 2.



Scheme 3.

salt of thiocarbamoyl derivative **3**, which was then acidified with dilute hydrochloric acid to afford the thiocarbamoyl derivative **5** (Scheme 1).

The reaction of **5** with ethyl choroacetate, chloroacetone, or phenancyl chloride in DMF under refluxing conditions afforded the corresponding thiazolidinone and thiazolidine derivatives **6** and **7a**, **b**, respectively. The analytical and spectral data are in agreement with the proposed structure. Thus, the IR spectrum of compound **6** showed an absorption band at 1737 cm^{-1} due to the carbonyl group of thiazolidin-4-one nucleus, and the ^1H NMR spectrum displayed a singlet signal, equivalent to two protons at 4.15 ppm, which represented to C_5 protons of thiazolidin-4-one nucleus. Moreover, the IR spectrum of compounds **7a** and **7b** showed the presence of an NH group in the 3448–3065 cm^{-1} region, a cyano group in the 2179–2178 cm^{-1} region, and two carbonyl groups in the 1669–1655 cm^{-1} region, whereas the reaction of **5** with chloroacetone or phenacyl chloride in DMF and in the presence of a catalytic amount of triethylamine (TEA) yielded thiophene derivatives **8a**, **b**. The structures of compounds **8a** and **8b** were established by spectral data. The IR spectrum of compound **8a** showed the absence of the typical cyano group at the region 2187 cm^{-1}, indicating that the cyano group was lost during the reaction. The ^1H NMR revealed three singlet signals at 1.85, 10.9, and 12 ppm due to CH_3, NHPh, and NHCO protons, respectively (Scheme 2).

On the other hand, 2-[4-oxothiazolidinone]-cyanoacetamido derivative **9** was obtained by the reaction of **3** with thioglycolic acid through modification of the previously reported method for the synthesis of analogs.[24–27] The ^1H NMR spectrum of compound **9** revealed the presence of methylene protons of the thiazolidinone ring at δ 4.09 ppm, while its mass spectrum exhibited the molecular ion peak at m/z 368 (M^+), corresponding with the molecular formula $C_{13}H_{15}N_3O_3S_2$. In view of the growing biological importance of the 4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole derivative,[24] we decide to synthesize novel derivatives. Thus,

stirring **3** with sulfur and phenyl isothiocynate in a mixture of DMF and absolute ethanol containing a catalytic amount of triethylamine at 60 °C yielded the corresponding 2-[2-thioxothiazoline]-cyanoacetamido derivative **10**. The mass spectrum of **10** exhibited the molecular ion peak at m/z 430 (M^+), corresponding to the molecular formula $C_{19}H_{18}N_4O_2S_3$.

2-[2-Cycloalkylidene]-cyanoacetamido derivatives **11a**, **b** were prepared by condensation of compound **3** with the appropriate cyclic ketone in ethanol and sodium acetate. Treatment of compounds **11a** or **11b** with elemental sulfur in absolute ethanol containing morpholine as catalyst under refluxing conditions yielded **12a** and **12b**, respectively. Compounds **12a** and **12b** were also obtained directly by one-pot Gewald reaction of **3** with the same selected cyclic ketones and elemental sulfur in ethanol containing morpholine. Mass spectrum of **12b** exhibited the molecular ion peak at m/z 375 (M^+), corresponding to the molecular formula $C_{18}H_{21}N_3O_2S_2$. Similarly, 2-[2-arylidene]cyanoacetamido derivatives **13a, b** were obtained by condensation of **3** with the appropriate aromatic aldehyde in ethanol containing a catalytic amount of pipridine. The ^{1}H NMR spectra of **13a, b** revealed signals at δ 8.43 and 8.59 ppm, respectively, due to a methine proton. The mass spectrum of compound **13a** exhibited the molecular ion peak at m/z 385 (M^+), corresponding to the molecular formula $C_{18}H_{16}N_3O_2SCl$. Diazo coupling of compound **3** with of *p*-tolyldiazonium chloride in pyridine yielded the hydrazone derivative **14**. The IR and the ^{1}H NMR spectra of compound **14** revealed the existence of two possible tautomeric forms, −CH(CN)−N=N−Ar and −C(CN)=N−NH−Ar. The IR spectrum showed NH stretching absorption at 3166 cm^{-1} and N=N at 1527 cm^{-1}. Also, the ^{1}H NMR spectrum revealed NH signals at δ 12.3 and 13.3 ppm (Scheme 3).

Pharmacology

Antimicrobial evaluation. Ten compounds were screened in vitro for their antimicrobial activities against two strains of bacteria, *Bacillus thuringiensis* and *Klebsiella pneumoniae*, and two strains of fungi, *Botrytis fabae* and *Fusarium oxysporum*, by the agar diffusion technique.[28] A 0.15 mg/ml solution in dimethylsulfoxide (DMSO) was used. The bacteria and fungi were maintained on nutrient agar and Czapek–Dox agar media, respectively. DMSO showed no inhibition zones. The agar media were incubated with different microorganism cultures. After 24 h of incubation at 30 °C for bacteria and 72 h of incubation at 28 °C for fungi, the diameter of inhibition zone (mm) was measured (Table 1). Ampicillin from the Egyptian market used in a concentration of 25 μg/ml was as reference for antibacterial and antifungal activities. The results for antibacterial activities are depicted in Table 1.

The results depicted in Table 1 reveal that most of the synthesized compounds showed good antimicrobial activity, especially compounds **10**, **12b**, and **13c**, with respect to the reference chemotherapeutic. It is worth mentioning that incorporation of the thiophene or thiazole nucleus to 4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide nucleus produced high antimicrobial activity. In conclusion, we report herein a simple and convenient route for the synthesis of some new heterocycles based on 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide **(3)** for antimicrobial evaluation.

Table 1. Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial and antifungal activities of the newly synthesized compounds

	Bacteria		Fungi	
Compound	Gram-positive bacteria *Bacillus Theringiensis*	Gram-negative bacteria *K. Pneumoniae*	*B. Fabe*	*F. Oxysporum*
6	20	17	14	12
7a	24	20	20	—
7b	20	19	17	13
8a	20	17	17	12
8b	18	15	13	11
9	23	20	20	—
10	22	19	20	18
12a	17	15	15	11
12b	25	22	23	20
13c	24	20	22	19
Reference drugs Ampicillin	18	19	17	15

EXPERIMENTAL

All melting points are recorded on a Gallenkamp electric melting-point apparatus and are uncorrected. The IR spectra ν cm^{-1} (KBr) were recorded on a Perkin-Elmer IR spectrophotometer (model 157, Grating). The ^1H NMR spectra were obtained on a Varian spectrophotometer at 200 MHz using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as solvent. The mass spectra (EI) were recorded at 70 eV with Kratos MS equipment and/or a Varian MAT 311 A spectrometer. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The results were found to be in good agreement (±0.3%) with the calculated values. Microbiology screening was carried out in the Botany Department, Faculty of Science, Mansoura University, under the supervision of Prof. Dr. Yhia A. O. Ellazeik and Dr. Ehab Ali Metwally.

Synthesis of 2-(2-Cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (3)

Chloroacetylamino derivative **2** (1.09 g, 4 mmol) was dissolved in DMF (20 cm^3), and the resulting clear solution was heated to 70 °C. The latter was added cautiously and gradually to a solution of potassium cyanide (0.26 g, 4 mmol) in 5 cm^3 water with stirring. Addition was controlled so that the temperature of the reaction mixture was maintained at 70 °C. After the complete addition to the cyanide solution, stirring was continued for a further 15 min, and then the reaction mixture was cooled and added in portions to an ice-cooled solution of hydrochloric acid (2 cm^3 of conc. HCl in 100 cm^3 H_2O). The precipitate was filtered off and recrystallized from ethanol to give compound **3**: brown powder; yield 70%; mp 175 °C; IR (KBr) $\nu_{max.}$ cm^{-1}: 3436, 3342, 3268 (NH), 2242 (CN) and 1677, 1643 (2C=O);

^{1}H NMR (DMSO-d_6) δ ppm: 1.75 (m, 4H, C_5-2H, C_6-2H), 2.51 (s, 2H, C_4-2H), 2.66 (s, 2H, C_7-2H), 7.38 (s, 2H, NH_2), and 11.66 (s, 1H, NH); MS: m/z (%) 263 (M^+, 40.6), 246 (78.4), 206 (100), 178 (24.5), 151 (27.4), 123 (11.9), 91 (16.4) and 68 (40.4). Anal. calcd. for $C_{12}H_{13}N_3O_2S$ (263.32): C, 54.74; H, 4.98; N, 15.96%. Found: C, 54.80; H, 5.13; N, 16.1%.

Synthesis of 2-(2-Cyano-2-phenylthiocarbamoyl-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (5)

An equimolar mixture of cyanoacetamide derivative **3** (1.05 g, 4 mmol) and KOH (0.22 g, 4 mmol) in dry dimethylformamide (10 cm^3) was stirred for 30 min, and then phenyl isothiocyanate (0.54 gm, 4 mmol) was added. The mixture was stirred at room temperature overnight, then poured into ice-cold water and acidified with 0.1 N HCl to pH 3–4. The resulting precipitate was filtered off, dried, and crystallized from aqueous ethanol to give compound **5**; yellow crystals; yield 60%; mp 212 °C; IR (KBr) $\nu_{max.}$ cm^{-1}: 3384, 3324, 3197 (NH), 2187 (CN), and 1629 (br, 2C=O); ^{1}H NMR (DMSO-d_6) δ ppm; 1.71 (m, 4H, C_5-2H, C_6-2H), 2.52 (m, 2H, C_4-2H), 2.54 (m, 2H, C7–2H), 6.91–7.73 (m, 7H, Ar-H, CH, NH), and 13.3 (s, 1H, NH); MS: m/z (%) (246) (M^+-C_7H_7SN), 222 (17.4), 206 (51.8), 179 (38.8), 151 (35.8), 135 (28.8), 93 (100), and 51 (86.6). Anal. calcd. for $C_{19}H_{18}N_4O_2S_2$ (398.50): C, 57.27; H, 4.55; N, 14.06%. Found: C, 57.42; H, 4.74; N, 14.23%.

Synthesis of 2-[2-Cyano-2-(3-phenyl-thiazolidin-2-ylidene)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide Derivatives (6, 7a, 7b)

Purified thiocarbamoyl derivative **5** (1.594 g, 4 mmol) was dissolved in dimethylformamide (20 cm^3), and the appropriate α-halogenated compounds (4 mmol) were added. The reaction mixture was heated under reflux for 6 h, cooled, and neutralized with saturated sodium carbonate solution. The resulting precipitate was filtered off, dried, and crystallized from benzene–ethanol.

2-[2-Cyano-2-(4-oxo-3-phenyl-thiazolidin-2-ylidene)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (6). Brown crystals; yield 70%; mp 187 °C; IR (KBr) $\nu_{max.}$$cm^{-1}$: 3384, 3324, 3197 (NH), 2187 (CN) and 1737, 1629 (br) (3C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.73 (m, 4H, C_5-2H, C_6-2H), 2.55 (m, 2H, C_4-2H), 2.64 (m, 2H, C_7-2H), 4.15 (s, 2H, CH_2CO), 7.10–7.49 (m, 6H, Ar-H, NH_2), and 11.3 (s, 1H, NH). Anal. calcd. for $C_{21}H_{18}N_4O_3S_2$ (438.52): C, 57.52; H, 4.14; N, 12.78%. Found: C, 57.71; H, 4.32; N, 12.68%.

2-[2-Cyano-2-(4-methyl-3-phenyl-3*H*-thiazol-2-ylidene)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (7a). Brown crystals; yield 70%; mp 253 °C; IR (KBr) $\nu_{max.}$$cm^{-1}$: 3388, 3339, 3187 (NH), 2179 (CN), 1669 (br, 2C=O); ^{1}H NMR (DMSO-d_6) δ ppm; 1.71 (m, 4H, C_5-2H, C_6-2H), 1.85 (s, 3H, CH_3), 2.58 (m, 2H, C_4-2H), 2.66 (m, 2H, C_7-2H), 6.98 (s, 1H, thiazolidine C_5-H), 7.51–7.59 (m, 7H, Ar-H, NH_2), and 12.02 (s, 1H, NH). Anal. calcd. for $C_{22}H_{20}N_4O_2S_2$ (436.55): C, 60.53; H, 4.62; N, 12.83%. Found: C, 60.73; H, 4.87; N, 12.92%.

2-[2-Cyano-2-(3,4-diphenyl-3*H*-thiazol-2-ylidene)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (7b). Brown crystals; yield 70%; mp 275 °C; IR (KBr) $\nu_{max.}$cm^{-1}: 3419, 3400, 3256 (NH), 2178 (CN), 1655 (br, 2C=O); ^{1}H NMR (DMSO-d$_6$) δ ppm: 1.77 (m, 4H, C$_5$-2H, C$_6$-2H), 2.59 (m, 2H, C$_4$-2H), 2.73 (m, 2H, C$_7$-2H), 7.16 (s, 1H, thiazolidine C$_5$-H), 7.23–7.55 (m, 12H, Ar-H, NH$_2$), and 11.02 (s, 1H, NH). Anal. calcd. for $C_{27}H_{22}N_4O_2S_2$ (498.62): C, 65.04; H, 4.45; N, 11.24%. Found: C, 65.21; H, 4.39; N, 11.50%.

Synthesis of 2-[(5-Substituted-4-amino-2-phenylamino-thiophene-3-carbonyl)-amino]-4,5,6,7–tetrahydro-benzo[b]thiophene-3-carboxamide (8a, b)

A mixture of compound **5** (1.594 g, 4 mmol) and α-halogenated compounds (0.04 mmol) in dimethylformamide (20 cm^3) in the presence of a catalytic amount of triethylamine (0.2 cm^{-3}) was refluxed for 6 h. Then, the reaction mixture was cooled, and the resulting precipitate was filtered off, dried, and crystallized from benzene–ethanol.

2-[(5-Acetyl-4-amino-2-phenylamino-thiophene-3-carbonyl)-amino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (8a). Brown crystals; yield 70%; mp 243 °C; IR (KBr) $\nu_{max.}$cm^{-1}: 3331, 3257, 3189 (NH), 1641, 1654, 1747 (br, 3C=O); ^{1}H NMR (DMSO-d$_6$) δ ppm: 1.73 (m, 4H, C$_5$-2H, C$_6$-2H), 1.85 (s, 3H, COCH$_3$), 2.59 (m, 2H, C$_4$-2H), 2.71 (m, 2H, C$_7$-2H), 6.98–7.6 (m, 7H, Ar-H, NH$_2$), 10.9 (s, 1H, NH), and 12.0 (s, 1H, NH). Anal. calcd. for $C_{22}H_{22}N_4O_3S_2$ (454.57): C, 58.13; H, 4.88; N, 12.33%. Found: C, 58.02; H, 4.82; N, 12.19%.

2-[(5-Benzoyl-4-amino-2-phenylamino-thiophene-3-carbonyl)-amino]-4,5,6,7–tetrahydro-benzo[b]thiophene-3-carboxamide (8b). Brown crystals; yield 70%; mp 250 °C; IR (KBr) $\nu_{max.}$cm^{-1}: 3412, 3062 (NH), 1748, 1633 (br, 3C=O); ^{1}H NMR (DMSO-d$_6$) δ ppm; 1.73 (m, 4H, C$_5$-2H, C$_6$-2H), 2.64 (m, 2H, C$_4$-2H), 2.70 (m, 2H, C$_7$-2H), 7.08–8.10 (m, 7H, Ar-H, NH$_2$), 8.2 (br, 1H, NH) and 12.6 (s, 1H, NH). Anal. calcd. for $C_{27}H_{24}N_4O_3S_2$ (516.63): C, 62.77; H, 4.68; N, 10.84%. Found: C, 62.68; H, 4.59; N, 10.72%.

Synthesis of 2-[2-(4-Oxo-4,5-dihydro-thiazol-2-yl)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (9)

Thioglycolic acid (0.368 g, 4 mmol) was added to a solution of compound **3** (1.05 g, 4 mmol) in dioxane (20 cm^3). The reaction mixture was heated under reflux for 10 h and then left to cool to room temperature. The separated crystalline product was filtered off, dried, and crystallized from benzene–ethanol to give compound **9.** Yellow crystals; yield 65%; mp 314 °C; IR (KBr) $\nu_{max.}$cm^{-1}: 3444, 3309, 3168 (NH) and 1698, 1645 (2C=O); ^{1}H NMR (DMSO-d$_6$) δ ppm; 1.73 (m, 4H, C$_5$-2H, C$_6$-2H), 2.62 (m, 2H, C$_4$-2H), 2.66 (m, 2H, C$_7$-2H), 4.12 (s, 2H, CH$_2$ thiazolidinone), 7.40 (m, 2H, NH$_2$), and 11.61 (s, 1H, NH); MS: m/z (%) 368 (M$^+$, 17.1), 337 (34.3), 245 (22.9), 218 (25.7), 196 (82.9), 179 (100), 151 (57.1), 121 (20), 93 (37.1), and 68 (65.7). Anal. calcd. for $C_{14}H_{15}N_3O_3S_2$ (337.42): C, 49.83; H, 4.48; N, 12.45%. Found: C, 49.98; H, 4.62; N, 12.69%.

Synthesis of 4-Amino-3-phenyl-2-thioxo-2,3-dihydro-thiazole-5-carboxylic Acid (3-Carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (10)

A mixture of compound **3** (1.05 g, 4 mmol), finely divided sulfur (0.128 g, 4.4 mmol), and triethylamine (four drops) in DMF (20 cm^3) and ethanol (2:1) was stirred at 60 °C for 30 min. The phenyl isothiocyanate (0.54 g, 4 mmol) was gradually added, and stirring was continued for 4 h. The separated crystalline product was filtered off, dried, and crystallized from benzene–ethanol to yield compound **10**. Pale yellow crystals; yield 75%; mp 258 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3451, 3396, 3324, 3255, 3178 (NH) 1625 (br, 2C=O) and 1341 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 1.76 (m, 4H, C_5-2H, C_6-2H), 2.64 (m, 2H, C_4-2H), 2.75 (m, 2H, C_7-2H), 7.00 (br., 2H, NH_2), 7.41–7.62 (m, 5H, Ar-H) and 12.29 (s, 1H, NH); MS: m/z (%) 430 (M^+, 16.9), 413 (19.1), 371 (15.2), 235 (32.4) 196 (33.8), 179 (53.7), 151 (22.8), 135 (45.6), 104 (34.6), 77 (100), 51 (61.8). Anal. calcd. for $C_{19}H_{18}N_4O_2S_3$ (430.57): C, 53.00; H, 4.21; N, 13.01%. Found: C, 53.26; H, 4.32; N, 13.17%.

Synthesis of 2-(2-Cyano-2-[cycloalkylidene]acetamido)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide Derivatives (11a, b)

A mixture containing compound **3** (1.05 g, 4 mmol), sodium acetate (0.328 g, 4 mmol), and cycloalkanone (4 mmol) was refluxed in absolute ethanol (30 cm^3) for 6 h and left to cool at room temperature. The separated crystalline product was filtered, washed with water, dried, and recrystallized from DMF–methanol to give compounds **11a**, **b**.

2-(2-Cyano-2-cyclopentylidene-acetylamino)-4,5,6,7-tetrahydro-benzo[b] thiophene-3-carboxamide (11a). Brown crystals; yield 75%; mp 243 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3420, 3253, 3186, (NH), 2214 (CN) and 1668, 1631 (2C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.76 (m, 8H, C_5-2H, C_6-2H, 'C_3-2H, 'C_4-2H), 2.65 (m, 6H, C_4-2H, 'C_2-2H, 'C_5-2H,), 2.78 (m, 2H, C_7-2H), 7.56 (s, 2H, NH_2), and 12.79 (s, 1H, NH); MS: m/z (%): 312 (M^+, 100), 179 (79.6), 134 (36.1), 79 (73.3). Anal. calcd. for $C_{17}H_{19}N_3O_2S$ (329.42): C, 61.98; H, 5.81; N, 12.76%. Found: C, 62.02; H, 5.94; N, 12.93%.

2-(2-Cyano-2-cyclohexylidene-acetylamino)-4,5,6,7-tetrahydro-benzo[b] thiophene-3-carboxamide (11b). Brown crystals; yield 75%; mp > 320 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3430 (br, NH), 2184 (CN), and 1646 (br, 2C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.73–1.86 (m, 10H, C_5-2H, C_6-2H, 'C_3-2H, 'C_4-2H, 'C_5-2H), 2.54 (m, 6H, C_4-2H, 'C_2-2H, 'C_6-2H), 2.67 (m, 2H, C_7-2H), 6.99 (s, 2H, NH_2), and 13.00 (s, 1H, NH). Anal. calcd. for $C_{18}H_{21}N_3O_2S$ (343.44): C, 62.95; H, 6.16; N, 12.23%. Found: C, 62.85; H, 6.07; N, 12.20%.

Synthesis of Thiophene Derivatives 12a, b

Method A. Morpholine (0.33 cm^3), elemental sulfur (0.141 g, 4.4 mmol), and cycloalkanone (4 mmol) were added to solution of compound **3** (1.05 g, 4 mmol) in absolute ethanol (20 cm^3). The reaction mixture was heated under reflux at

60–80 °C for 3 h and left to cool to room temperature. The separated crystalline product was filtered, dried, and recrystallized from DMF–acetone to give compounds **12a**, **b**.

Method B. 2-Cycloalkylideneacetamido derivatives **11a** (1.318 g, 4 mmol) or **11b** (1.374 g, 4 mmol), morpholine (0.33 cm^3), and elemental sulfur (0.141 g, 4.4 mmol) in absolute ethanol (20 cm^3) were stirred at 60–80 °C for 3 h. The reaction mixture allow to cool at room temperature; the separated crystalline product was filtered, dried, and recrystallized from the proper solvent to give compounds **12a**, **b**.

2-[(2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carbonyl)-amino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (12a). Brown crystals; yield 75%; mp > 320 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3395, 3194 (NH), 2204 (CN), and 1633 (br, 2C=O); ^{1}H NMR (DMSO-d_6) δ ppm; 1.72 (m, 6H, C_5-2H, C_6-2H, 'C_5-2H), 2.62 (m, 4H, C_4-2H, 'C_4-2H), 2.71 (m, 4H, C_7-2H, 'C_6-2H), 7.06–7.93 (br, 4H, $2NH_2$), and 11.65 (s, 1H, NH). Anal. calcd. for $C_{17}H_{19}N_3O_2S_2$ (361.48): C, 56.48; H, 5.30; N, 11.62%. Found: C, 56.63; H, 5.45; N, 11.81%.

2-[(2-Amino-5,6-dihydro-4*H*-cyclohexa[b]thiophene-3-carbonyl)-amino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (12b). Brown crystals; yield 75%; mp 243 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3444, 3397 (NH) and 1637 (br, 2C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.75 (m, 8H,C_5-2H, 'C_5-2H, C_6-2H, 'C_6-2H), 2.63 (m, 4H, C_4-2H, 'C_4-2H), 2.73 (m, 4H, C_7-2H, 'C_7-2H), 7.43 (s, 2H, NH_2), and 11.73 (s, 1H, NH); MS m/z (%): 375 (M^+, 33), 358 (37), 196 (30.8), 180 (100), 151 (20.4), 91 (17.9), 65 (11.1). Anal. calcd. for $C_{18}H_{21}N_3O_2S_2$ (375.51): C, 57.57; H, 5.64; N, 11.19%. Found: C, 57.64; H, 5.79; N, 11.35%.

Synthesis of 2-[3-(Aryl)-2-cyano-acryloylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (13a, b)

A well-stirred solution of compound **3** (1.05 g, 4 mmol) in absolute ethanol (20 cm^3), piperidine (0.2 cm^3), and appropriate aromatic aldehyde (4 mmol) were added to the solution. The reaction mixture was stirred at 80 °C for 3 h, during which time crystals separated out. The crystalline product was filtered, washed with ethanol, dried, and recrystallized from ethanol–benzene to give compounds **13a**, **b**.

2-[3-(4-Chloro-phenyl)-2-cyano-acryloylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (13a). Yellow crystals; yield 65%; mp 285 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3430, 3289, 3270 (NH), 2213 (CN), and 1668, 1639 (2C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.78 (m, 4H, C_5-2H, C_6-2H), 2.52 (m, 2H, C_4-2H), 2.90 (m, 2H, C_7-2H), 7.36 (br, 2H, NH_2), 7.68–8.43 (m, 5H, Ar.H, =CH), and 13.16 (s, 1H, NH); MS m/z (%): 385 (M^+, 46.5), 368 (100), 333 (30.2), 305 (14.1), 206 (15), 190 (66.8), 162 (54.1), 127 (48.3), 91 (19.9), 75 (25.2). Anal. calcd. for $C_{18}H_{16}N_3O_2SCl$ (385.87): C, 59.14; H, 4.18; N, 10.89%. Found: C, 59.32; H, 4.29; N, 10.98%.

2-(2-Cyano-3-thiophen-2-yl-acryloylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (13b). Yellow crystals; yield 65%; mp 280 °C; IR (KBr) $\nu_{max.}cm^{-1}$: 3432, 3317, 3253, 3190 (NH), 2208 (CN), and 1661, 1633 (2C=O); ^{1}H

NMR (DMSO-d_6) δ ppm: 1.74 (m, 4H, C_5-2H, C_6-2H), 2.52 (m, 2H, C_4-2H), 2.65 (m, 2H, C_7-2H), 7.38–8.17 (m, 6H, Ar-H, NH_2), 8.59 (s, 1H, CH=C), and 13.01 (s, 1H, NH). Anal. calcd. for $C_{17}H_{15}N_3O_2S_2$ (357.45): C, 57.12; H, 4.23; N, 11.76%. Found: C, 57.41; H, 4.36; N, 11.92%.

2-[2-Cyano-2-(*p*-tolyl-hydrazono)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic Acid Amide (14)

Preparation of the diazonium salt. A solution of sodium nitrite (0.283 g, 4.1 mmol, in 2 cm^3 water) was gradually added to a well-cooled solution of *p*-toluidine (0.429 g, 4 mmol) in conc. hydrochloric acid [(1.5 cm^3) in water (2 cm^3)]. The diazonium salt solution was added dropwise with continuous stirring to a cold solution of **3** (1.05 g, 4 mmol) in pyridine (10 cm^3). The reaction mixture was stirred at 0–5 °C for 2 h and left to stand at room temperature. The solid products that obtained were filtered off, dried, and recrystallized from ethanol to give compound **14**: orange powder; yield 80%; mp 300 °C; IR (KBr) $\nu_{max.}$ cm^{-1}: 3166, 3237, 3315, 3409, 3432 (NH), 2215 (CN) 1656 (br, 2C=O), and 1527 (N=N); ^{1}H NMR (DMSO-d_6) δ ppm: 1.76 (m, 4H, C_5-2H, C_6-2H), 2.32 (s, 3H, CH_3), 2.65 (m, 2H, C_4-2H), 2.76 (m, 2H, C_7-2H), 7.2–7.9 (m, 6H, Ar-H, NH_2), 12.26 (br, 1H, NH), 12.89 (s, 1/2 H, NH=N), and 13.25 (s, 1/2 H, NH=N); MS: m/z (%) 381 (M^+, 52.2), 331 (19.8), 179 (43.8), 91 (100). Anal. calcd. for $C_{19}H_{19}N_5O_2S$ (381.45): C, 59.82; H, 5.02; N, 18.36%. Found: C, 59.74; H, 4.91; N, 18.16%.

ACKNOWLEDGMENTS

We express our sincere thanks to Prof. Dr. Yhia A. O. Ellazeik and Dr. Ehab Ali Metwally, Botany Department, Faculty of Science, Mansoura University, for microbiological screening.

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