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Original article

Synthesis and antimicrobial activities of some new thiazole and pyrazole derivatives based on 4,5,6,7-tetrahydrobenzothiophene moiety

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ABSTRACT

2-(5-oxothiazolidinone)-cyanoacetamido derivative **3** was prepared in two steps by reaction of 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**1**) with phenyl isothiocyanate and chloroacetyl chloride, which diazocoupled with *p*-tolyldiazonium chloride in pyridine to afford the corresponding hydrazono derivative **4**. Also, condensation of **3** with *p*-anisaldehyde gave the corresponding arylidine derivative **5**. Treatment of **2** with dimethyl sulfate afforded the ketene *N,S*-acetal **9** which give **5**-amino pyrazole derivative **10** upon treatment with hydrazine hydrate. Compound **10** was used as key intermediate for synthesis of pyrazolo[5,1-c][1,2,4]triazine **13a**, **b**, pyrazolo[5,1-a]pyrimidine **14**–**17** and pyrolo pyrazole **18** derivatives. Finally, condensation of **1** with DMF-DMA afforded the corresponding acryloamide derivative **19**, which afforded the corresponding pyrazole derivative **20** upon heating with hydrazine hydrate. All new synthesized compounds were evaluated as antimicrobial agents; some of them exhibited promising activities.

1. Introduction

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities [1,2], recently found application in drug development for the treatment of allergies [3], hypertension [4], inflammation [5], schizophrenia [6], bacterial [7], HIV infections [8], hypnotics [9] and more recently for the treatment of pain [10], as fibrinogen receptor antagonists with antithrombotic activity [11] and as new inhibitors of bacterial DNA gyrase B [12].

On the other hand, the class of pyrazoles and isoxazoles possess a broad spectrum of biological effectiveness such as antiviral [13], antidepressant [14] and antibacterial activity [15]. Recently, substituted pyrazole derivatives were used as analytical reagents in the complexation of transition metal ions [16–20]. Besides, great interest in the pyrazole molecule has been stimulated by some promising pharmacological, agrochemical and analytical applications of its derivatives [21,22]. Furthermore, tetrahydrbenzothiophene derivatives were found to possess analgesic and antiinflammatory activities [23].

In view of the above biological importance and in continuation our studies on the chemistry of 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**1**) [24–27] and as a part of our program directed towards developing new approaches to variety of heterocycles incorporating thiophene moiety [24,28–30] of expected potential activity we reported herein of the utility of the highly versatile multifunctional intermediate (**1**) as building block for the synthesis of the title compounds.

2. Results and discussion

2.1. 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 (**1**) was prepared according to the previous reported method [24]. Compound 1 reacted with phenyl isothiocyanate in dry DMF in the presence of potassium hydroxide followed by addition of chloroacetyl chloride to afford 2-(5-oxothiazolidinone)-cyanoacetamido derivative **3**, *via* the intermediate **2**. The structure of **3** was characterized by the presence of a singlet signal equivalent to two protons at δ 4.10 ppm in the ^{1}H NMR spectrum, which represent the C_5 protons of the thiazolidinone ring. Also, the ^{13}C NMR spectrum of compound **3** reveals a signal at δ 77.28 ppm corresponding to C-4 of thiazoline ring. Diazocoupling of compound 3 with *p*-tolyldiazonium chloride in pyridine afforded the corresponding 2-[4-(tolylhydrazono)-5-oxothiazolidinone]-cyanoacetamido derivative **4**.

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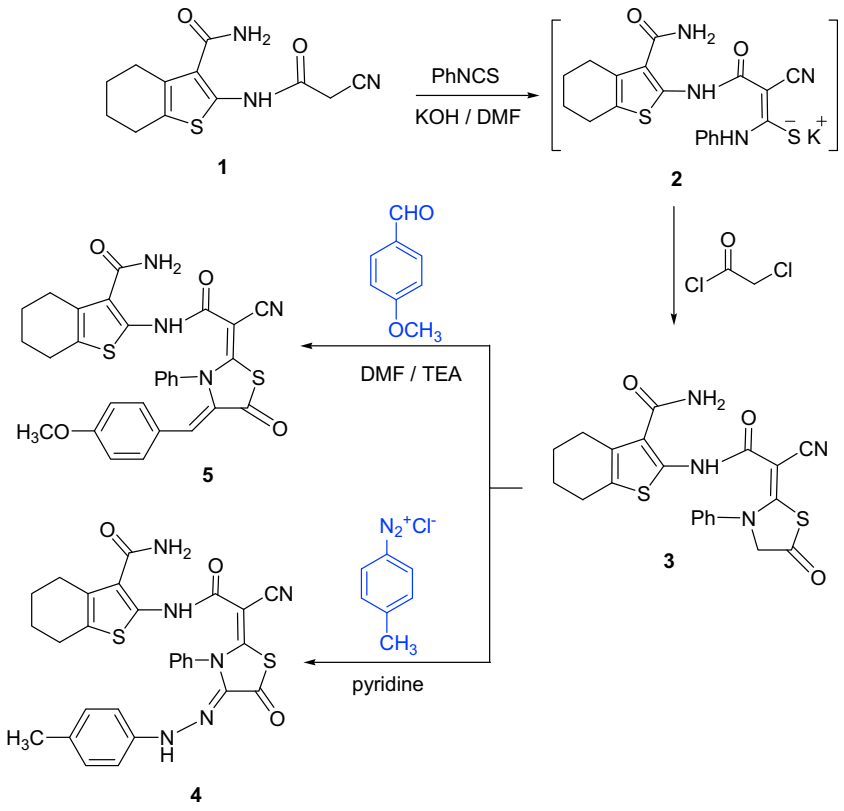
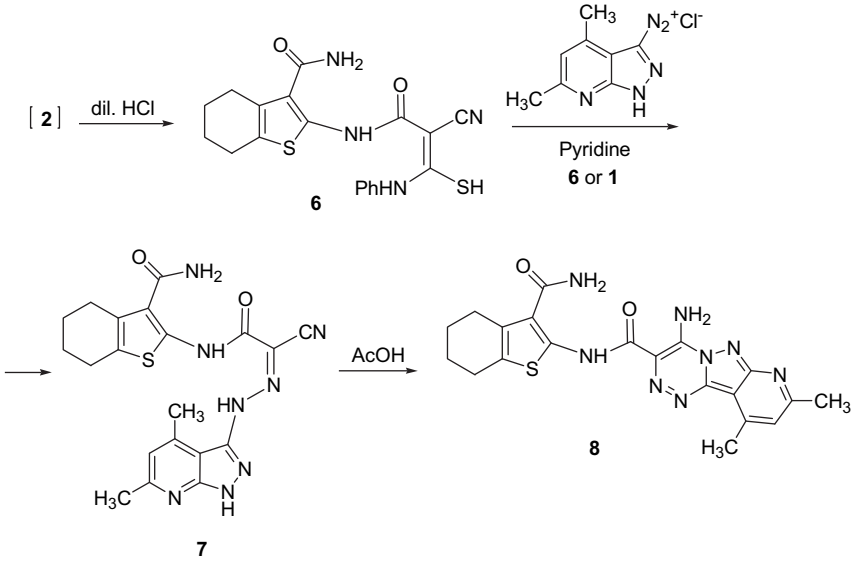


Scheme 1.

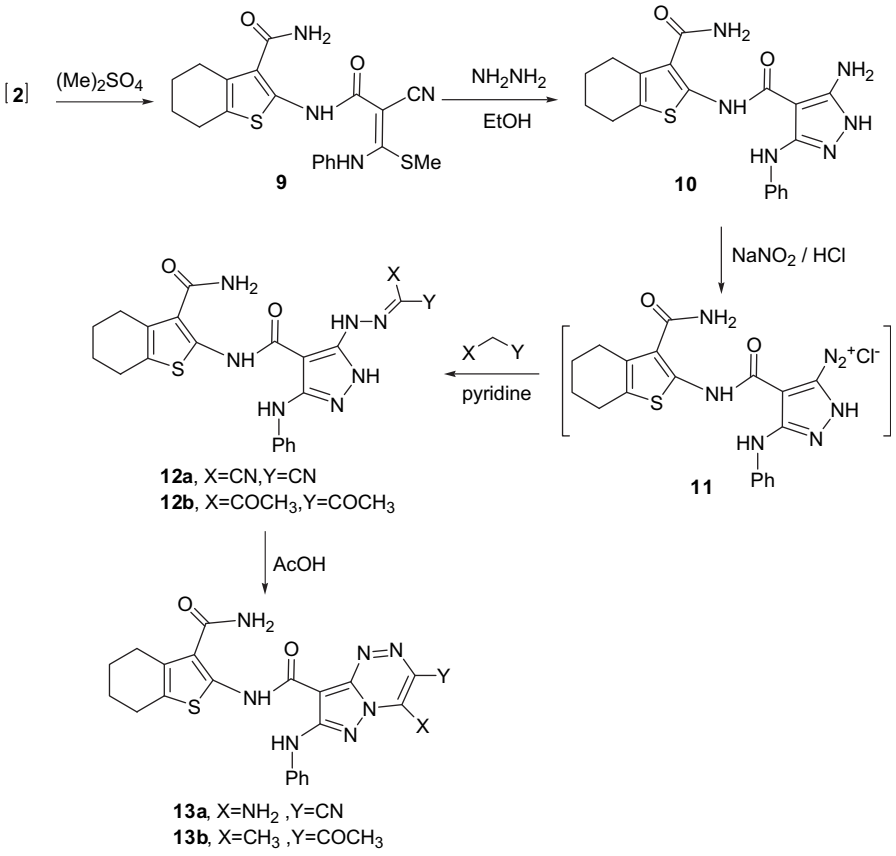
Its ^{1}H NMR spectrum exhibited three singlet signals at δ 2.32, 11.37, 12.31 ppm due to CH_3, NH=N, NHCO protons, respectively.

Condensation of compound **3** with *p*-anisaldehyde in DMF and in the presence of a catalytic amount of piperidine gave 2-[4-(4-methoxy-benzylidene)-5-oxo-3-phenyl-thiazolidin-2-ylidene]-acetylamino derivative **5**. The structure of **5** was compatible with its ^{1}H NMR spectrum which displayed singlet signal at δ 3.93 ppm corresponding to three protons of methoxy group.

In continuation of our interest in the synthesis of bridged head nitrogen heterocyclic systems [30], we have found that diazotized heterocyclic amine is an excellent building block for the synthesis of the target compound. Thus, coupling of compounds **1** or **6** [24], with 4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl-diazonium chloride [31], in pyridine at 0–5 °C afforded the corresponding hydrazono compound **7**, also compound **7** was obtained by coupling of **3** (which obtained by acidification with dilute HCl [24]), with the previous diazonium chloride, the formation of **7** may be interpreted through α-phenyl thiocarbamoyl cleavage [32], when compound **7** is refluxed in acetic acid, it can be cyclized to pyrazolo[5,1-c][1,2,4]triazine-derivative **8** (Scheme 2). Its ^{1}H NMR



Scheme 2.



Scheme 3.

spectrum revealed two singlet signals at δ 2.82 and 2.97 ppm due to two methyl groups of pyridine.

Moreover, treatment of **2** with dimethyl sulfate afforded the ketene *N,S*-acetal **9**. The ^{1}H NMR spectrum displayed singlet signal at δ 2.19 equvalent to three protons of SCH_3 group, also, its ^{13}C NMR revealed a signal at 17.1 due to SCH_3 group.

5-Amino pyrazole derivative **10** was achieved by the refluxing of **9** with hydrazine hydrate in ethanol. Its ^{1}H NMR spectrum displayed two broad signals at δ 6.00 and 6.82 corresponding to $2NH_2$ groups, three singlet signals at δ 8.30, 11.33 and 11.89 due to (NH–Ph), (NH-pyrazole) and (NH–CO) protons, respectively. We found also, diazotized 5-amino-3-phenylamino-1*H*-pyrazole-4-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide **10** is an excellent building block for the synthesis of bridge head nitrogen heterocyclic system. Thus, diazotization of compound **10** with sodium nitrite and conc. HCl gave the corresponding diazonium chloride **11**, which was coupled with different active methylene, namely; malononitrile and acetylacetone in pyridine to afford the corresponding hydrazono derivatives **12a**, **b** respectively. When compounds **12a**, **b** were refluxed in glacial acetic acid, the target pyrazolo[5,1-c][1,2,4]triazine derivatives **13a**, **b** were obtained. The formation of **13a**, **b** may be interpreted through the nucleophilic attack of ring nitrogen on cyano or acetyl group. The structures **12a**, **b** and **13a**, **b** were elucidated on the basis of analytical and spectral data. The IR spectra of **12a**, **b** revealed the azo peaks at 1522 and 1560 cm^{-1}, respectively. Furthermore, the ^{1}H NMR spectrum of compound **12b** displayed a broad signal at δ 2.56, which corresponding to six protons of two methyl groups. The ^{1}H NMR spectrum of compound **13a** displayed multipliet signals at δ 7.10–7.62 due to two NH_2 group, aromatic protons and a broad signal at δ 8.30 for NH–Ph proton. The Mass spectrum of **12b** displayed the molecular ion peak at *m/z* 504 ($M^+ - 3H$), which matching with its molecular formula $C_{24}H_{25}N_7O_4S$. Also, compound **13a**, displayed the molecular ion peak at *m/z* 391 ($M^+ - (N_2C–CN)$) and the base peak at *m/z* 51 (acrylonitrile moiety), finally, compound **13b** displayed the molecular ion peak at 470 ($M^+ - H_2O$) and the base peak at 77 (phenyl).

Pyrazolo[3,4-a]pyrimidine are of considerable chemical and pharmacological importance as purine analogues [33,34]. Various related compounds of these also have antitumor, anti-leukemic activities. Several biological activities have been established for some pyrazolo derivatives [35,36]. Also, the insecticidal activities have been investigated for some pyrazolo derivatives [37,38]. Thus, compound **10** interacted with acetylacetone, 5-chloro-3-methyl-phenyl-pyrazolo-4-carboxaldehyde [39], 1-chloro-3,4-dihydro-naphthalene-2-carboxaldehyde [40] and 1-phenyl-3-(pipridin-1-yl)propan-1-one hydrochloride [41] in the appropriate solvent to afford the corresponding pyrazolo[1,5-a]pyrimidine derivatives **14**–**17**, respectively.

The structures **14**–**17** were confirmed on the basis of the analytical and spectral data. The protons of two methyl groups in compound 14 resonated as two singlet at δ 2.68, 2.69 in the ^{1}H NMR spectrum. Also, **15** reveals a singlet signal at δ 2.51 due to methyl protons and **16** displayed multiplite signals at δ 2.94 and 3.03 ppm due to C_7-2H, C_6-2H protons of quinazoline moiety. The mass spectrum of **14** showed the molecular ion peak at *m/z* 460 (M^+) and the base peak at *m/z* 265 (5,7-dimethyl-2-(phenyl-amino)pyrazolo[5,1-a]pyrimidine-3-carbonyl moiety). Also, compound **16** exhibited the molecular ion peak at *m/z* 530 ($M^+ - 2$) which in agreement with molecular formula $C_{30}H_{26}N_6O_2S$ and the fragment ion peak at *m/z* 338 due to 2-anilino-6,7-dihydro-benzo[h]pyrazolo[5,1-a]quinozoline-3-carbonyl moiety. Finally, compound **17** showed the molecular ion peak at *m/z* 508 (M^+)

which in agreement with molecular formula $C_{28}H_{24}N_6O_2S$ and the fragment ion peak at *m*/*z* 313 due to 7-phenyl-2-(phenylamino) pyrazolo[5,1-a]pyrimidine-3-carbonyl moiety. Moreover, cyclo-condensation reaction of **10** with 2,5-hexadione in boiling acetic acid furnished the corresponding pyrrole derivative **18**. Its ^{1}H NMR spectrum revealed appearance of a characteristic broad signal at δ 2.00 due to two methyl protons (Scheme 4).

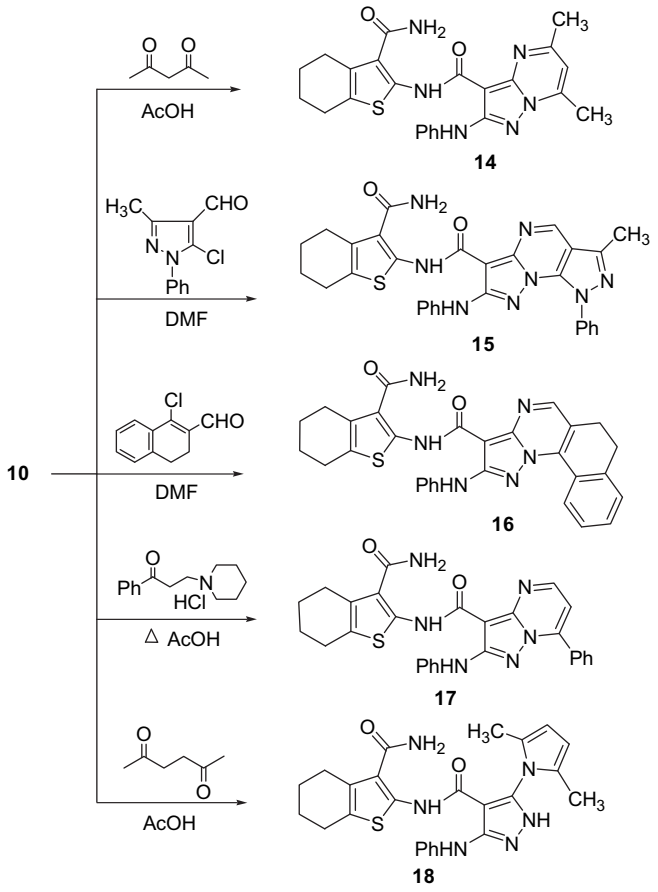
On the other hand, the reaction of **1** with DMF-DMA in dry dioxane afforded 2-[2-cyano-3-(dimethylamino)acryloamido]thiophene derivative **19**, which afforded the corresponding pyrazole derivative **20** upon heating with hydrazine hydrate. The structures **19** and **20** were established on the basis of analytical and spectral data. The IR spectrum of compound **20** was characterized by the disappearance of CN group. The ^{1}H NMR spectrum of compound 19 displayed two singlet signals at δ 3.25 and 3.31 due to two methyl groups of dimethylamine group. Also, the ^{1}H NMR spectrum of **20** displayed two broad signals at δ 6.05 and 7.60 due to protons of $2NH_2$ groups and another three singlet signals at δ 8.21, 11.00 and 12.23 assignable to =CH, NH and NH_2CO protons, respectively. The mass spectrum of compound **19** showed a molecular ion peak at *m*/*z* 300 ($M^+ - H_2O$) and the base peak at *m*/*z* 51 (acrylonitrile moiety). In addition, to the mass spectrum of compound **20** displayed the molecular ion peak at *m*/*z* 305 (M^+) which is in agreement with the molecular formula $C_{13}H_{15}N_5O_2S$ and the fragment ion peak at 110 due to 1*H*-pyrazole-4-carbonyl moiety Scheme 5.

3. Antimicrobial activity

Some of the new synthesized compounds were screened *in vitro* for their antimicrobial activity. The diameter of inhibition zone was measured as an indicator for the activity of the compounds; Ampicillin is used as reference drug.

The results for antibacterial activities depicted in Table 1 revealed that compounds **3**, **4**, **5**, **10**, **18** and **20** exhibited good activities against the reference chemotherapeutics, while compounds **8**, **14**, **15**, **16** and **17** showed moderate antibacterial activity. Also, compound **13b** exhibited moderate activities against *Klebsiella pneumoniae* and negative against *Bacillus theringiensis*, on the other hand, most of the prepared compounds exhibited moderate antifungal activities against the reference drugs, whereas, **4**, **14**, **18** and **20** exhibited good antifungal activities against *Fusarium. oxysporum*. Also, compounds **13a**, **13b** exhibited good antifungal activities against *F. oxysporum* and negative against *B. fabe.* It is worth mentioning that the incorporation of benzothiophene nucleus to thiazole or pyrazole moieties caused significant activity against *B. theringiensis*, *K. pneumoniae, B. fabe* and *F. oxysporum*.

In conclusion, we reported herein a simple and convenient route for the synthesis of some new heterocyclic based on benzothiophene for antimicrobial evaluation.



Scheme 4.

4. Experimental

4.1. General

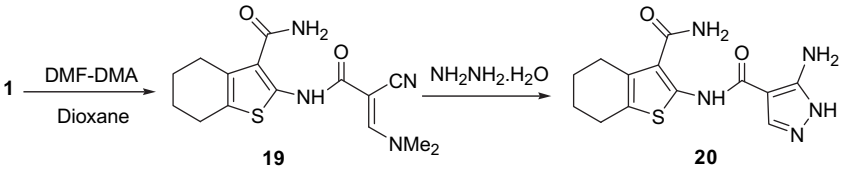
All melting points are recorded on Gallenkamp electric melting point apparatus. The IR spectra υ cm^{-1} (KBr) were recorded on Perkin Elmer Infrared Spectrophotometer Model 157, Grating. The ^{1}H NMR spectra were obtained on a Varian Spectrophotometer at 200 MHz using TMS as an internal reference and DMSO-d_6 as solvent. The ^{13}C NMR spectra were recorded on JEOL-ECA500 (National Research Center, Egypt). The mass spectra (EI) were recorded on 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 Micro Analytical Center of Cairo Univ., Giza, Egypt. The results were found to be in good agreement (±0.3%) with the calculated values. Microbiology screening was carried out in Botany Department, Faculty of Science Mansoura University, under supervision Prof. Dr. Yhia A. O. Ellazeik.

Compounds 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydro-benzo[b] thiophene-3-carboxamide (**1**) [24–27] and 2-(2-cyano-3-mercapto-3-phenylamino-acryloylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**6**) [24] were prepared according to the previously reported method.

4.1.1. Synthesis of 2-[2-cyano-2-(5-oxo-3-phenyl-thiazolidin-2-ylidene)-acetylamino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**3**)

To a cold suspension of finally divided KOH (0.22 g, 4 mmol) in dry DMF (25 ml) were added compound **1** (1.05 g, 4 mmol) followed by phenyl isothiocyanate (0.54 g, 4 mmol). The mixture was stirred at room temperature for 12 h, then cooled again to 0 °C, treated with chloroacetyl chloride (0.45 g, 4 mmol) and left to stand at room temperature for 24 h. The mixture was poured into ice cold-water. The resulting precipitate was filtered off, dried and recrystallized from mixture of EtOH:DMF to give compound **3**.

Yellow crystals; Yield 75%; 1.32 g; mp 291 °C; IR (KBr): ν/cm^{-1} = 3420, 3329, 3265 (NH), 2200 (CN), 1726, 1644 (br) (3C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.78 (m, 4H, C_5-2H, C_6-2H), 2.69 (m, 2H, C_4-2H), 2.75 (m, 2H, C_7-2H), 4.10 (s, 2H, C_5-2H-thiazolidinone), 7.19–7.61 (m, 7H, Ar-H, NH_2), 12.57 (s, 1H, NH–CO); ^{13}C NMR (DMSO): δ_{ppm} = 173.2 (C_2-thiophene), 171.0, 167.3, 160.9 (3CO), 142.6, 130.5, 129.3, 129.2, 128.8, 126.3 (sp^2, C), 115.4 (CN), 112.4 (C_2, acetylamino), 77.2 (C_4-thiazoline), 29.1, 28.9, 22.2 (2C), (cyclohexene ring); EIMS (*m*/*z*) (%) = 439 (M^+ + 1, 4.3), 438 (M^+, 11.3), 421 (1.9), 243 (19.6), 215



Scheme 5.

(48.6), 179 (16.1), 151 (10.4), 132 (32.1), 116 (10.1), 77 (100), 51 (44.4). Anal. for $C_{21}H_{18}N_4O_3S_2$ (438.52): calcd.: C, 57.52; H, 4.14; N, 12.78%; found: C, 57.61; H, 4.18; N, 12.86%.

*4.1.2. Synthesis of 2-{2-cyano-2-[5-oxo-3-phenyl-4-(p-tolyl-hydrazono)-thiazolidin-2-ylidene]-acetylamino}-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**4**)*

To a well-stirred cooled solution of *p*-toluidine (0.43 g, 4 mmol) in (1.5 ml) conc. HCl and (2 ml), a solution of $NaNO_2$ (0.28 g, 4.1 mmol in 5 ml H_2O) was added drop wise. The above cooled diazonium solution was added slowly to a well-stirred solution of **3** (1.75 g, 4 mmol) in pyridine (10 ml). The reaction mixture was stirred for 2 h. The crude product was filtered off, dried well and recrystallized from the EtOH:benzene to give **4**.

Orange crystals; Yield 75%; 1.67 g; mp 307 °C; IR (KBr): ν/cm^{-1} = 3408, 3252, 3222, 3170 (NH), 2202 (CN), 1725, 1683 (br, 3C=O), 1551 (N=N); ^1H NMR (DMSO): δ_{ppm} = 1.80 (m, 4H, C_5-2H, C_6-2H), 2.32 (s, 3H, CH_3), 2.70 (m, 2H, C_4-2H), 2.73 (m, 2H, C_7-2H), 7.23–7.33 (m, 11H, Ar-H, NH_2), 11.37 (s, 1H, NH=N), 12.31 (br, 1H, NHCO); EIMS (*m*/*z*) (%) = 557 (M^+ + 1, 0.8), 556 (M^+, 1.0), 539 (1.1), 306 (11.2), 222 (19.0), 179 (23.0), 77 (100). Anal. for $C_{28}H_{24}N_6O_3S_2$ (556.66): calcd.: C, 60.41; H, 4.35; N, 15.10%; found: C, 60.48; H, 4.42; N, 15.16%.

*4.1.3. Synthesis of 2-{2-cyano-2-[4-(4-methoxy-benzylidene)-5-oxo-3-phenyl-thiazolidin-2-ylidene]-acetylamino}-4,5,6,7-tetrahydro-benzo[b] thiophene-3-carboxamide (**5**)*

To a well-stirred solution of compound **3** (1.75 g, 4 mmol) in DMF (20 ml), TEA (0.2 ml) and *p*-anisaldehyde (0.54 g, 4 mmol) were added. The reaction mixture was stirred at 80 °C for 3 h. The separated crystals was filtered, dried and recrystallized from mixture of EtOH:benzene to give compounds 5.

Brown crystals; Yield 60%; 1.34 g; mp > 320 °C; IR (KBr): ν/cm^{-1} = 3403, 3255, 3025 (NH), 2200 (CN), 1707, 1640 (br, 3C=O); ^1H NMR (DMSO): δ_{ppm} = 1.79 (m, 4H, C_5-2H, C_6-2H), 2.73 (m, 2H, C_4-2H), 2.79 (m, 2H, C_7-2H), 3.93 (s, 2H, OCH_3), 7.29–8.01 (m, 12H, Ar-H,=CH, NH_2), 12.78 (s, 1H, NH). Anal. for $C_{29}H_{24}N_4O_4S_2$ (556.66): calcd.: C, 62.57; H, 4.35; N, 10.06%; found: C, 62.51; H, 4.29; N, 10.01%.

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

Compound no.	Inhibition zone in mm			
	Bacteria		Fungi	
	Gram positive bacteria *Bacillus theringiensis*	Gram negative bacteria *K. pneumoniae*	*B. fabe*	*F. oxysporum*
3	21	19	16	12
4	22	19	16	18
5	20	23	15	13
8	16	18	13	13
10	24	22	14	–
13a	16	18	–	16
13b	–	12	–	18
14	15	17	13	15
15	16	18	14	16
16	15	17	17	–
17	15	19	19	15
18	18	22	14	18
20	17	20	12	16
Ampicillin	17	20	17	15

*4.1.4. Synthesis of 2-{2-cyano-2-[(4,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-hydrazono]-acetylamino}-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**7**)*

Preparation of the diazonium salt: A solution of sodium nitrite (0.28 g, 4.1 mmol, in 2 ml water) was gradually added to a well cooled solution of 4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl-amine (0.65 g, 4 mmol) in conc. hydrochloric acid [(1.5 ml) in water (2 ml)]. The diazonium salt solution was added drop wise with continuous stirring to cold solution of **1** (1.05 g, 4 mmol) or **6** (1.59 g, 4 mmol) in pyridine (10 ml) 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 mixture of EtOH:DMF.

Black crystals; Yield 80%; 1.397 g, when using compound **1**; Yield 60%; 1.05 g, while using compound 6, mp > 320 °C; IR (KBr): ν/cm^{-1} = 3370, 3335, 3263, 3203 (br, NH), 2216 (CN), 1637 (br, 2C=O), 1521 (N=N); EIMS (*m*/*z*) (%) = 436 (M^+, 1.21), 324 (1.2), 293 (100), 262 (13), 26 (14), 212 (25), 183 (68), 149 (20), 138 (15), 96 (16), 77 (2.18). Anal. for $C_{20}H_{20}N_8O_2S$ (436.49): calcd.: C, 55.03; H, 4.62; N, 25.67%; found: C, 55.12; H, 4.70; N, 25.73%.

*4.1.5. Synthesis of 8-amino-2,4-dimethyl-1,5,6,8a,9-pentaaza-fluorene-7-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**8**)*

A solution of compound **7** (1.75 g, 4 mmol) in glacial acetic acid (20 ml) was refluxed for 4 h. The reaction mixture was left to stand at room temperature overnight, and the separated solid product was filtered and crystallized from a mixture of EtOH:benzene to give **8**.

Black powders; Yield 80%; 1.397 g; mp > 320 °C; IR (KBr): ν/cm^{-1} = 3377–3215 (NH), 1656, 1630 (br, 2C=O); ^1H NMR (DMSO): δ_{ppm} = 1.82 (m, 4H, C_5-2H, C_6-2H), 2.68 (m, 2H, C_4-2H), 2.74 (m, 2H, C_7-2H), 2.82 (s, 3H, C_{10}-CH_3), 2.97 (s, 3H, C_8-CH_3), 7.18 (br., 2H, $CONH_2$), 7.40 (s, 1H, pyridine), 9.45 (br., 2H, NH_2), 13.45 (s, 1H, NH). Anal. for $C_{20}H_{20}N_8O_2S$ (436.49): calcd.: C, 55.03; H, 4.62; N, 25.67%; found: C, 55.10; H, 4.69; N, 25.73%.

*4.1.6. Synthesis of 2-(2-cyano-3-methylsulfanyl-3-phenylamino-acryloylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxamide (**9**)*

To a stirred solution of potassium hydroxide (0.22 g, 4 mmol) in DMF (20 ml) was added compound **1** (1.05 g, 4 mmol). After the mixture was stirred for 30 min, phenyl isothiocyanate (0.54 g, 4 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then dimethyl sulfate (0.50 g, 4 mmol) was added and stirring was continued for additional 6 h. The reaction mixture was poured on to ice water. The solid product that formed was filtered off, dried and recrystallized from mixture of EtOH:DMF to afford **9**.

Yellow crystals; Yield 86%; 1.42 g; mp 238 °C; IR (KBr): ν/cm^{-1} = 3294, 3237, 3157 (2NH), 2195 (C≡N), 1624 (br, 2C=O); ^1H NMR (DMSO): δ_{ppm} = 1.72 (m, 4H, C_5-2H, C_6-2H), 2.19 (s, 3H, CH_3), 2.59

(m, 2H, C_4-2H), 2.70 (m, 2H, C_7-2H), 7.28–7.42 (m, 7H, Ar-H, NH_2), 11.74 (br., 1H, NH–Ph), 12.53 (br, 1H, NH); ^{13}C NMR (DMSO): δ_{ppm} = 168.7 (C_2-thiophene), 168.1, 162.0 (2CO), 143.3, 138.6, 129.8, 127.1, 126.8, 124.9 (sp^2, C), 118.1 (CN), 112.4 (C_2, acryloyl), 25.7, 24.3, 22.8 (2C), (cyclohexene ring), 17.1 (SCH_3); EIMS (*m*/*z*) (%) = 379 (M^+ – [H_2O, CH_3], 10.6), 328 (12.8), 256 (27.7), 93 (57.4), 55 (100). Anal. for $C_{20}H_{20}N_4O_2S_2$ (412.53): calcd.: C, 58.23; H, 4.89; N, 13.58%; found: C, 58.34; H, 4.98; N, 13.69%.

*4.1.7. Synthesis of 5-amino-3-phenylamino-1H-pyrazole-4-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**10**)*

A mixture of compound **9** (1.65 g, 4 mmol) and hydrazine hydrate 98% (0.2 g, 4 mmol) was heated on water bath for 3 h, then left to cool. The reaction mixture was triturated with ethanol and the resulting solid was filtered off and recrystallized from mixture of EtOH:DMF to give compound **10**.

Pale yellow crystals; Yield 80%; 1.27 g; mp 268 °C; IR (KBr): ν/cm^{-1} = 3433, 3381, 3296, 3210 (NH), 1634 (2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.73 (m, 4H, C_5-2H, C_6-2H), 2.62 (m, 2H, C_4-2H), 2.70 (m, 2H, C_7-2H), 6.00 (br, 2H, NH_2), 6.82 (br, 2H, NH_2), 7.18–7.31 (m, 5H, Ar-H), 8.30 (s, 1H, NH–Ph), 11.33 (s, 1H, NH-pyrazole), 11.89 (s, 1H, NHCO); ^{13}C NMR (DMSO): δ_{ppm} = 170.0 (C_2-thiophene), 167.9, 161.2 (2CO), 143.75, 143.68, 129.08, 125.68, 119.5, 116.8, 115.34, (sp^2, C), 88.2 (C_4, pyrazole), 25.8, 24.3, 23.1 (2C), (cyclohexene ring); EIMS (*m*/*z*) (%) = 397 (M^+ + 1, 14.5), 396 (M^+, 4.8), 379 (14.5), 201 (77.2), 174 (33.1), 77 (100), 51 (86.9). Anal. for $C_{19}H_{20}N_6O_2S$ (396.47): calcd.: C, 57.56; H, 5.08; N, 21.20%; found: C, 57.51; H, 5.02; N, 21.12%.

*4.1.8. Coupling of 5-amino pyrazole derivative **10** with malononitrile and acetylacetone*

General procedure: Preparation of the diazonium salt: A solution of sodium nitrite (0.32 g, 4 mmol; in 2 ml water) was gradually added to a well cooled solution of **10** (1.59 g, 4 mmol) in a mixture of acetic acid and conc. HCl [(8:2) 10 ml (1/4) Vol.]. The diazonium salt solution was added drop wise with continuous stirring to cold solution of malononitrile (0.26 g, 4 mmol) and acetylacetone (0.4 g, 4 mmol) in pyridine (10 ml) the reaction mixture was stirred at 0–5 °C for 2 h and left to stand at room temperature. The separated solid products that obtained were filtered off, dried and recrystallized from mixture of EtOH:benzene to give **12a**, **b**.

*4.1.8.1. Synthesis of 5-(N′-dicyanomethylene-hydrazino)-3-phenylamino-1H-pyrazole-4-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**12a**).* Black crystals; Yield 55%; 1.04 g; mp 328 °C; IR (KBr): ν/cm^{-1} = 3338 (br, NH), 2142 (2C≡N), 1632 (br,2C=O), 1522 (N=N); ^{1}H NMR (DMSO): δ_{ppm} = 1.75 (m, 4H, C_5-2H, C_6-2H), 2.68 (m, 2H, C_4-2H), 2.76 (m, 2H, C_7-2H), 5.32 (s, 1H, NH–N=C), 6.80 (br, 2H, NH_2), 7.25–7.62 (m, 5H, Ar-H), 8.30 (br, 1H, NH–Ph), 9.8 (br, 1H, NH-pyrazole), 11.80 (br, 1H, NH-C=O). Anal. for $C_{22}H_{19}N_9O_2S$ (473.51): calcd.: C, 55.80; H, 4.04; N, 26.62%; found: C, 55.87; H, 4.11; N, 26.71%.

*4.1.8.2. Synthesis of 5-[N′-(1-acetyl-2-oxo-propylidene)-hydrazino]-3-phenylamino-1H-pyrazole-4-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**12b**).* Pale yellow crystals; Yield 50%; 1.02 g; mp > 320 °C; IR (KBr): ν/cm^{-1} = 3298 (br, NH), 1721, 1632 (2C=O), 1560 (N=N); ^{1}H NMR (DMSO): δ_{ppm} = 1.81 (m, 4H, C_5-2H, C_6-2H), 2.56 (br, 6H, 2CH_3), 2.73 (m, 2H, C_4-2H), 2.74 (m, 2H, C_7-2H), 7.02 (br, 2H, NH_2), 7.52–8.07 (m, 5H, Ar-H), 9.08 (s, 1H, NH–Ph), 12.5 (br, 1H, NH-pyrazole), 13.8 (s, 1H, NH–C=O); EIMS (*m*/*z*) (%) = 504 (M^+ – 3, 16.2), 265 (21.6), 157 (27.0), 91 (67.6) 58 (100). Anal. for $C_{24}H_{25}N_7O_4S$ (507.56): calcd.: C, 56.79; H, 4.96; N, 19.32%; found: C, 56.81; H, 5.01; N, 19.41%.

*4.1.9. Synthesis of pyrazolo[5,1-c][1,2,4]triazine compounds **13a**, **b***

General procedure: A solution of compound **12a** (1.89 g, 4 mmol) or **12b** (2.03 g, 4 mmol) in glacial acetic acid (30 ml) was refluxed for 3 h, and then allowed to cool. The precipitate that formed was filtered off, washed with ethanol, dried and recrystallized from mixture of EtOH:DMF to give compounds **13a** and **13b**.

*4.1.9.1. Synthesis of 4-amino-3-cyano-7-phenylamino-pyrazolo[5,1-c][1,2,4]triazine-8-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**13a**).* Black crystals; Yield 55%; 1.04 g; mp 308 °C; IR (KBr): ν/cm^{-1} = 3385 (br, NH), 2223 (C≡N), 1628 (2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.79 (m, 4H, C_5-2H, C_6-2H), 2.51 (m, 2H, C_4-2H), 2.68 (m, 2H, C_7-2H), 6.84–8.10 (m, 7H, Ar-H, NH_2), 8.3 (br, 1H, NH–Ph), 11.89 (br, 1H, NH–CO); EIMS (*m*/*z*) (%) = 391 (M^+ – N_2–C–CN, 27.3), 135 (18.2), 134 (22.7), 127 (22.7), 114 (27.3), 79 (22.7), 65 (31.8), 51 (100). Anal. for $C_{22}H_{19}N_9O_2S$ (473.51): calcd.: C, 55.80; H, 4.04; N, 26.62%; found: C, 55.87; H, 4.13; N, 26.71%.

*4.1.9.2. Synthesis of 3-acetyl-4-methyl-7-phenylamino-pyrazolo[5,1-c][1,2,4]triazine-8-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**13b**).* Pale yellow crystals; Yield 55%; 1.08 g; mp > 320 °C; IR (KBr): ν/cm^{-1} = 3335 (br, NH), 1628 (2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.77 (m, 4H, C_5-2H, C_6-2H), 2.08 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 2.68 (m, 4H, C_4-2H, C_7-2H), 7.27–7.48 (m, 5H, Ar-H), 8.3 (br, 1H, NH–Ph), 11.89 (br, 1H, NH–CO); EIMS (*m*/*z*) (%) = 470 (M^+ – H_2O, 5.9), 234 (3.7), 172 (10.4), 152 (25.3), 120 (70.9), 91 (85.8), 77 (100). Anal. for $C_{24}H_{23}N_7O_3S$ (489.55): calcd.: C, 58.88; H, 4.74; N, 20.03%; found: C, 58.93; H, 4.83; N, 20.16%.

*4.1.10. Synthesis of 5,7-dimethyl-2-phenylamino-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**14**)*

A mixture of compound 10 (1.59 g, 4 mmol) and acetylacetone (0.40 g, 4 mmol) in glacial acetic acid (20 ml) was refluxed for 3 h, then the reaction mixture was poured into crushed-ice, and the separated solid was filtered off, dried well and recrystallized from mixture of EtOH:benzene to give **14**.

Yellow crystals; Yield 86%; 1.58 g; mp 328 °C; IR (KBr): ν/cm^{-1} = 3484, 3316, 3270, 3167 (NH), 1642 (2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.77 (m, 4H, C_5-2H, C_6-2H), 2.68 (s, 3H, C_7-CH_3), 2.69 (s, 3H, C_5-CH_3), 2.73 (m, 4H, C_4-2H, C_7-2H), 7.02–7.79 (m, 8H, Ar-H, NH_2), 9.29 (br., 1H, NH–Ph) and 12.44 (br, 1H, NH); EIMS (*m*/*z*) (%) = 462 (M^+ + 2, 1.3), 461 (M^+ + 1, 3.4), 460 (M^+, 8.8), 265 (100), 65 (21.4). Anal. for $C_{24}H_{24}N_6O_2S$ (460.55): calcd.: C, 62.59; H, 5.25; N, 18.25%; found: C, 62.64; H, 5.31; N, 18.32%.

*4.1.11. Reaction of **10** with 5-chloro-3-methyl-phenylpyrazolo-4-carboxaldehyde and 1-chloro-3,4-dihydronaphthalene-carboxaldehyde*

To a solution of compound **10** (1.59 g, 4 mmol) in DMF (30 ml), 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (0.88 g, 4 mmol) or 1-chloro-3,4-dihydro-naphthalene-2-carbaldehyde (0.76 g, 4 mmol) was added. The reaction mixture was heated under reflux for 12 h, and then was poured into crushed-ice and the separated solid was filtered and recrystallized from EtOH:benzene to give compounds **15** and **16**.

*4.1.11.1. Synthesis of 3-methyl-1-phenyl-7-phenylamino-1H-1,2,5,8,8a-pentaaza-as-indacene-6-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**15**).* Black crystals; Yield 66%; 1.49 g; mp > 320 °C; IR (KBr): ν/cm^{-1} = 3450, 3432 (NH), 1636 (br, 2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.81 (m, 4H, C_5-2H, C_6-2H), 2.51 (s, 3H, CH_3), 2.89 (m, 2H, C_7-2H), 5.69 (s, 1H, C_4-H-pyrimidine), 6.83 (br, 2H, NH_2), 8.5 (br, 1H, NH–Ph), 13.39 (br, 1H, NH–CO),

13.39 (s, 1H, NH). Anal. for $C_{30}H_{26}N_8O_2S$ (562.64): calcd.: C, 64.04; H, 4.66; N, 19.92%; found: C, 64.12; H, 4.72; N, 19.98%.

*4.1.11.2. Synthesis of 2-phenylamino-6,7-dihydro-1,4,11c-triaza-cyclopenta[c]phenanthrene-3-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**16**).* Brown crystals; Yield 85%; 1.82 g; mp 251 °C; IR (KBr): ν/cm^{-1} = 3415, 3300 (br, NH), 1639 (2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.85 (m, 4H, C_5-2H, C_6-2H), 2.73 (m, 2H, C_4-2H), 2.79 (m, 2H, C_7-2H-quinazoline), 2.94 (m, 2H, C_7-2H-quinazoline), 3.03 (m, 2H, C_6-H_2-quinazoline), 6.88–8.01 (m, 12H, Ar-H, CH-pyrimidine, NH_2), 9.41 (br., 1H, NH–Ph), 11.11 (br, 1H, NH–CO); EIMS (*m*/*z*) (%) = 530 (M^+ − 2, 22.7), 338 (27.3), 205 (59.1), 170 (31.8), 119 (45.5), 77 (100). Anal. for $C_{30}H_{26}N_6O_2S$ (534.63): calcd.: C, 67.40; H, 4.90; N, 15.72%; found: C, 67.37; H, 4.86; N, 15.69%.

*4.1.12. Synthesis of 7-phenyl-2-phenylamino-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**17**)*

A solution of compound **10** (1.59 g, 4 mmol) in glacial acetic acid (20 ml) which was treated with 1-phenyl-3-piperidin-1-yl-propan-1-one hydrochloride (1.02 g, 4 mmol) was heated under reflux for 5 h. The reaction mixture was poured into crushed-ice and the separated solid was the separated solid was filtered off, dried well and recrystallized from mixture of benzene:ethanol to give **17**.

Yellow crystals; Yield 75%; 1.53 g; mp 240 °C; IR (KBr): ν/cm^{-1} = 3392, 3311, 3202 (NH), 1635 (br, 2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.82 (m, 4H, C_5-2H, C_6-2H), 2.70 (m, 2H, C_4-2H),2.77 (m,2H, C_7-2H), 6.95 (br, 2H, $CONH_2$), 7.31–7.76 (m, 10H, Ar-H), 8.75 (br, 1H, NH–Ph), 12.81 (br, 1H, CONH); EIMS (*m*/*z*) (%) = 508 (M^+, 12.2), 421 (52.4), 379 (14.6), 313 (81.7), 243 (11.0), 116 (45.1), 77 (100). Anal. for $C_{28}H_{24}N_6O_2S$ (508.59): calcd.: C, 66.12; H, 4.76; N, 16.52%; found: C, 66.18; H, 4.82; N, 16.59%.

*4.1.13. Synthesis of 5-(2,5-dimethyl-pyrrol-1-yl)-3-phenylamino-1H-pyrazole-4-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**18**)*

A mixture of compound **10** (1.59 g, 4 mmol) and hexane-2,5-dione (0.46 g, 4 mmol) in glacial acetic acid (20 ml) was refluxed for 5 h, then the reaction mixture was poured into crushed-ice, and the separated solid was filtered off, dried well and recrystallized from mixture of EtOH:benzene to give **18**.

Yellow crystals; Yield 75%; 1.42 g; mp 256 °C; IR (KBr): ν/cm^{-1} = 3379, 3337 (NH), 1633 (br, 2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.71 (m, 4H, C_5-2H, C_6-2H), 2.00 (br, 6H, CH_3), 2.62 (m, 2H, C_4-2H), 2.68 (m, 2H, C_7-2H), 5.83 (m, 2H, C_3-H,C_4-H pyrole), 6.91, (br, 2H, NH_2), 7.28–7.53 (m, 5H, Ar-H), 8.69 (br, 1H, NH–Ph), 11.06 (br, 1H, NH pyrole), 13.27 (br, 1H, NH). Anal. for $C_{25}H_{26}N_6O_2S$ (474.58): calcd.: C, 63.27; H, 5.52; N, 17.71%; found: C, 63.35; H, 5.61; N, 17.78%.

*4.1.14. Synthesis of 2-(2-cyano-3-dimethylamino-acryloylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid amide (**19**)*

To a solution of compound **1** (1.05 g, 4 mmol) in dioxane (20 ml) the DMF–DMA (0.48 g, 4 mmol) was added. The reaction mixture was heated under reflux for 4 h, then filtered and recrystallized from benzene: ethanol to give **19**.

Yellow crystals; Yield 60%; 0.76 g; mp 235 °C; IR (KBr): ν/cm^{-1} = 3474, 3430, 3331, 3246 (NH) 2190 (CN), 1636 (br, 2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.78 (m, 4H, C_5-2H, C_6-2H), 2.65 (m, 2H, C_4-2H), 2.74(m, 2H, C_7-2H), 3.25 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 6.95 (br., 2H, NH_2), 8.24 (s, 1H, CH=), 12.30 (s, 1H, NHCO); EIMS (*m*/*z*) (%) = 300 (M^+ − 18, 34.0), 222 (40.4), 178 (48.9), 123 (95.7), 91 (85.1), 51 (100). Anal. for $C_{15}H_{18}N_4O_2S$ (318.39): calcd.: C, 56.58; H, 5.70; N, 17.60%; found: C, 56.63; H, 5.76; N, 17.71%.

*4.1.15. Synthesis of 5-amino-1H-pyrazole-4-carboxylic acid (3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-amide (**20**)*

A solution of compound **19** (1.27 g, 4 mmol) in DMF (30 ml) and hydrazine hydrate 98% (0.2 g, 4 mmol) was refluxed for 4 h and then separated solid was filtered and recrystallized from a mixture of EtOH:benzene to give **20**.

Gray crystals; Yield 65%; 0.79 g; mp > 320 °C; IR (KBr): ν/cm^{-1} = 3200 (br., NH), 1644 (br, 2C=O); ^{1}H NMR (DMSO): δ_{ppm} = 1.75 (m, 4H, C_5-2H, C_6-2H), 2.71 (m, 2H, C_4-2H), 2.85 (m, 2H, C_7-2H), 6.05 (br., 2H, NH_2-pyrazole), 7.60 (br., 2H, NH_2), 8.21 (s, 1H, C_3-H, pyrazole), 11.00 (s, 1H, NH-pyrazole), 12.24 (s, 1H, NHCO); EIMS (*m*/*z*) (%) = 306 (M^+ + 1, 25.0), 305 (M^+, 62.5), 163 (75.0), 110 (75.0), 71 (100). Anal. for $C_{13}H_{15}N_5O_2S$ (305.36): calcd.: C, 51.13; H, 4.95; N, 22.94%; found: C, 51.22; H, 5.02; N, 23.06%.

4.2. In vitro antimicrobial activity

The tested compounds were evaluated by the agar diffusion technique [42] using a 2 mg ml^{-1} solution in DMSO. The test organisms were two bacterial strains: *B. theringiensis*, *K. pneumoniae,* and two fungi: *B. fabe* and *F. oxysporum*. A control using DMSO without the test compound was included for each organism. *Ampicillin* was purchased form The Egyptian market and used in a concentration 2 mg/ml as reference drugs. The bacteria and fungi were tested on nutrient agar and potato dextrose agar media, respectively. Three plates were used for each compound as replicates. The plates were incubated for 24 h, and seven days for bacteria and fungi, respectively. After the incubation period, the diameter of inhibition zone was measured as an indicator for the activity of the compounds.

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