ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2012, Vol. 38, No. 5, pp. 526–532. © Pleiades Publishing, Ltd., 2012.

Synthesis and Reactions of Some New Pyrrolylthieno[2,3-*D*]Quinoxaline and Pyrrolopyrazinothienoquinoxalines[1]

Ahmed A. Geies, Yasser A. Elossaily[2], and Osama Sh. Moustafa

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

Received August 1, 2011; in final form, August 15, 2011

Abstract—The synthesis of 3-pyrrolyl-2-substituted thieno[2,3-*b*]quinoxalines from the precursor 3-amino derivatives are described. Synthesized compounds were subjected to reactions with other reagents to synthesize polyfused heterocyclic incorporated thienoquinoxaline moiety. Some of the synthesized compounds were screened for their antibacterial and antifungal activities.

Keywords: pyrrolylthienoquinoxaline, pyrrolopyrazinothienoquinoxalines, pyrrolyl triazolylthienoquinoxaline, synthesis, antimicrobial activity

DOI: 10.1134/S1068162012050020

INTRODUCTION

During the last few years, quinoxalines have been of special interest due to their biological activity. This has led to the development of a new class of structural elements for mycobacteriostatic drugs [1–3] based quinoxaline derivatives that have been explored for developing pharmaceutic ally important molecules for examples, imidazoquinoxalines ribonucleosides as linear of antivirals [4], pyrazoloquinoxaline showed a relatively high antibacterial activity wherein MIC value was 25 mg/mL against *Bacillus licheniformis* and *Cellulomonas* sp. [5], quinoxaline-1,4-di-*N*-oxides for treatment of tuberculosis [6], pyrimido[4,5-*b*]quinoxaline used as anti-hypertensive and blood platelet ant aggregating agents [7], also some quinoxaline derivatives have a cytotoxic effects on human cancer cell lines [8, 9], commercially impotent as agrochemicals [10], herbicides [11], hypoxic-cytoxic agents [12], antivirus [13] (Hepatitis B), antimicrobial [14], and amebicides [15].

On the other hand, several series of heterocyclic compounds possessing a bridgehead pyrrolyl moiety play a vital role in many biological activities [10–12].

Thus, as part of an ongoing program for the synthesis of poly fused heterocyclic systems with expected biological activity [13–18], in the present report, we present the full experimental details and biological evaluation of novel pyrrolylfuro[2,3-*d*] pyrimidine series.

[1] The article is published in the original.

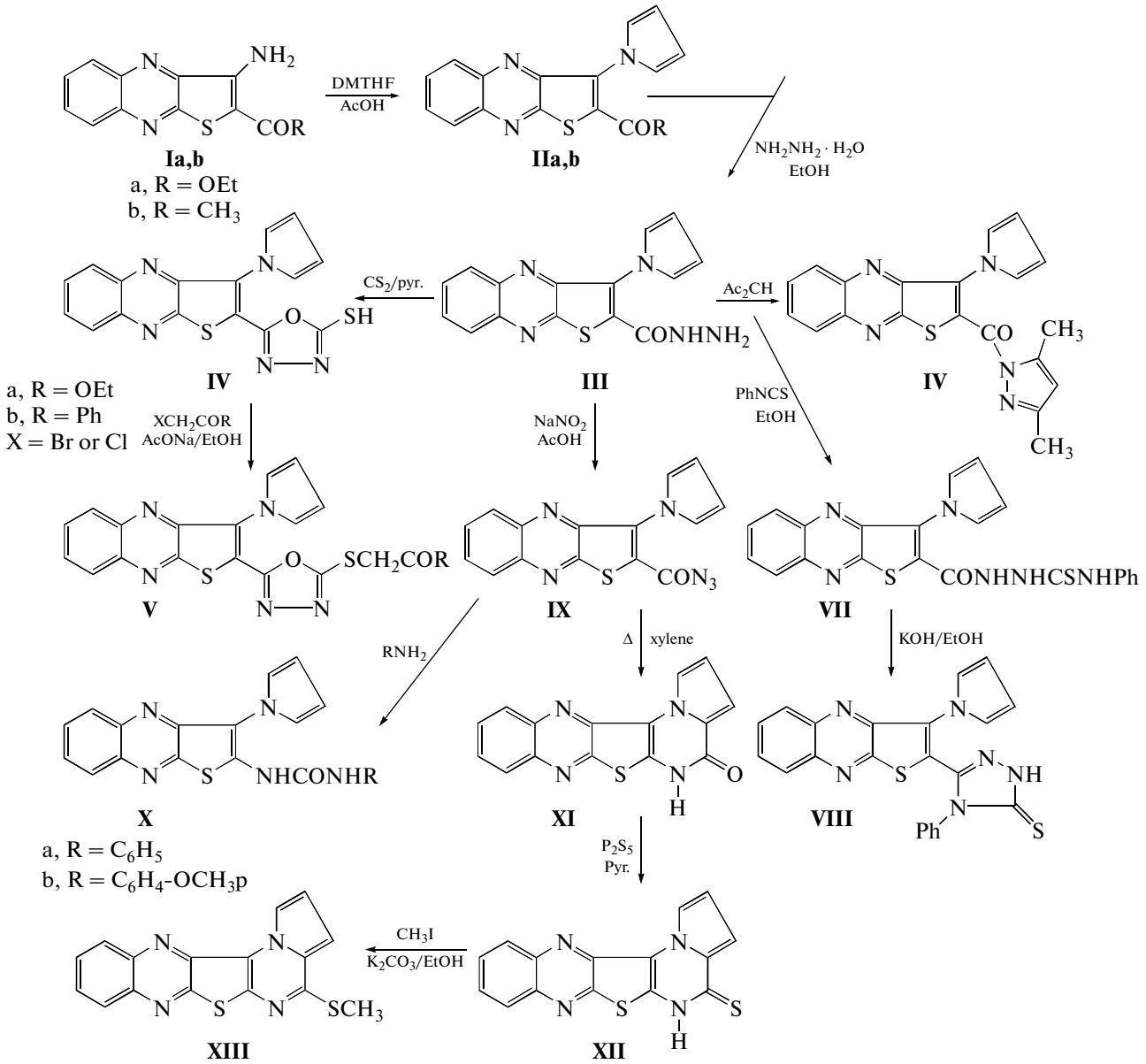
[2] Corresponding author: e-mail: yasserabdelmoez@yahoo.com.

RESULTS AND DISCUSSION

The starting compounds ethyl 3-aminothieno[2,3-*b*]quinoxaline-2-carboxylate (**Ia**) and 3-acetyl-3-aminothieno[2,3-*b*]quinoxaline (**Ib**) were synthesized from the reaction of 2-mercaptoquinoxaline-3-carbonitrile with ethyl chloroacetate and chloroacetone according our previous procedure. The amino group of (**Ia,b**) was converted to the 1-pyrrolyl moiety via the interaction with 2,5-dimethoxytetrahydrfuran in boiling acetic acid to afford 3-pyrrolyl-2-substitutedthieno[2,3-*b*]quinoxalines (**IIa,b**) in good yield. IR spectra of the pyrrolyl derivatives represent the disappearance of the bands corresponding the amino group and show high value for the carbonyl group as a result of cancel the effect of the amino group. On the other hand ^{1}H NMR spectra of compounds (**IIa,b**) showed bands characteristic for two sets of pyrrole CH protons.

Compounds (**IIa,b**) were used as key intermediates in the synthesis of other substituted thieno[2,3-*b*]quinoxalines. Thus, reaction of ethyl 3-pyrrolylthieno[2,3-*b*]quinoxaline-2-carboxylate **IIa**) with hydrazine hydrate leads to the formation of the corresponding carbohydrazide derivative (**III**) (Scheme 1). Several pyrrolythieno quinoxaline substituted at position-2 with different heterocyclic residues were obtained via treatment of compound (**IV**) with different reagents. Thus, the mercaptoxadiazolyl derivative (**IV**) was synthesized from the reaction of (**III**) with carbon disulfide in pyridine. The mercapto compound (**IV**) was easily converted into the corresponding *S*-alkylated products (**Va,b**) upon treatment with ethyl chloroacetate or phenacyl bromide respectively. Also, interaction of compound (**III**) with acetyl acetone afforded the dimethylpyrazolyl derivative (**VI**). The carbohydrazide added easily phenyl isocyanate in

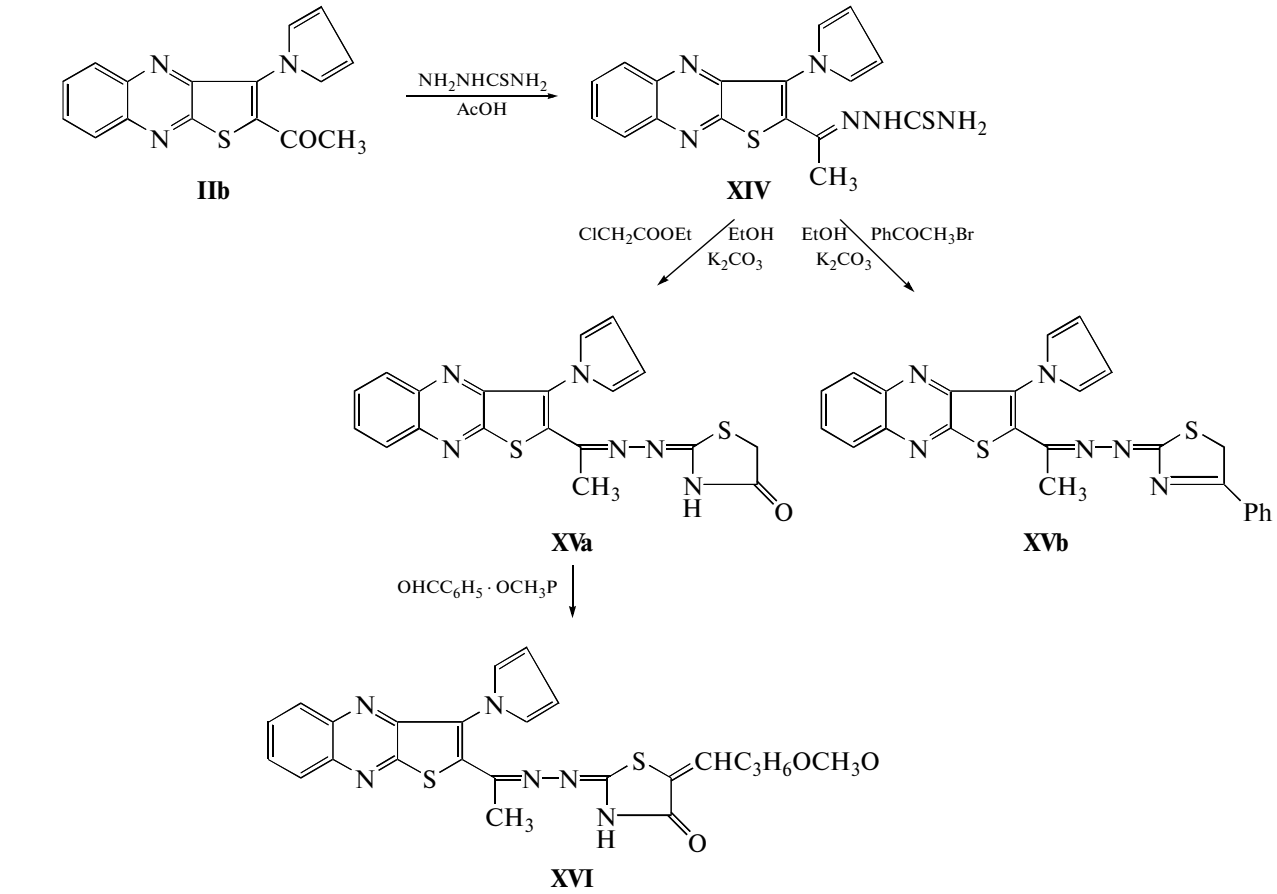
absolute ethanol to afford the thiosemicarbazide derivative (**VII**) which upon treatment with alcoholic potassium hydroxide result in the triazolethione derivative (**VIII**). Diazotization of the carbohydrazide (**III**) leads to the formation of the carboazide derivative (**IX**). The reaction of (**IX**) with aromatic amines gave urea derivatives (**Xa,b**). Furthermore refluxing of the azide derivative in an inert high boiling point solvent such as xylene, led to the formation of pyrrolo[1",2":1',6']pyrazino[2',3':4,5]thieno[2,3-*b*]quinoxalin-2-(1*H*)-ne (**XI**) through a *Curitus* rearrangement. The pyrazinone derivative was subjected to thionation by reacting with phosphorus pentasulfide in dry pyridine to give the corresponding pyrazinthione (**XII**). S-Methylation of (**XII**) using methyl iodide in ethanol in the presence of anhydrous potassium carbonate as basic catalyst afforded (**XIII**) in good yield.



Scheme 1.

On the other hand, 2-acetyl-3-pyrrolyl derivative (**IIb**) was allowed to react with thiosemicarbazide in glacial acetic acid to give the corresponding thiosemicarbazone (**XIV**), which was further reacted with ethyl chloroacetate and phenacyl bromide in boiling ethanol in the presence of anhyd-

rous potassium carbonate to afford compounds (**XVa,b**) in a considerable yield (Scheme 2). The thiazolidinone derivative (**XVa**) was condensed with anisaldehyde in ethanol in presence of piperidine as basic catalyst to afford the anisylidene derivative (**XVI**).



Scheme 2.

Biological activity. Five compounds were selected and screened in vitro for their antimicrobial activity against four strains of bacteria (*Bacillus cereus*, *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus albus*) and six fungal species (*Aspergillus flavus, Aspergillus niger, Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis* and *Trichophyton rubrum*) using the filter paper disc method [17]. The biological activity, as expressed by the growth of the inhibition zones of the tested microorganism are summarized in Table 1 and Table 2. From Table 1, it is obvious that, as bactericides there is no activity for the tested compounds against except for compound (**V**) and (**VIa**). As for fungicides in Table 2, moderate activity was shown against *A. flavus, A. niger, C. albicansand*, *G. candidum, S. brevicaulis* and *T. rubrum*.

EXPERIMENTAL

Melting points are uncorrected and were measured on a Gallenkamp apparatus. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer using KBr discs. ^{1}H NMR spectra were obtained with a Joel LA 400 MHz FT.NMR spectrometer (δ in ppm, *J* in Hz). MS—on a Joel JMS–600 mass spectrometer. Elemental analyses were determined using a Perkin-Elmer 240C microanalyzer and all compounds gave results in acceptable range.

Ethyl 3-aminothieno[2,3-*b*]quinoxaline-2-carboxylate (Ia) and 3-acetyl-3-aminothieno[2,3-*b*]quinoxaline (Ib). These compounds were synthesized according to our previous reports [18].

3-Pyrrolyl-2-substituted thieno[2,3-*b*]quinoxaIines (IIa,b). A mixture of compound (**Ia**) or (**Ib**) (0.01 mol) and 2,5-dimethoxytetrahydrofuran (0.01 mol) in glacial acetic acid (30 mL) was refluxed for 2 h, the solvent was reduced to one third of volume under reduced pressure and then cool. The brown precipitate was extracted several times on cold with ethanol; the extracts were combined together and evaporated

under reduced pressure. The pyrrolyl derivatives (**IIa,b**) were collected by filtration.

Ethyl 3-Pyrrolylthieno[2,3-*b*]quinoxaline2-carboxylate (IIa) was separated from ethanol as yellow crystals, mp 160°C, yield 58%. Found, %: C 57.33; H 4.02; N 15.60; S 11.70. $C_{17}H_{13}N_3O_2S$. Anal. calcd., %: C 57.13; H 4.06; N 15.37; S 11.73. IR (ν, cm^{-1}): 1720 (C=O), 1620 (C=N). ^1H NMR ($CDCl_3$): 1.36–1.39 (3 H, t, *J* 7.2, CH_3), 4.39–44.44 (2 H, q, *J* 8, CH_2), 6.47–6.49 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.23–7.24 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.81–7.91 (2 H, m, Ar–H), 8.16–8.28 (2 H, m, Ar–H). MS: *m/z* 323.3 (M^+).

2-Acetyl-3-pyrrolylthieno[2,3-*b*]quinoxaline (IIb) was separated from ethanol as yellow crystals, mp 210°C, yield 62%. Found, %: C 59.49; H 3.51; N 17.03; S 13.36. $C_{16}H_{11}N_3OS$. Anal. calcd., %: C 59.24; H 3.73; N 17.27; S 13.18. IR (ν, cm^{-1}): 1680 (C=O), 1610 (C=N). ^1H NMR ($CDCl_3$): δ 2.23 (3 H, s, CH_3), 6.51–6.52 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.05–7.06 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.75–7.86 (2 H, m, Ar–H), 8.13–8.20 (2 H, m, Ar–H).

3-Pyrrolylthieno[2,3-*b*]quinoxaline2-carbohydrazide (III). A mixture of compound (**IIa**) (0.01 mol) and hydrazine hydrate (3 mL) was refluxed in absolute ethanol (30 mL) for 4 h. The solid product separated from the hot mixture was filtered off and recrystallized from dioxane to give pale yellow crystals of the carbohydrazide derivative (**III**), mp 192–193°C, yield 71%. Found, %: C 58.48; H 3.52; N 22.90; S 10.43. $C_{15}H_{11}N_5OS$. Anal, calcd., %: C 58.24; H 3.58; N 22.64; S 10.36. IR (ν, cm^{-1}): 3400–3250 ($NHNH_2$), 1660 (C=O), 1610 (C=N). ^1H NMR (DMSO-d_6): 4.55 (2 H, br.s, NH_2), 6.5–6.51 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.11–7.13 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.72–7.76 (2 H, m, Ar–H), 8.15–8.21 (2 H, m, Ar–H). MS: *m/z* 309.4 (M^+).

3-Pyrrolyl-2-(5-mercapto-1,3,4-oxadiazol-2-yl)thieno[2,3-*b*]quinoxaline (IV). A mixture of the carbohydrazide (**III**) (0.005 mol) and carbon disulfide (5 mL) in pyridine (20 mL) was heated on a water bath for 24 h and then cooled. The precipitated product was filtered off and washed several times with ethanol. Recrystallisation from dioxane afforded orange crystals of compound (**IV**), mp 280–281°C, yield 78%. Found, %: C 54.82; H 2.43; N 20.22; S 18.55. $C_{16}H_9N_5OS_2$. Anal. calcd., %: C 54.69; H 2.58; N 19.93; S 18.25. ^1H NMR (DMSO-d_6): 3.83 (1 H, br.s, SH), 6.53–6.54 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.15–7.17 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.76–7.79 (2 H, m, Ar–H), 8.18–8.23 (2 H, m, Ar–H).

3-Pyrrolyl-2-(5-substituted thio-1,3,4-oxadiazol-2-yl)thieno[2,3-*b*]quinoxaline (Va,b). A mixture of the mercapto derivative (**IV**) (0.005 mol) and ethylchloroacetate or phenacyl bromide (0.005 mol) in ethanol containing anhydrous sodium acetate (2 g) was refluxed for 2 h. After cooling, the crude product was filtered off, washed with water and air dried.

Table 1. Antibactertial activity (inhibition zone, mm)

Organisms	Chloramphenicol*	(IIIa)	(IIIc)	(V)	(VIa)	(XIIIb)
B. cereus	25	–	–	17	8	–
E. coli	25	–	–	–	–	–
P. aeruginosa	25	–	–	–	–	–
S. albus	25	–	–	–	–	–

* Chloramphenicol as antibacterial standard.

Table 2. Antifungal activity (inhibition zone, mm)

Organisms	Dermatine*	(IIIa)	(IIIc)	(V)	(VIa)	(XIIIb)
A. flavus	28	8	8	8	–	–
A. niger	35	15	10	8	–	–
C. albicans	22	10	–	–	–	–
G. candidum	35	10	7	7	–	–
S. brevicaulis	25	–	–	–	–	–
T. rubrum	25	–	–	–	–	–

* Dermatine as antifungal standard.

3-Pyrrolyl-2-(5-ethoxcarbonylmethylthio-1,3,4-oxadiazol-2-yl)thieno[2,3-*b*]quinoxaline (Va) was separated from ethanol as yellow crystals, mp 190–191°C, yield 82%. Found, %: C 55.02; H 3.23; N 16.30; S 14.81. $C_{20}H_{15}N_5O_3S_2$. Anal.calcd., %: C 54.91; H 3.46; N 16.01; S 14.66. IR (ν, cm^{-1}): 17320 (C=O), 1600 (C=N). ^1H NMR ($CDCl_3$): 1.27–1.30 (3 H, t, *J* 6.8, CH_3), 3.98 (2 H, s, CH_2), 4.20–4.26 (2 H, q, *J* 7.6, CH_2), 6.46–6.48 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.11–7.12 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.80–7.89 (2 H, m, Ar–H), 8.17–8.25 (2 H, m, Ar–H).

3-Pyrrolyl-2-(5-phenylcarbonylmethylthio-l,3,4-oxadiazol-2-yl)thieno[2,3-*b*]quinoxaline (Vb) was separated from dioxane as yellow crystals, mp 210–211°C, yield 74%. Found, %: C 61.72; H 3.02; N 15.01; S 13.65%. $C_{24}H_{15}N_5O_2S_2$. Anal, calcd., %: C 61.39; H 3.22; N 14.92; S 13.66. IR (ν, cm^{-1}): 1680 (C=O), 1610 (C=N). ^1H NMR (DMSO-d_6): 4.08 (2 H, s, CH_2), 6.47–6.49 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.12–7.13 (2 H, t, *J* 2, 2 CH_{pyrrol}), 7.82–7.89 (5 H, m, Ar–H), 8.18–8.27(4 H, m, Ar–H).

3-Pyrrolyl-2-(3,5-dimethylpyrazolylcarbonyl) thieno[2,3-*b*]quinoxaline (VI). A mixture of the carbohydrazide (**III**) (5 mmol) and acetyl acetone (5 mmol) in absolute ethanol (30 mL) was heated on a water bath for 12 h, the solid product separated from the hot mixture was filtered off and recrystallized from dioxane into yellow crystals of compound (**VI**), mp 182–183°C, yield 64%. Found, %: C 64.35; H 4.09; N

18.90; S 8.52. $C_{20}H_{15}N_5OS$. Anal. calcd., %: C 64.33; H 4.05; N 18.75; S 8.59. IR (ν, cm^{-1}): 1690 (C=O). ^1H NMR ($CDCl_3$): 2.23 (3 H, s,CH_3), 2.42 (3 H, s, CH_3), 6.15 (1 H, s, H pyrazole), 6.44–6.46 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.15–7.16 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.47–7.50 (2 H, m, Ar–H), 8.39–8.43 (2 H, m, Ar–H).

N^1-[Phenyl]-N^2-[3-pyrrolylthieno[2,3-*b*]quinoxalin-2-ylcarbonyl]thiosemicarbazide (VII). A mixture of the carbohydrazide (**III**) (5 mmol) and phenyl isothiocyanate (0.005 mol) in absolute ethanol (30 mL) was heated on a water bath for 30 min, the solid product separated from the hot mixture was filtered off and recrystallized from ethanol into white crystals of compound (**VII**), mp 150–152°C, yield 77%. Found, %: C 59.22; H 3.80; N 18.62; S, 14.62. $C_{22}H_{16}N_6OS_2$. Anal. calcd., %: C 59.44; H 3.63; N 18.90; S 14.43. IR (ν, cm^{-1}): 3300, 3400 (NH), 1670 (C=O), 1230 (C=S). ^1H NMR ($CDCl_3$): 6.4–6.42 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.14–7.15 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.36–7.48 (5 H, m, Ar–H), 8.07, 8.22 (2 H, 2s, 2 NH), 8.33–8.41 (4 H, m, Ar–H), 9.2 (1 H, s, NH).

3-Pyrrolyl-2-(4-phenyl[1,2,4]triazol-3-yl-2(*1H*) thione)thieno[2,3-*b*]quinoxaline (VIII). A mixture of thiosemicarbazide derivative (**VII**) (0.005 mol) and alcoholic potassium hydroxide (50 mL, 10%) was refluxed for 3 h, the solvent was reduced to one half under reduced pressure, then cooled. Acidification with dilute hydrochloric acid gave orange precipitate which was washed with water and air dried. Recrystallisation from dioxan afford orange crystals of compound (**VIII**), mp 150–152°C, yield 51%. Found, %: C 62.05; H 3.28; N 19.84; S 14.93. $C_{22}H_{14}N_6S_2$. Anal. calcd., %: C 61.95; H 3.31; N 19.70; S 15.03. IR (ν, cm^{-1}): 3320 (NH). ^1H NMR (DMSO-d_6): 6.36–6.38 (2, t, *J* 2.4, 2$CH_{pyrrolyl}$), 7.09–7.10 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.41–7.47 (5 H, m, Ar–H), 8.16 (1 H, s, NH), 8.37–8.45 (4 H, m, Ar–H).

3-Pyrrolylthieno[2,3-*b*]quinoxaline-2-carboazide (IX). To a cooled solution of compound (**III**) (5 mmol) in acetic acid (20 mL), sodium nitrite solution (0.01 mol in 2 mL H_2O) was added dropwise with stirring. After addition was finished, the stirring was continued for another 1 h and the mixture was allowed to stand for 3 h. The solid product was filtered off, washed several times with water and air dried. Compound (**IX**) was subjected to the next step without further purification. mp 127°C, yield 66%. Found, %: C 56.02; H 2.96; N 26.22; S 9.83. $C_{15}H_8N_6OS$. Anal. calcd., %: C 55.89; H 3.13; N 26.07; S 9.95. IR (ν, cm^{-1}): 2130 (N_3), 1670 (C=O); 1610 (C=N). ^1H NMR ($CDCl_3$): 6.51–6.52 (2, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.15–7.17 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.76–7.81 (2 H, m, Ar–H), 8.15–8.22 (2 H, m, Ar–H).

N^1-[Phenyl or 4-methoxyphenyl]-N^2-[3-pyrrolylthieno[2,3-*b*]quinoxalin-2-yl] urea (Xa,b). A mixture of the azide derivative (2 mmol) and aromatic amine (2 mmol) was fused together until nitrogen gas effervescence was ceased then ethanol 10 mL was added and the mixture was refluxed for 1 h. The solid product was filtered off washed several times with ethanol and air dried.

Compound (**Xa**) was separated from ethanol as yellow crystals, mp 184–185°C, yield 52%. Found, %: C 65.24; H 4.02; N 18.02; S 8.43. $C_{21}H_{15}N_5OS$. Anal. calcd., %: C 65.44; H 3.92; N 18.17; S 8.32. IR (ν, cm^{-1}): 1660 (C=O); 1600 (C=N). ^1H NMR ($CDCl_3$): 6.46–6.48 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.12–7.14 (2 H, t, *J* 2A, 2 $CH_{pyrrolyl}$), 7.43–7.61 (4 H, m, Ar–H), 8.15–8.37 (7 H, m, Ar–H and 2 NH).

Compound (**Xb**) was separated from ethanol as yellow crystals, mp 166–168°C, yield 54%. Found, %: C 63.48; H 4.42; N 16.65; S 7.66. $C_{21}H_{15}N_5OS$. Anal. calcd., %: C 63.60; H 4.12; N 16.86; S 7.72. IR (ν, cm^{-1}): 1660 (C=O), 1600 (C=N). ^1H NMR ($CDCl_3$): 6.46–6.48 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.12–7.14 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.43–7.61 (4 H, m, Ar–H), 8.15–8.37 (7 H, m, Ar–H and 2 NH).

Pyrrolo[1",2":1',6']pyrazino[2',3':4,5]thieno[2,3-*b*]quinoxalin-]2]-(1*H*)-one (XI). A sample of compound (**IX**) (1 g) in dry xylene (20 mL) was refluxed for 2 h till effervescence due to nitrogen gas evolution was ceased and a solid was separated. The solid product was filtered off and recrystallized from dioxane into pale yellow crystals of compound (**XI**), mp 313–314°C, yield 58%. Found, %: C 61.81; H 2.63; N 19.54; S 11.03. $C_{15}H_8N_4OS$. Anal. calcd., %: C 61.63; H 2.76; N 19.17; S 10.97. IR (ν, cm^{-1}): 3300 (NH), 1670 (C=O); 1610 (C=N). ^1H NMR (DMSO-d_6): 6.58–6.6 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.19–7.21 (2 H, t, *J* 2.6, 2 $CH_{pyrrolyl}$), 7.83–7.86 (2 H, m, Ar–H), 8.17–8.25 (2 H, m, Ar–H), 8.32 (1 H, s, NH).

Pyrrolo[1",2":1',6')pyrazino[2',3':4,5]thieno[2,3-*b*]quinoxalin-2-(1*H*)-thione (XII). A mixture of compound (**XI**) (5 mmol) and phosphorus pentasulfide (5 mmol) in dry pyridine was refluxed for 54 h then cooled. The reaction mixture was poured onto ice/water mixture containing 20 mL acetic acid. The solid separated was filtered off and recrystallised from dioxane into orange crystals of compound (**XII**) mp 345–346°C, yield 68%. Found, %: C 58.64; H 2.51; N 18.35; S 20.63. $C_{15}H_8N_4S_2$. Anal. calcd., %: C 58.42; H 2.61; N 18.17; S 20.79. IR (ν, cm^{-1}): 3320 (NH). ^1H NMR (CF_3CO_2D): 6.71–6.73 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.35–6.37 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 8.06–8.13 (2 H, m, Ar–H), 8.33–8.37 (2 H, m, Ar–H).

2-Methylthiopyrrolo[1",2":1',6']pyrazmo[2',3':4,5] thieno[2,3-*b*]quinoxaline (XIII). A mixture of pyrazinethione derivative (**XII**) (2 mmol) and methyl iodide (5 mmol) in ethanol (30 mL) in presence of anhydrous potassium carbonate (2 g) was refluxed for 2 h, then filtered. The solid product separated from the cold solution was filtered off and recrystallised from ethanol into yellow crystals of compound (**XIII**) mp 269–270°C, yield 71%. Found, %: C 59.63; H 3.22; N 17.45; S 19.82. $C_{16}H_{10}N_4S_2$. Anal. calcd.: C 59.61; H 3.13; N 17.38; S 19.89. ^1H NMR (DMSO-d_6): 3.10

(3 H, s, CH_3), 6.55–6.57 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.19–7.21 (1 H, d, *J* 2.6, $CH_{pyrrole}$), 7.79–7.84 (2 H, m, Ar–H), 8.16–8.25 (2 H, m, Ar–H).

Condensation of compound (IIb) with thiosemicarbazide (formation of thiosemicarbazone (XIV)). A mixture of compound (**IIb**) (0.01 mol) and thiosemicarbazide (0.01 mol) in glacial acetic acid (30 mL) was refluxed for 3 h, the solid product separated from the hot mixture was filtered off and recrystallized from acetic acid into yellow crystals of thiosemicarbazone (**XIV**), mp 275–276°C, yield 70%. Found, %: C 55.53; H 3.90; N 23.02; S 17.35. $C_{17}H_{14}N_6S_2$. Anal. calcd., % : C 55.72; H 3.85; N 22.93; S 17.50. IR (ν, cm^{-1}): 3280–3320 (NH, NH_2), 1600 (C=N). ^1H NMR (CF_3CO_2D): 2.33 (3 H, s, CH_3), 6.58–6.6 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.13–7.15 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.83–7.92 (2 H, m, Ar–H), 8.23–8.29 (2 H, m, Ar–H).

Reaction of thiosemicarbazone (XIV) with ethyl chloroacetate and phenacyl bromide (formation of compounds (XVa,b)). To a mixture of compound (**XIV**) (0.005 mol) and the corresponding α-haloesters or α-haloketones (0.005 mol) in ethanol (50 mL), anhydrous potassium carbonate (2 g) was added. The mixture was refluxed for 4 h, then filtered off and the solid precipitated on cooling was diluted with water. The solid thus obtained, was filtered off washed with water, and air dried.

Compoud (XVa) was separated from ethanol as pale yellow crystals, mp 148–149°C, yield 58%. Anal. calcd. for $C_{19}H_{14}N_6OS_2$ (406.49): C, 56.14; H, 3.47; N, 20.67; S, 15.78%. Found: C, 56.42; H, 3.32; N, 20.77; S, 15.85%. IR: ν 3310 (NH), 1670 (C=O); 1600 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.53 (3 H, s, CH_3), 3.96 (2 H, s, CH_2); 6.53–6.55 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$); 7.11–7.12 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.71–7.84 (2 H, m, Ar–H), 8.14–8.21 (2 H, m, Ar–H), 8.9 (1 H, s, NH).

Compoud (XVb) was separated from ethanol as yellow crystals, mp 181–182°C, yield 66%. Found, %: C 64.56; H 3.73; N 18.30; S 13.65. $C_{25}H_{18}N_6S_2$. Anal. calcd., %: C 64.36; H 3.89; N 18.01; S 13.74. IR (ν, cm^{-1}): 1610 (C=N). ^1H NMR ($CDCl_3$): 2.49 (3 H, s, CH_3), 3.9 (2 H, s, CH_2); 6.51–6.53 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$); 7.09–7.10 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.53–7.84 (5 H, m, Ar–H), 8.03–8.21 (4 H, m, Ar–H).

Synthesis of 4-methoxybenzylidene derivative of compound (XVa), formation of compound (XVI). A mixture of compound (**XVa**) (0.002 mol) and 4-methoxybenzaldehyde (0.002 mol) was fused together in presence of few drops of piperidine for 10 min, then ethanol (30 mL) was added and the mixture was refluxed for 2 h. The solid product separated from the hot solution was filtered off and recrystallized from acetic acid into yellow crystals of compound (**XVI**). Mp 297–298°C, yield 62%. Found, %: C 61.75; H 3.90; N 16.20; S 12.15. $C_{27}H_{20}N_6O_2S_2$. Anal. calcd., %: C 61.82; H 3.84; N 16.02; S 12.22. IR (ν, cm^{-1}): 3310 (NH), 1670 (C=O); 1600 (C=N). ^1H NMR (DMSO): 2.53 (3 H, s, CH_3), 3.90 (3 H, s, CH_3); 6.54–6.56 (2 H, t, *J* 2.4, 2 $CH_{pyrrolyl}$), 7.11–7.12 (2 H, t, *J* 2, 2 $CH_{pyrrolyl}$), 7.25–7.79 (6 H, m, Ar–H), 8.14–8.21 (2 H, m, Ar–H), 8.26 (1 H, s, CH), 9.10 (1 H, s, NH).

Biological Screening Assays

Antibacterial activity. Four bacterial species representing both Gram-positive and Gram-negative strains were used to test the antibacterial activities of the target compounds **(IIIa)**, **(IIIc)**, **(V)**, **(VIa)** and **(XIIIb)** in vitro, in comparison to Chloramphenicol as a reference drug using the standard agarpaper disc diffusion method [17]: *B. cereus*, *E. coli*, *P. aeruginosa* and *S. albus* cell suspensions of bacterialstains were prepared from 48 h old cultures grown on potato dextrose agar (PDA) or Sabouraud agar (SA) media. One mL of the cell suspension was added to Petri dishes of 9 cm in diameter, and then 15 mL of nutrient agar was poured onto the plates. Plates were shaken gently to homogenize the innoculum. Sterile 5 mm filter paper (Whatmann, UK) was saturated with 10 mg mL^{-1} of the test compound, Chloramphenicol solutions (200,100, 50, 25, 15.5, 6 mg/mL concentrations) as reference drug or DMSO as negative control. Impregnated discs were then dried for 1 h and placed in the centre of each plate. The seeded plates were incubated at 35 ± 2°C for 24–48 h. The radii of the inhibition zones in mm of triplicate sets were measured and the results are given in Table 1.

Antifungal Activity

Compounds **(IIIa)**, **(IIIc)**, **(V)**, **(VIa)** and **(XIIIb)** were screened for their antifungal activity in vitro, in comparison to *Dermatin* as a reference drug using the standard agar paper disc diffusion method against sex fungi: *A. flavus*, *A. niger*, *C. albicans*, *G. candidum*, *S. brevicaulis* and *T. rubrum*. A spore suspension in sterile distilled water was prepared from 2–3 days old culture of the fungi growing on potato dextrose agar (PDA) or Sabouraud agar (SA) media. The final spore concentration was 56104 spores/mL. About 15 mL of the growth medium was placed into sterile Petri dishes of 9 cm in diameter and incubated with 1 mL of the spore suspension. Plates were shaken gently to 28 ± 2°C for 7 days. The radii of the inhibition zones in mm of triplicate sets were measured and the results had shown in Table 2.

REFERENCES

1. Waisser, K., Odlerova, Z., Beckert, R., and Mayer, R., *Pharmazie*, 1989, vol. 44, pp. 234–235.
2. Cheng, M., Lobowski, E.B., and Coates, G.W., *J. Am. Chem. Soc.*, 1998, vol. 120, pp. 11018–11019.
3. Beckert, R., Waisser, K., Lindauer, D., Käpplinger, C., and Walther, R., *Pharmazie*, 1997, vol. 52, pp. 638–639.

4. De Clercq, E., *Med. Res. Rev.*, 2003, vol. 23, pp. 253–274.
5. Amblard, F., Aucagne, V., Guenot, P., Schinazi, R.F., and Agrofoglio, L.A., *Bioorg. Med. Chem.*, 2005, vol. 13, pp. 1239–1248.
6. Martin-Kohler, A., Widmer, J., Bold, G., Meyer, T., Séquin, U., and Traxler, P., *Helv. Chim. Acta*, 2004, vol. 87, pp. 956–975.
7. Renault, J., Jourdan, F., Laduree D., and Robba, M., *Heterocycles*, 1995, vol. 41, pp. 937–945.
8. McGuigan, C., Yarnold, C.J., Jones, G., Velazquez, S., Barucki, H., and Brancale, A., *J. Med. Chem.*, 1999, vol. 42, pp. 4479–4484.
9. McGuigan, C., Barucki, H., Blewett, S., Carangio, A., Erichsen, J.T., and Andrei, G., *J. Med. Chem.*, 2000, vol. 43, pp. 4993–4997.
10. Kamal El-Dean, A.M., Geies, A.A., El-Kashef, H.S., Rault, S., Allemagne, P.D., and Lancelot, J.C., *J. Heterocycl. Chem.*, 2000, vol. 37, pp. 1521–1526.
11. Bakhite, E.A., Geies, A.A., and El-Kashef, H.S., *Phosphorus, Sulfur and Silicon*, 2002, vol. 177, pp. 303–323.
12. Geies, A.A., Bakhite, E.A., and El-Kashef, H.S., *Pharmazie*, 1998, vol. 53, pp. 686–690.
13. Badr, M.Z.A., Geies, A.A., Abbady, M.S., and Dahy, A.A., *Can. J. Chem.*, 1998, vol. 76, pp. 469–476.
14. Abdel-Hafez, Sh.H., *Russ. J. Org. Chem.*, 2005, vol. 41, pp. 396–401.
15. Abdel-Hafez, Sh.H., *Phosphorus, Sulfur and Silicon*, 2003, vol. 178, pp. 2563–2579.
16. Abdel-Mohsen, Sh.A., *J. Chin. Chem. Soc.*, 2003, vol. 50, pp. 1085–1092.
17. Kalyoncuoglu, N., Rollas, S., Sur-Altiner, D., Yegenoglu, Z., and Ang, O., *Pharmazie*, 1992, vol. 47, pp. 769–773.
18. Abdel Moneam, M.I., Geies, A.A., El-Naggar, G.M., and Mousa, S.M., *J. Chin. Chem. Soc.*, 2004, vol. 51, pp. 1357–1366.