New Fused Quinoxalines : Synthesis and Reactions of Pyrimidothienoquinoxaline and Oxadizolylthienoquinoxalines

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Diazotization of 3-amino-2-ethoxycarbonylthieno[2,3-b]quinoxaline **1** gave the diazonium salt **2** which was reacted with SO_2 and *N*-methylaniline to give sulfamoylquinoxaline derivatives **3**-**5**. Imidazothienoquinoxaline **8** was obtained from the reaction of carboxylic acid hydrazide **6** with nitrous acid and followed by boilling the carboazide **7** in dry xylene. Also, compound **6** react with $CH(OEt)_3$ to give aminopyrimidine **9** which was reacted with arylidene malonodinitrile, furfural and/or dimethoxy-tetrahydrofuran to afford compounds **10**, **11** and/or **12** respectively. Refluxing of **6** with CS_2 gave oxadiazolylthienoquinoxaline **13**, reaction of **13** with hyrazine hydrate, $CH(OEt)_3$, nitrous acid, CS_2 and α-halocompounds to give **14**-**19**.

Keywords : Synthesis, Diazotization, Heterocycles, Pyrimidothienoquinoxalines.

Introduction

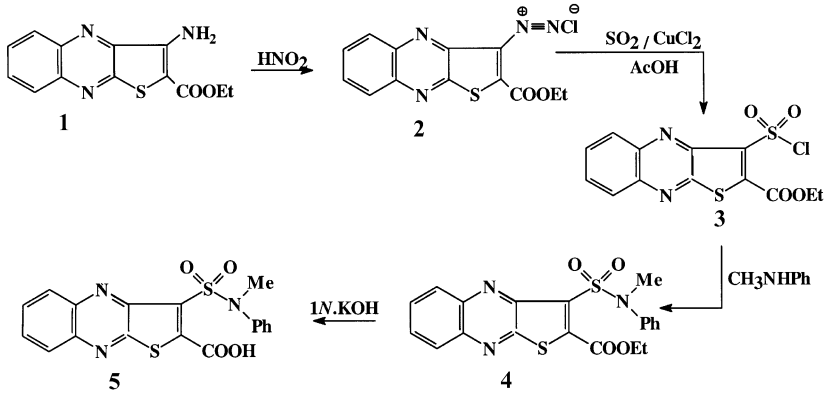
Among the wide variety of quinoxaline derivatives that have been explored for developing pharmaceutically important molecules for examples, imidazoquinoxalines ribonucleosides as linear of antiviral,[1] pyrazoloquinoxaline showed a relatively high antibacterial activity wherien MIC value was 25 μg/mL against *Bacillus Licheniformis* and *Cellulomonas* Sp.,[2] quinoxaline-1,4-di-*N*-oxides for treatment of tuberculosis,[3] pyrimido[4,5-b]quinoxaline used as anti-hypertensive and blood platelet antiaggregating agents,[4] also some quinoxaline derivatives have a cytotoxic effects on human cancer cell lines,[5,6] commercially impotant as agrochemicals,[7] herbicides,[8] hypoxic-cytoxic agents,[9] antivirus (Hepatitis B),[10] antimicrobial,[11] and amebicides,[12] we are taking all the above benefits into consideration and in continuation of our work in synthesis of fused heterocyclic rings with quinoxaline moiety.[13-19]

Results and Discussion

In this work we aimed to synthesize some diferent heterocycles systems fused with thieno[2,3-b]quinoxaline hoping that they may be highly biological activity. The reaction of 3-amino-2-ethoxycarbonylthieno[2,3-b]quinoxaline **1**[15] with nitrous acid and then sulfur dioxide and cupric chloride in acetic acid gave the 2-ethoxycarbonylthieno[2,3-b]quinoxaline-3-sulfonylchloride **3** *via* the diazonium salt **2**.[15] The reaction of **3** with *N*-methylaniline afforded the 3-sulfamoylthienoquinoxaline **4**, whose hydrolysis provided the 3-sulfamoyl-2-carboxylic acid **5** (Scheme 1).

3-Amino-2-thieno[2,3-b]quinoxaline-2-carboxylic acid hydrazide **6** was obtained by refluxing the coressponding ethyl ester **1** in ethanolic hydrazine hydrate[14] which was reacted with nitrous acid ($NaNO_2$/AcOH) to produce the corresponding 3-amino-2-carboazide derivative **7**, which underwent Curtius rearrengment when refluxed in dry xylene to the imidazothieno[2,3-b]quinoxalinone **8** (Scheme 2).

The reaction of carohydrazide **6** with triethyl orthoformate in ethanol in the presence of catalytic amount of acetic acid led to the formation of 3-aminopyrimidothieno[2,3-b]quinoxalinone **9,** which was subjected to Michael reaction when reacted with benzylidene malonodinitrile in ethanol in the presence of a few drops of piperidine to give the pyrida-



Scheme 1

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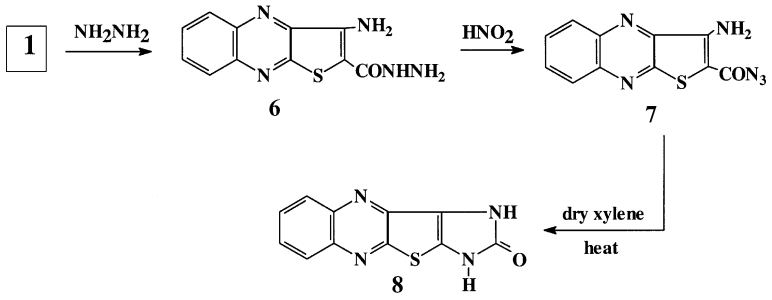
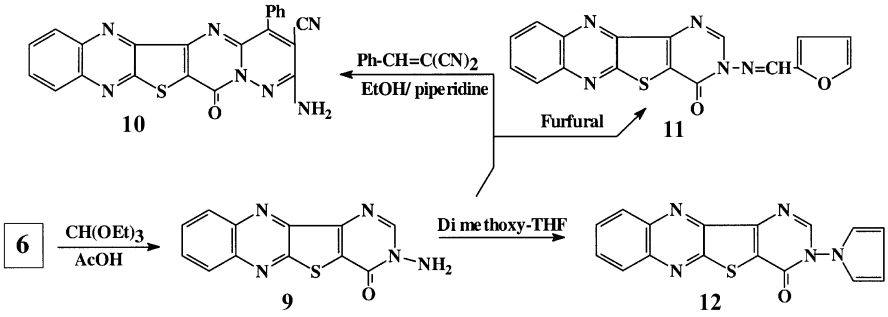


Scheme 2



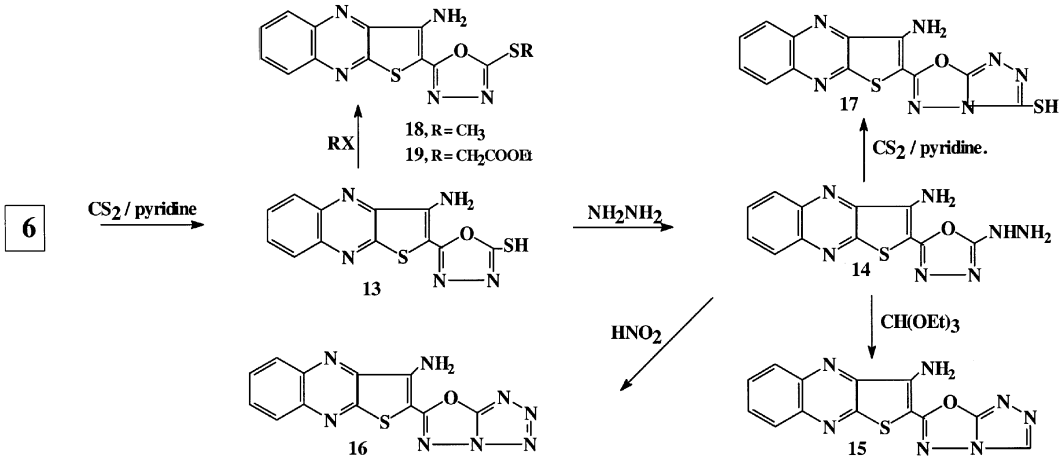
Scheme 3

zinopyrimidothieno[2,3-b]quinoxalinone **10**. While the reaction of aminopyrimidine **9** with furfural and with dimethoxytetrahydrofuran provided the Schiff bases **11** and 3-(1-pyrryl) derivative **12**, respectively (Scheme 3).

When the carbohydrazide **6** was refluxed with carbon disulfide in pyridine gave oxadiazolylthienoquinoxaline **13** which was refluxed with hydrazine hydrate to produce 3-amino-2-(2-hydrazino-1,3,4-oxadiazol-5-yl)thieno[2,3-b]quinoxaline **14**. The latter compound was reacted with triethyl orthoformate and with nitrous acid to give (triazolo and tetrazolo)oxadiazolylthienoquinoxalines **15** and **16** resectively. Also, when **14** was allowed to react with carbon disulfide in pyridine the sulfanyltriazolooxadiazolyl derivative **17** was formed. Furthermore, the reaction of the thiooxadiazol **13** with α-halocompounds in the presence of sodium acetate yield S-alkylated derivatives **18** and **19** (Scheme 4).

Experimental Section

Melting points were determined on a Gallen Kamp melting point apparatus and were uncorrected. IR spectra were recorded on a Pye-Unicam SP^3-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a 90 MHz Varian EM-390 NMR spectrometer in a suitable deutreated solvent (TMS) as the internal standard. Elemental analyses were determined on a Perkin-Elmer 240 C microanalyzer. Elemental analysis, melting points, yields and



Scheme 4

Table 1. Melting Points, Yields and Analytical Data of Compounds **3-19**

Comp. No	M.P°C (Yield%)	Formula Mol. Wt	Calculated/found C	H	N	S
3[a]	310	$C_{13}H_9N_2O_4S_2Cl$	43.75	2.52	7.85	17.95
	(80)	356.5	43.67	2.41	7.79	17.89
4	180	$C_{20}H_{17}N_3O_4S_2$	56.20	3.98	9.83	14.98
	(68)	427	56.07	3.86	9.78	14.88
5	220-21	$C_{18}H_{13}N_3O_4S_2$	54.13	3.25	10.52	16.04
	(75)	399	54.17	3.20	10.43	15.89
7	240	$C_{11}H_6N_6OS$	48.88	2.22	31.11	11.85
	(83)	270	48.79	2.18	31.07	11.78
8	190	$C_{11}H_6N_4OS$	54.54	2.47	23.14	13.22
	(80)	242	54.49	2.38	23.09	13.11
9	290	$C_{12}H_7N_5OS$	53.53	2.60	26.02	11.89
	(70)	269	53.44	2.56	26.12	11.90
10	225	$C_{22}H_{11}N_7OS$	62.70	2.61	23.27	7.60
	(77)	421	62.61	2.54	23.00	7.54
11	>360	$C_{17}H_9N_5O_2S$	58.78	2.59	20.17	9.22
	(70)	347	58.67	2.44	20.12	9.13
12	115	$C_{16}H_9N_5OS$	60.18	2.82	21.94	10.03
	(90)	319	59.98	2.77	21.84	10.00
13	320	$C_{12}H_7N_5OS_2$	47.84	2.32	23.25	21.26
	(81)	301	47.76	2.23	23.14	21.19
14	260	$C_{12}H_9N_7OS$	48.16	3.01	32.77	10.70
	(82)	299	48.29	3.10	33.00	10.68
15	>360	$C_{13}H_7N_7OS$	50.48	2.26	31.71	10.35
	(75)	309	50.30	2.22	31.61	10.27
16	>360	$C_{12}H_6N_8OS$	46.45	1.93	36.12	10.32
	(69)	310	46.50	1.90	36.21	10.36
17	120	$C_{13}H_7N_7OS_2$	45.74	2.05	28.73	18.76
	(90)	341	45.61	2.00	28.66	18.59
18	150	$C_{13}H_9N_5OS_2$	49.52	2.85	22.22	20.31
	(78)	315	49.60	2.86	22.16	20.22
19	240	$C_{16}H_{13}N_5O_3S_2$	49.61	3.35	18.08	16.53
	(83)	387	49.44	3.32	18.00	16.41

[a]Cl (calc. 9.95, found 9.88%).

spectroscopic data of compounds **3-19** are listed in Tables 1 and 2.

3-Amino-2-ethoxycarbonylthieno[2,3-b]quinoxaline (1)

2-Ethoxycarbonylthieno[2,3-b]quinoxaline-3-diazonium chloride (2). Compounds **1** and **2** were prepared according to the literature, mp 145 and 258 °C, respectively; Lit [15].

2-Ethoxycarbonylthieno[2,3-b]quinoxaline-3-sulfonyl-chloride (3). To a solution of compound **2** (0.01 mol) in glacial acetic acid (30 mL) was added cupric chloride (0.015 mol), a slow rate of SO_2 was passed through this solution for 1 hr, stand the reaction mixture for 2 h at RT and the mixture was poured into water. The solid separated was filtered and crystallized from acetic acid as greenish crystals.

Ethyl 3-(N-methyl-N-phenyl)sulfamoylthieno[2,3-b]quinoxaline-2-carboxylate (4). A mixture of **3** (0.01 mol) and *N*-methylaniline (0.01 mol) in absolute ethanol was refluxed for 3 h, after cooling. The solid product thus formed was recrystallized from ethanol as red crystals.

3-(N-Methyl-N-phenyl)sulfamoylthieno[2,3-b]quinoxaline-2-carboxylic acid (5). A sample of **4** (0.5 g) in 10% KOH (25 mL) was heated under reflux for 2 h, then allowed to cool, neutralized with dilute HCl. The solid product thus formed was recrystallized from ethanol as red crystals.

3-Amino-2-thieno[2,3-b]quinoxaline-2-carboxylic acid hydrazide (6). Compound **6** was prepared according to the literature m.p. 305-306 °C; Lit [14].

3-Amino-2-thieno[2,3-b]quinoxaline-2-carboazide (7). To a mixture of **6** (0.01 mol) and acetic acid (15 mL) was added sodium nitrite solution (14 mL, 0.01 mol) at 0° with stirring for 30 min and the resulting solid was filtered and recrystallized from ethanol as yellow crystals.

Imidazo[4',5':4,5]thieno[2,3-b]quinoxalin-2(1H, 3H)-one (8). A sample of **7** (0.5 g) in dry xylene (15 mL) was heated under reflux for 30 min, then allowed to cool. The solid product thus formed was recrystallized from ethanol as yellow crystals.

Table 2. Spectroscopic Data of Compounds **3-19**

Compound No.	IR (ν cm^{-1}) / ^{1}H NMR δ (ppm)
3	1720 (CO), 1620 (C=N); (DMSO-d_6): δ 1.3-1.45 (t, 3H, CH_3) 4.2-4.4 (q, 2H, CH_2), 7.3-7.8 (m, 4H, Ar-H).
4	1730 (CO), 1610 (C=N); (DMSO-d_6): δ 1.3-1.4 (t, 3H, CH_3), 3.2 (s, 3H, CH_3), 4.2-4.4 (q, 2H, CH_2), 7.4-7.9 (m, 9H, Ar-H).
5	1740 (CO), 1630 (C=N); (CF_3COOD): δ 3.2 (s, 3H, CH_3), 7.4-8.1 (m, 9H, Ar-H).
7	3380 (NH_2), 2180 (N_3), 1730 (N_3-CO); (DMSO-d_6): δ 6.2 (s, 2H, NH_2), 7.5-8.0 (m, 4H, Ar-H).
8	3210, 3185 (NH), 1670 (CO); ($CDCl_3$): δ 7.5-8.3 (m, 4H, Ar-H), 9.2,10.3 (s, 2H, NH).
9	3340 (NH_2), 1680 (C=O); (DMSO-d_6): δ 6.3 (s, 2H, NH_2), 7.5-7.8 (m, 4H, Ar-H), 9.5 (s, 1H, CH).
10	3420 (NH_2), 2220 (CN), 1700 (C=O); (DMSO-d_6): δ 6.2 (s, 2H, NH_2), 7.4-7.9 (m, 9H, Ar-H).
11	2960 (CH, aliph.), 1690 (CO), 1620 (C=N).
12	1700 (CO) 1640 (C=N); (DMSO-d_6): δ 6.1, 6.3 (2d, 4H, CH-pyrrole), 7.6-8.2 (m, 4H, Ar-H), 9.4 (s, 1H, CH).
13	3430 (NH_2), 1230, 1060 (SH); (DMSO-d_6): δ 6.24 (s, 2H, NH_2), 7.5-8.2 (m, 4H, Ar-H).
14	3220, 3500 (NH, NH_2), 1630 (C=N); (CF_3COOD): δ 7.5-7.95 (m, 4H, Ar-H).
15	3430 (NH_2); (DMSO-d_6): δ 6.15 (s, 2H, NH_2), 7.5-8.2 (m, 4H, Ar-H), 9.4 (s, 1H, CH).
16	3400 (NH_2), 1620 (C=N); (CF_3COOD): δ 7.5-7.95 (m, 4H, Ar-H).
17	3400 (NH_2), 1220, 1050 (SH); (DMSO-d_6): δ 6.25 (s, 2H, NH_2), 7.45-8.0 (m, 4H, Ar-H).
18	3410 (NH_2); ($CDCl_3$): δ 3.3 (s, 3H, CH_3), 6.1 (s, 2H, NH_2) 7.6-8.2 (m, 4H, Ar-H)
19	3420 (NH_2), 2930 (CH, aliph.), 1720 (C=O); ($CDCl_3$): δ 1.4-1.6 (t, 3H, CH_3), 4.1-4.25 (q, 2H, CH_2), 6.2 (s, 2H, NH_2), 7.4-8.1 (m, 4H, Ar-H).

3-Amino-pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(2H)-one (9). To a mixture of **6** (0.015 mol) and triethyl orthoformate (5 mL) in methanol (30 mL), few drops of acetic acid were added. The mixture was heated under reflux for 5 h, then allowed to cool. The solid product thus formed was recrystallized from ethanol as red crystals.

2-Amino-3-cyano-4-Phenylpyridazino[2'',3'':1',2']pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-13-one (10). A solution of **9** (0.01 mol), arylidene malonodinitrile (0.01 mol) in absolute ethanol (10 mL) and (1 mL) of triethylamine, was stirred at reflux for 2 h. After cooling the solid product was filtered, washed with cool ethanol and recrystallized from ethanol as pale yellow crystals.

3-(2-Furfurilidene)aminopyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H)-one (11). A solution of compound **9** (0.01 mol) and furfural (0.015 mol) in glacial acetic acid (40 mL) was heated at 80° for 4 h. After cooling the separated solid was filtered and crystallized from acetic acid as browinsh crystals.

3-(1-Pyrryl)pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H)-one (12). To a solution of compound **9** (0.01 mol) in glacial acetic acid (20 mL) was added dimethoxy-tetrahydrofuran (0.015 mol), and the mixture was refluxed, stirred for 2 h, evaporated under redused pressure, the residue was crystallized from ethanol/acetic acid as redish crystals.

3-Amino-2-(5-sulfanyl-1,3,4-oxadiazol-2-yl)thieno[2,3-b]quinoxaline (13). A mixture of **6** (0.01 mol) and carbon disulfide (5 mL) in pyridene (25 mL) was refluxed on steam bath for 8 h, then allowed to cool. The solid product thus formed was recrystallized from ethanol as red crystals.

3-Amino-2-(5-hydrazino-1,3,4-oxadiazol-2-yl)thieno[2,3-b]quinoxaline (14). A mixture of **13** (0.01 mol) and hydrazine hydrate (6 mL) was refluxed in ethanol (35 mL) for (5 h, or until evoluation of H_2S cease) then allowed to cool, the yellow precipitate was filtered off and recrystallized from ethanol.

3-Amino-2-(1,2,4-triazolo[3,4-b][1,3,4]oxadiazol-6-yl)-thieno[2,3-b]quinoxaline (15). To a mixture of **14** (0.015 mol) and triethyl orthoformate (3 mL) in methanol (20 mL), few drops of acetic acid were added. The mixture was heated under reflux for 3 h, then allowed to cool. The solid product thus formed was recrystallized from acetic acid as pale red crystals.

3-Amino-2-(tetrazolo[4,5-b][1,3,4]oxadiazol-6-yl)thieno-[2,3-b]quinoxaline (16). To a solution of **14** (0.01 mol) in acetic acid (25 mL) was added dropwise sodium nitrite solution (14 mL, 0.01 mol) at 0° with stirring for 2 h. The resulting solid was filtered and recrystallized from ethanol as yellowish crystals.

3-Amino-2-(3-sulfanyl-1,2,4-triazolo[3,4-b]oxadiazol-6-yl)thieno[2,3-b]quinoxaline (17). A mixture of **14** (0.01 mol) and carbon disulfide (5 mL) in pyridine (35 mL) was refluxed on steam bath for 6 h, then allowed to cool. The solid product thus formed was recrystallized from acetic acid as pale red crystals.

3-Amino-2-(5-methylthio-1,3,4-oxadiazol-2-yl)thieno[2,3-b]quinoxaline (18). A mixture of **13** (0.01 mol), methyl iodide (0.01 mol) and anhydrous sodium acetate (5 g) in ethanol (40 mL) was refluxed for 2 h, poured onto cold water. The solid obtained was filtered off and recrystallized from ethanol as pale yellow crystals.

3-Amino-2-(5-ethylacetatethio-1,3,4-oxadiazol-2-yl)thieno-[2,3-b]quinoxaline (19). A mixture of **13** (0.01 mol), ethyl chloroacetate (0.01 mol) and anhydrous sodium acetate (5 g) in ethanol (30 mL) was refluxed for 2 h, poured onto cold water. The solid obtained was filtered off and recrystallized from ethanol as pale yellow crystals.

References

1. Zhu, Z.; Saluja, S.; Drach, C. J.; Townsend, L. P. *J. of the Chinese Chem. Soc.* **1988**, *45*(4), 465.
2. (a) Makino, K.; Kim, H. S.; Yoshihisa, K. *J. Heterocycl. Chem.* **1998**, *35*, 321. (b) Makino, K.; Kim, H. S.; Yoshihisa, K. *J. Heterocycl. Chem.* **1998**, *35*, 489.
3. Sainz, Y.; Montoya, M. E.; Martinez, F. J.; Ortega, M. A.; Lopez, A.; Monge, A. *Arzniem. Forsch.* **1999**, *49*, 55. [*Chem. Abstr.* **1999**, *130*, 3827P].
4. Mange, A.; Palop, J. A.; Urbasos, I.; Fernandez-Alvarez, E. *J. Heterocycl. Chem.* **1989**, *26*, 1623.
5. Yoo, H. W.; Yun-Sil, L.; Suh, M. E.; Kim, D. J.; Park, S. W. *Arch. Pharm.* **1998**, *331*, 10331.
6. Gozyo, S.; Kenzi, M.; Yoshihisa, K. *Heterocycles* **1988**, *27*, 2481.
7. Kaneko, C.; Katagiri, S. (Asahi Glass Co.Ltd), Japan Kokai Tokkyo Koho Jp. (patent) **1988**, *62*, 207, 264. [*Chem. Abstr.* **1988**, *109*, 231061f].
8. Hiramatsu, T.; Azuma, S.; Nakagawa, K.; Ichikawa, Y. (Teijin Ltd.) Japan Kokai Tokkyo Koho Jp. (patent), **1988**, *62*, 163, 263, [*Chem. Abstr.* **1988**, *109*, 73473k].
9. Miguel, A. O.; Maria, J. M.; Francisco, J. M.; Yolanda, S.; Maria, E. M.; Adele, L. C.; Antonio, M. *Eur. J. Med. Chem. Chim. Ther.* **2000**, *35*, 121.
10. El-Ashry, E. S. H.; Abdel-Rahman, A. A. H.; Rashed, N.; Rasheed, H. A. *Pharmazie* **1999**, *54*(12), 893.
11. El-Hawash, S. A.; Habib, N. S.; Fanaki, N. H. *Pharmazie* **1999**, *54*, 808.
12. Bindumhavan, V.; Prabhakar, B. C.; Kumar, C. D.; John, D. N.; Helmut, R. R. (Hoechst India Ltd.) Indian IN 167,425 (patent) **1993**, [*Chem. Abstr.* **1993**, *119*, 117279q].
13. Moustafa, O. S. *Phosphorus, Sulfur and Silicon* **1997**, *131*, 49.
14. Badr, M. Z. A.; Mahgoub, S. A.; Moustafa, O. S. *J. Chem. Soc. Pakestan* **1993**, *15*, 264.
15. Badr, M. Z. A.; Mahgoub, S. A.; Moustafa, O. S. *Phosphorus, Sulfur and Silicon* **1993**, *79*, 477.
16. Moustafa, O. S. *Phosphorus, Sulfur and Silicon* **1999**, *155*, 235.
17. Moustafa, O. S. *J. of the Chinese Chem. Soc.* **2000**, *47*(2), 351.
18. Geies, A. A.; El-Deen, A. M. K.; Moustafa, O. S. *Pharmazie* **1996**, *52*(6), 437.
19. Moustafa, O. S.; Badr, M. Z. A.; Kamel, E. M. *Pharmazie* **2000**, *55*(12), 896.