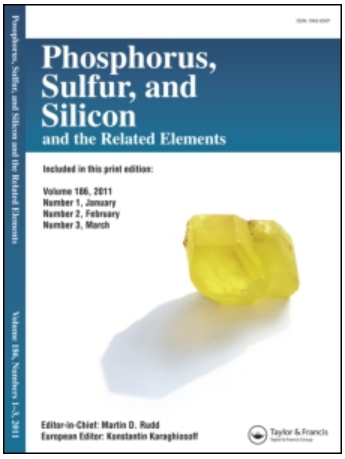

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SYNTHESIS AND REACTIONS OF NEW TRIAZINO THIADIAZINO AND PYRIMIDO THIENO[2,3-*b*]-QUINOXALINE

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SYNTHESIS AND REACTIONS OF NEW TRIAZINO THIADIAZINO AND PYRIMIDO THIENO[2,3-*b*]-QUINOXALINE

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3-Amino-2-carbamoylthieno[2,3-*b*]quinoxaline **3** was synthesized and allowed to react with chloroacetyl chloride to give N-chloroacetyl derivative **4**. Cyclization of **4** into the title compund **5** was achieved in boiling acetic anhydride. Reactions of **5** with morpholine and diethylamine afforded pyrimidinones **6** and **7**. Reaction of **3** with sulfuryl chloride, thionyl chloride and nitrous acid gave thiadiazine derviatives **8** and **9** and triazinothienoquinoxaline **11**. Thionation and chlorination of **11** by P_2S_5 and/or $POCl_3$ gave thioxotriazino and chlorotriazinothienoquinoxalines **12 and 13**, respectively. Treatment of either **12** or **13** with hydrazine hydrate afford the hydrazinotriazinoquinoxaline **14** which was utilized as precursor for producing other new triazinothienoquinoxalines **15–17**.

Keywords: Quinoxaline; morpholine; triazinothienoquinoxalines

Numerous quinoxaline derivatives have been synthesized and still attract the attention of many research groups due to their biological importance.[1–5] For example quinoxalin-2-one has been shown to exhibit anti-inflammatory,[6] tranqulizing, and antidepressent properties.[7] Triazoloquinoxaline and pyrroloquinoxaline derivatives have shown excellent bactericidal and fungicidal activity.[8,9] In this context and in continuation of our investigation of the synthesis of polyheterocyclic systems containing a quinoxaline moiety,[10–13] the synthesis of some new triazinothienoquinoxalines, thiadiazinothienoquinoxalines, and triazolotriazinothienoquinoxalines of potential biological activity is reported.

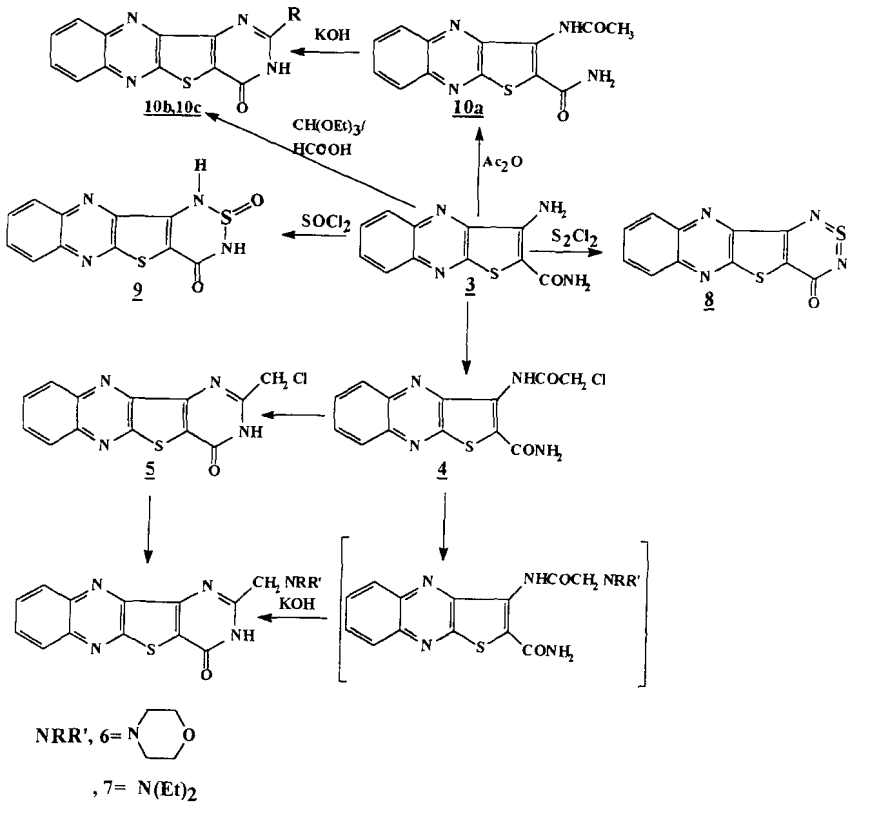
Treatment of quinoxaline-2(1H)thione-3-carbonitrile (**1**) with chloroacetamide and fused sodium acetate in refluxing absolute ethanol gave (3-cyano-2-quinoxalinylthio)acetamide (**2**) which was further cyclized by refluxing with sodium ethoxide solution to produce 3-amino-2-carbamoyl thieno[2,3-b]quinoxaline (**3**). The latter compound **3** was also produced directly by refluxing **1** with chloroacetamide in the presence of K_2CO_3.[14] Chloroacetylation of **3** gave 3-chloro-

acetyl derivative **4** which was subjected to ring closure in boiling acetic anhydride and furnished 2-chloromethyl pyrimidinone **5**. Reaction of compound **5** with a slight excess of morpholine resulted in the formation 2-(N-morpholinomethyl) pyrimido[4′,5′:4,5]-thieno[2,3,-b]quinoxalin-4-one (**6**). Refluxing of **5** with diethylamine in ethanol gave the pyrimidinone derivative **7**. The latter compounds (**6** and **7**) were also obtained upon reaction of the chloro-intermediate **4** with morpholine or diethylamine, and the products were then cyclized with 10% KOH solution. Treatment of **3** with sulfuryl chloride or thionyl chloride gave thiadiazino[4′,5′:4,5]thieno[2,3-b] quinoxalinone (**8**) and thiadiazino[4′,5′:4,5]thieno[2,3-b]quinoxalinon-2-oxide (**9**).[15]

Another method for the cyclization of **3** involved acetylation via refluxing with acetic anhydride and then cyclization by treatment with 10% potassium hydroxide solution, which gave pyrimido[4′,5′:4,5]thieno[2,3-b]quinoxalin-4-one derivatives[13] **10b,c**. Compound **3** was also cyclized in one step to **10c** by treatment with triethyl orthoformate and formic acid (Scheme 1). Compound **3** reacted with concentrated hydrochloric acid and sodium nitrite in the presence of acetic acid at −5°C to give 1,2,3-triazino[4′,5′:4,5]- thieno[2,3-b]-quinoxalin-4(3*H*)-one (**11**) (Scheme 2). Compound **11** reacted with freshly distilled phosphorus oxychloride to give chlorotriazino derivative **12**. The structure of **12** was proven by an independent synthesis which involved the reaction of 3 amino 2-carbonitril thieno[2,3-b]quinoxaline with sodium nitrite, HCl, and acetic acid. Treatment of the triazino compound **11** with phosphorous pentasulfide in dry pyridine gave the corresponding 1,2,3-triazino [4′,5′:4,5]thieno[2,3-b] quinoxalin-4(3H)thione (**13**), Compound **13** reacted with hydrazine hydrate in ethanol to give 4-hydrazino-1,2,3-triazino[4′,5′:4,5]thieno[2,3-b]quinoxaline **14**, which was alternatively produced by refluxing **12** with hydrazine hydrate. Reaction of **14** with acetylacetone gave the pyrazolotriazinothienoquinoxaline derivative (**15**) Compound **14** underwent several cyclization reactions, for example, boiling **14** with benzoyl chloride and/or formic acid gave triazolotriazinothienoquinoxaline derivatives **16** and **17** respectively (Scheme 2). The structures of all compounds prepared were elucidated and confirmed on the basis of their elemental analyses (Table I) and spectroscopic data (Table II).

EXPERIMENTAL

All melting points were determined an a Fisher John melting point apparatus and were uncorrected. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer using KBr pellets. ^{1}H NMR spectra were measured on a Varian 390 (90 MHz) NMR spectrometer in a suitable deutrated solvent, using TMS



SCHEME 1

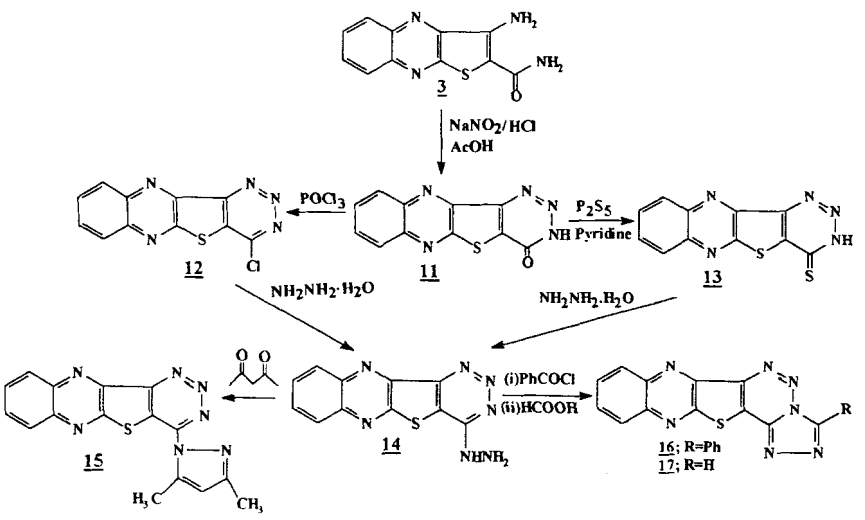
as internal standard. Table II. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer (Table I).

Quinoxalin-2(1H)thione-3-carbonitrile (1)

It was prepared according to the reported method[11] m.p 254–255°C (lit 255°C).

3-Carbonitrile-2-quinoxalinthioacetamide (2)

A mixture of **1** (1.87 g 0.01 mol) and chloroacetamide (0.92 g, 0.01 mol) and anhydrous sodium acetate (5 gm) in ethanol (30 ml) was refluxed for 2 hr. The separated solid was recrystallized from ethanol as buff crystals.



SCHEME 2

3-Amino-2-carbamoyl thieno[2,3-b]quinoxaline (3)

A suspension of compound **2** (4.9 g, 0.02 mol) in ethanol (40 ml) containing dissolved sodium (250 mg) was refluxed for 15 min, and then allowed to cool. The separated precipitate was filtered off and recrystillized from ethanol as orange crystals of **3**.

2-Carbamoyl-3-chloroacetylamino thieno[2,3-b]quinoxaline (4)

The title compound was prepared by heating **3** (2,4 g, 0.01 mol) in chloroacetyl chloride (25 ml) under reflux for 20 mins, the mixture was allowed to cool and then poured into ice-water (100 ml). The precipitate was collected and recrystallized from ethanol as pale yellow crystals.

2-Chloromethylpyrimido[4',5':4,5]thieno[2,3,-b]quinoxalin-4(3H) one (5)

Compound **4** (1.6 g, 0.005 mol) in acetic anhydride (50 ml) was refluxed for 4 hr. The solid thus seperated after cooling was collected and recrystallized from ethanol as yellow crystals.

TABLE I Melting points yields and analytical data of the prepared compounds.

Compound No.	*M.P (°C) (Yield %)*	*Formula (M.W)*	*Calculated/Found*				
			C	*H*	*N*	*S*	*cl*
2	212	$C_{11}H_8N_4OS$	54.09	3.27	22.45	13.11	–
	(88)	244	53.87	3.20	22.81	13.23	–
3	246	$C_{11}H_8N_4OS$	54.09	3.27	22.95	13.11	–
	(92)	244	53.93	3.10	22.83	13.18	–
4	251	$C_{13}H_9ClN_4O_2S$	48.75	2.81	17.50	10.00	10.93
	(80)	320	48.61	2.73	17.62	9.96	10.81
5	295	$C_{13}H_7ClN_4OS$	51.65	2.31	18.54	10.59	11.58
	(65)	302	51.49	2.35	18.40	10.70	11.62
6	>330	$C_{17}H_{15}N_5O_2S$	57.69	4.24	19.83	9.06	–
	(78)	353	57.72	4.18	19.73	9.21	–
7	287–289	$C_{17}H_{17}N_5OS$	60.17	5.01	20.64	9.43	–
	(69)	339	60.08	5.20	20.53	9.51	–
8	218	$C_{11}H_4N_4OS_2$	48.52	1.47	20.58	23.52	–
	(72)	272	48.56	1.42	20.53	23.40	–
9	341	$C_{11}H_6N_4O_2S_2$	45.51	2.06	19.31	22.06	–
	(85)	290	45.60	2.12	19.28	21.93	–
10_a*	260	$C_{13}H_{10}N_4O_2S$	54.54	3.49	19.58	11.18	–
	(83)	286	54.38	3.51	19.54	11.30	–
11	262	$C_{11}H_5N_5OS$	51.76	1.96	27.45	12.54	–
	(78)	255	51.79	1.83	27.52	12.43	–
12	193	$C_{11}H_4ClN_5S$	48.35	1.46	25.64	11.72	12.82
	(65)	273	48.28	1.39	25.53	11.81	12.73
13	287	$C_{11}H_5N_5S_2$	48.70	1.84	25.87	13.61	–
	(70)	271	48.63	1.92	25.75	13.50	–
14	268	$C_{11}H_7N_7S$	49.07	2.60	36.43	11.89	–
	(90)	269	49.21	2.48	36.35	11.72	–
15	281	$C_{16}H_{11}N_7S$	57.65	3.30	29.42	9.60	–
	76	333	57.78	3.20	29.53	9.72	–
16	252	$C_{18}H_9N_7S$	60.84	2.53	27.60	9.01	–
	(81)	355	60.79	2.46	27.47	9.21	–
17	275	$C_{12}H_5N_7S$	51.61	1.79	35.12	11.46	–
	(69)	279	51.49	1.82	34.90	11.37	–

*Full analysis of $\mathbf{10_b}$ and $\mathbf{10_c}$ present in lit.[10,13].

2(N-Morpholinomethyl)pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H) one (6)

(**A**) A mixture of **4** (1.6 g, 0.005 mol) and morpholine (1 ml) in ethanolic KOH (10%, 30 ml) was heated under reflux for 4 hr allowed to cool. The precipitated product was collected and recrystallized from dioxane as yellowish crystals.

(**B**) A mixture of **5** (1.5 g, 0.005 mol) and morpholine (1.2 ml) was refluxed for 2 hr. The reaction mixture on dilution with ethanol (35 ml) and cooling gave **6** as yellowish crystals, identical with the sample obtained above.

2-(N-Diethyl)methylpyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H) one (7)

(**A**) A mixture of **4** (1.6 g, 0.005 mol) and diethylamine (2 ml) in alcoholic KOH (10%, 40 ml) was refluxed for 3 hr. and allowed to cool. The solid product was collected and recrystallized from ethanol as pale yellow crystals.

TABLE II IR and ^{1}H-NMR spectral data of the prepared compounds.

Compound No.	*Spectral data*
2	IR: 3400, 3200(NH_2); 2215 (C≡N); 1680 (C=O). ^{1}H-NMR (DMSO); δ 2.2 (s, 2 H, NH_2); δ 4.3 (s, 2 H, CH_2), δ 7.7–8.5 (m, 4 H, ArH).
3	IR: 3460, 3320 (NH_2); 3420, 3180 (NH_2); 1660 (C=O). ^{1}H-NMR (DMSO); δ 2.2 (s, 2 H, $CONH_2$), δ 7.8–8–6 (m, 4H, ArH).
4	IR: 3370, 3160 (NH_2); 3260 (NH); 1690, 1650 (2C=O). ^{1}H-NMR (DMSO); δ 2.3 (s, 2 H, NH_2), δ 4.5 (s, 2 H, CH_2), δ 10.5(s, 1 H, NH); δ 7.9–8.7 (m, 4 H, ArH).
5	IR: 3200–3340 (NH); 1670 (C=O). ^{1}H-NMR (TFA); δ 4.2 (s, 2 H, CH_2); δ 7.5–8.4 (m, 4 H, ArH).
6	IR: 3180 (NH); 1655 (C=O), ^{1}H-NMR (DMSO): δ 3.4–3.7 (m, 6 H, CH_2 + CH_2-O-CH_2); δ 2,3–2.6 (t, CH_2-N-CH_2), δ 7.6–8.3 (m, 4 H, ArH).
7	IR: 3400–3160 br.(NH); 1645 (C=O). ^{1}H-NMR ($CDCl_3$): δ 1.2–1.4 (t, 6 H, CH_3), δ 4.2–4.5 (q, 4 H, CH_2); δ 3.9 (s, 2 H, CH_2), δ 10.2 (s, 1 H, NH), δ 7.6–8.2 (m, 4 H, ArH).
8	IR: 1720 (C=O). ^{1}H-NMR (TFA): δ 7.8–8.4 (m, 4 H, ArH).
9	IR: 3300, 3220 (NH); 1640 (C=O).
10_a*	IR: 3410, 3180 (NH,NH_2); 1665 (C=O). ^{1}H-NMR (TFA): δ 2.1 (s, 3 H, CH_3); δ 7.4–8 (m, 4 H, ArH).
11	IR: 3200 (NH); 1660 (C=O). ^{1}H-NMR (DMSO): δ 7.5–8.3 (m, 4 H, ArH), δ 9.2 (s, 1 H, NH).
12	IR: 1620 (C=N-).
13	IR: 3210 (NH); 1220 (C=S).
14	IR: 3340–3170 (NH, NH_2).
15	IR: 1620 (C=N-); ^{1}H-NMR ($CDCl_3$): δ 2.9 (s, 3 H, CH_3), δ 2.6 (s, 3 H, CH_3) both of pyrazole ring; δ 6.2 (s, 1 H, CH); δ 7.4–8 (m, 4 H, ArH).
16	IR: 1590 (C=N-); ^{1}H-NMR (DMSO): δ 7.6–8.4 (s, 9 H, ArH).
17	IR: 1600 (C=N-); ^{1}H-NMR (DMSO): δ 8.9 (s, 1 H, CH triazol ring); δ 7.5–8.1 (m, 4 H, ArH).

(**B**) A mixture of **5** (1.5 g, 0.005 mol) and diethylamine (2 ml) in absolute ethanol was heated under reflux for 3 hr. On cooling the solid product was filtered off and recrystallized from ethanol as pale yellow crystals, identical with the sample obtained above.

1,2,6-Thiadiazin[4',5':4,5]thieno[2,3-b]quinoxalin-4-one (8)

A mixture of **3** (1.22 g, 0.005 mol) and sulfuryl chloride (20 ml) was refluxed for 3 hr. The excess sulfuryl chloride was evaporated under reduced pressure. The viscous residue was poured into ice-water (100 ml). The solid product was collected and recrystallized from dioxane to give **8** as brownish crystals.

4-Oxo-1,2,3,4-tetrahydro-1,2,6-thiadiazino[4',5':4,5]thieno[2,3-b]quinoxalin-2-oxide (9)

The title compound was prepared by refluxing thionyl chloride (20 ml) with compound **3** (2,4 g, 0.01 mol) for 4 hr. The excess sulfonyl chloride was evaporated under reduced pressure. The solid product was filtered off and recrystallized from dioxane as pale brown needles.

3-Aminoacetyl-2-carbamoyl thieno[2,3-b]quinoxaline (10_a)

The title compound was prepared by refluxing **3** (4.88 g, 0.02 mol) in acetic anhydride for 3 hr. After cooling, the solid product was separated and recrystallized from acetic-ethanol as Lemon yellow needles of $\mathbf{10_a}$.

2-Methylpyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H) one (10b)

The title compound was prepared by cyclization of **10a** under treatment with 10% potassium hydroxide solution. It gave **10b** as yellow crystals, m.p. 360°C, which agree with the literature[10] m.p. (360°C).

Pyrimido[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H) one (10c)

Compound **3** was cyclized in one step to **10c** by refluxing with triethyl orthoformate and formic acid for 3 hr. to yield **10c** as yellowish crystals which agree with the literature.[13]

1,2,3-Triazino[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H) one (11)

The title compound was prepared by treatment of **3** (2,44 g, 0.01 mole) with hydrochloric acid while adding dropwise sodium nitrite solution (20 ml) at -5°C in presence of acetic acid (10 ml) and stirring for one hour. The solid separated was recrystallized from acetic acid as buff crystals.

4-Chloro-1,2,3-triazino[4',5':4,5]thieno[2,3-b]quinoxaline (12)

Compound **11** (0.510 g, 0.002 mol) in phosphorous oxychloride (30 ml) was refluxed for 3 hr and allowed to cool. The reaction mixture was poured into ice-cold water (100 ml) whereby a yellow solid was precipitated. It was filtered off and recrystallized from ethanol as yellow crystals.

1,2,3-Triazino[4',5':4,5]thieno[2,3-b]quinoxalin-4(3H)thione (13)

A mixture of **11** (1.77 g, 0.005 mol) and phosphorous pentasulphide (1.0 g, 0.005 mol) in dry pyridine was refluxed for 5 hr. The solid separated on water addition was filtered and recrystallized from acetic acid as redish needles.

4-Hydrazino-1,2,3-triazino[4',5':4,5]thieno[2,3-b]quinoxaline (14)

The title compound was prepared by refluxing hydrazine hydrate (6 ml) with either **12** (2.73 g, 0.01 mol) in absolute ethanol (35 ml) for 1 hr, or with **13** (2.71 g, 0.01 mol) for 4 hr. The solid separated was washed with ethanol and recrystallized from ethanol as red crystals.

5(3,4-Dimethyl-pyrazol-1-yl)1,2,3-triazino[4',5':4,5]thieno[2,3-b]quinoxaline (15)

A mixture of **14** (5.4 g, 0.02 mol) and acetylacetone (0.04 mol) in ethanol (50 ml) was refluxed for 4 hr. the seperated solid was recrystallized from ethanol as pale brown needles.

3-Phenyl-s-triazolo[4",3":1',6']1,2,3-triazino[4',5':4,5]thieno[2,3-b]-quinoxaline (16)

The title compound was prepared by refluxing **14** (1.35 g, 0.005 mol) in benzoyl chloride (15 ml) for 5 hr., after cooling. The solid product was filtered and washed several times with pet-ether (40–60°C) and recrystallized from acetic acid as yellowish crystals.

s-Triazolo[4",3":1',6']-1,2,3-triazino[4',5':4,5]thieno[2,3-b]quinoxaline (17)

A mixture of **14** (0.54 g, 0.002 mol) and formic acid (10 ml) was refluxed for 5 hr. The solid **17** isolated after addition of water was recrystallized from acetic acid as brownish crystals.

References

[1] J. Ohmori, S. Sakamoto, H. Kupota, M. Shimizu-Sasamata, M. Okada, S. Kawassaki, K. Hidaka, J. Togami, T. Furuya and K. Murase, *J. Med. Chem.*, **37**, 467 (1994).
[2] V. Milata, D. Ilavsky, M. Chudik, L. Zalibera, J. Lesko, M. Seman and A. Belicova, *Monatsh Chem.*, **126**, 1349 (1994).

[3] E. Terpetschnig, W. Ott, G. Kollenz, K. Peters, E. M. Peters and H. G. Schering, *Monatshefte für Chemie*, **119**, 367 (1988).
[4] Y. Kurasawa, R. Katoh and A. Takada, *J. Heterocyclic. Chem.*, **29**, 1001 (1992).
[5] W. Tian and S. Grivas, *J. Heterocyclic. Chem.*, **29**, 1305 (1992).
[6] H. Yamamoto, J. Patent. 6917136; *C.A.* **71**. 124505d (1969).
[7] T. O. Yellin, US Patent 3635971. *C.A.* **76**. 99708r (1972).
[8] K. Makino, O. Sakata, K. Morimoto and Y. Ochiai, *Heterocycles*, **23**, 1729 (1985).
[9] Ibid. 2025.
[10] M. Z. A. Badr, S. A. Mahgoub, A. A. Geies, O. S. Moustafa and F. M. Abd El-Latif, *Phosphorous, Sulfur and Silicon*, **73**, 27–34 (1992).
[11] M. Z. A. Badr, S. A. Mahgoub, O. S. Moustafa and A. A. Geies, *Phosphorous, Sulfur and Silicon*, **79**, 77–85 (1993).
[12] A. A. Geies, A. M. K. El-Dean and O. S. Moustafa, *Monatshefte für Chemie*, **127**, 1263 (1996).
[13] O. S. Moustafa and M. Z. A. Badr, *Phosphorous, Sulfur and Silicon*, **119**, 127–138 (1996), M. Z. A. Badr, S. A. Mahgoub, O. S. Moustafa and F. M. Atta., *Indian. J. Chem. Soc.*, **74**, 30, 1997; O.S. Moustafa, M. Z. A. Badr, Heterocyclic Communication **3**, 465 (1997).
[14] P. Carlos, O. Vicente and M. Q. Jose., *J. Heterocyclic, Chem.*, **29**, 1693 (1992).
[15] W. Offerman, K. Ereg, H. Roth and J. Hermann, *Arch Pharm (Weinherm. Ger)* 314(**2**), 168 (1981); *C.A.* **94**, 208819 (1981).