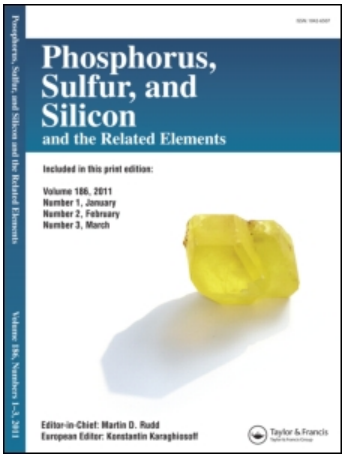

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SYNTHESIS AND SOME REACTIONS OF THIENO[2,3-c]PYRIDAZINE DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITY

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SYNTHESIS AND SOME REACTIONS OF THIENO[2,3-c]PYRIDAZINE DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITY

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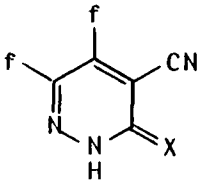
The title compounds (**4a–f**) were prepared by S-alkylation of 4-cyano-5,6-difur-2′-yl-2H-pyridazine-3-thione (**2**) and subsequent cyclization in ethanol in the presence of potassium carbonate. Reaction of *o*-disubstituted thienopyridazines (**4a–d**) with different reagents afforded tricyclic compounds namely, imidazothienopyridazine (**5**), pyridazinothienooxazine (**6**) and pyridazinothienopyrimidines (**7–9**). Most of the prepared compounds exhibited pronounced antibacterial activity.

Key words: Synthesis; thienopyridazine; imidazolothienopyridazine; pyridazinothienooxazine; pyridazinothienopyrimidine.

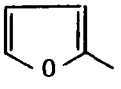
Literature reports the synthesis and utility of many pyridazine derivatives as insecticides, miticides, nematocides,[1] acaricides, fungicides[2] and as cardiotonics.[3] In addition, many substituted benzofurans show marked pharmacological activity; 2-(4-hydroxybenzoyl)benzofuran exhibits a relaxant effect[4] on histamine and acetylcholine spasm and other derivatives showed potent analgesic spinal reflex-depressing and adrenergic α-blocking activity *in vivo*.[5] Due to the biological importance of pyridazine and furan moieties we aim to synthesize some new pyridazine derivatives carrying the furan moiety in the hope that a number of them possess some biological activity.

The starting compound 4-cyano-5,6-difur-2′-yl-2H-pyridazine-3-one (**1**) was prepared by ternary condensation of furil, ethyl cyanoacetate and hydrazine hydrate in an ethanolic sodium ethoxide solution. Thionation of **1** with phosphorous pentasulfide in refluxing pyridine gave the thio analogue **2**.

The thione derivative (**2**) was used as a versatile compound for building fused heterocyclic systems condensed with the pyridazine moiety. Thus, reaction with an alkylating agent namely ethyl chloroacetate, chloroacetamide and 4-chlorophenacyl bromide furnished the alkylated products **3a–d**. Treatment of **3a–d** with potassium carbonate in refluxing alcohol underwent smooth ring closure to produce the cy-



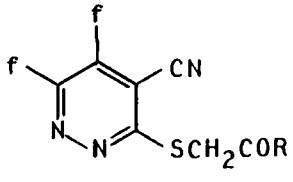
1 X=O
2 X=S

f = 

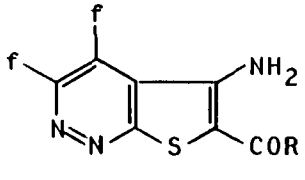
clized product thieno[2,3-c]pyridazines **4a–d**. Alternative one-step synthesis of **4a–d** was achieved by the reaction of **2** with the alkylating agents in presence of potassium carbonate in boiling ethanol.

The chemical structure of compounds **3a–d** and **4a–d** was supported by their IR and ^{1}H NMR. The IR spectra of compounds **3a–d** showed the characteristic band at 1655–1740 cm^{-1} due to carbonyl group and the disappearance of the bands at 3160, 1190 cm^{-1} due to NH and C=S groups of compound **2**. The ^{1}H NMR spectrum of **3a** showed a singlet at δ4.05–4.35 due to a methylene group and the characteristic signals at δ1.2–1.4(t), 4.05–4.35(q) for the ester group. The cyclized products **4a–d** exhibited in their IR spectra the characteristic absorption bands at 3480–3460, 3360–3120 cm^{-1} due to the amino group in addition to the absence of the absorption band at 2230 cm^{-1} due to the cyano group. The ^{1}H NMR showed the absence of the signal for the methylene protons and the appearance of a new signal at δ5.75–6.10 due to the amino group.

o-Disubstituted thienopyridazines (**4a–c**) were used as precursers for the synthesis of some interesting tricyclic compounds containing condensed pyrimidine nucleus which possesses a wide range of biological activity.[6] Thus, the carbohydrazide (**4e**), obtained from **4a** and hydrazine hydrate, reacts with nitrous acid to give the carboazide **4f** which on heating in xylene undergo curtius rearrangement to form imidazolo[4′,5′:4,5]thieno[2,3-c]pyridazine derivative (**5**). On the other hand, the oxazine (**6**), prepared by saponification of **4a** and subsequent cyclization with acetic anhydride, when reacted with hydrazine hydrate in ethanol or aniline in acetic acid furnished pyridazino[3′,4′:4,5]thieno[3,2-d]pyrimidines (**7a,b**).

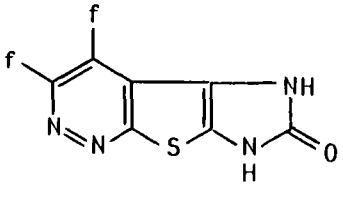


3a-d

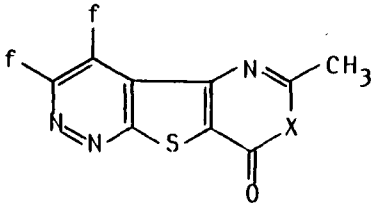


4a-f

In formulae **3,4**: a, R=OEt; b, R=NH_2; c, R=NHPh; d, R=$C_6H_5Cl(P)$; e, R=$NHNH_2$; f, R=N_3.



5



6 X=O

7a X=NNH_2

7b X=NPh

The chemical structure of compounds **4f–7** was confirmed by spectral data. The IR spectrum of **4f** showed the characteristic band at 2160 cm^{-1} due to the azido group which disappeared in the IR spectra of compound **5**. The IR spectra of compounds **7a–b** showed the carbonyl absorption band at 1680–1660 cm^{-1} whereas the carbonyl group appeared at 1750 cm^{-1} in compound **6** is characteristic for the oxazinone structure.

Refluxing compound **4b** or **4c** with urea in decalin results in the formation of substituted pyridazino[3',4':4,5]thieno[2,3-d]pyrimidine-2,4-diones (**8a,b**). Meanwhile, their reaction with triethyl orthoformate, pyridazino[3',4':4,5]thieno[3,2-d]pyrimidin-4-ones (**9a,b**) were obtained in moderate yield.

The chemical structure of compounds **8a,b**, **9a,b** was indicated by their IR and ^1H NMR. The IR spectra of compounds **8a,b** showed bands at 3450–3460 cm^{-1} (NH) and at 1650–1715 cm^{-1} (C=O). ^1H NMR of **8b** showed singlet at δ11.5 (NH-pyrimidine). The IR spectra of compounds **9a,b** showed the characteristic carbonyl absorption band at 1655–1675 cm^{-1} and band at 3140 cm^{-1} (NH). The ^1H NMR of **9b** showed a singlet at δ8.7 due to the pyrimidine proton.

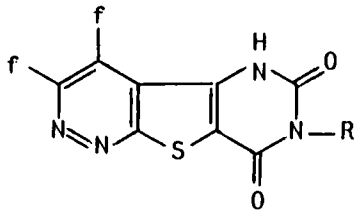
EXPERIMENTAL

Melting points were determined on Fischer-Johns melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 240 C elemental analyser. IR spectra were recorded on a Pye Unicam SP 3-100 spectrophotometer using KBr wafer technique. ^1H NMR spectra were recorded on a varian EM-390 90 MHz. NMR spectrometer in suitable deuterated solvent using TMS as internal standard.

4-Cyano-5,6-difur-2'-yl-2H-pyridazin-3-one (**1**). To a mixture of furil (7.9 g, 0.05 mole), ethyl cyanoacetate (5.65 ml, 0.05 mole) and hydrazine hydrate (2.5 ml, 0.05 mole) in absolute ethanol (100 ml) was added sodium metal (1.15 g, 0.05 mole) in absolute ethanol (50 ml), the reaction mixture was heated under reflux for one hour. Evaporation of the solvent to dryness, dilution with water and acidification with hydrochloric acid gave the desired compound in 74% yield. It was recrystallised from ethanol into greenish yellow crystals m.p. 252–4°C. IR: 3120 cm^{-1} (NH), 2230 cm^{-1} (C≡N), 1650 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ4.55 (s, 1H, NH), δ6.45–6.80 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.80, 8.05 (2s, 2H, $2XH_5$-furyl ring).

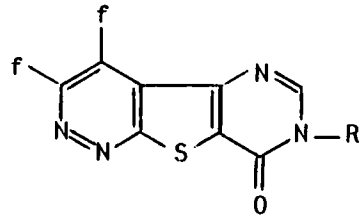
Anal. Calcd. for $C_{13}H_7N_3O_3$: C, 61.66; H, 2.79; N, 16.59
Found: C, 61.49; H, 2.82; N, 16.74.

4-Cyano-5,6-difur-2'-yl-2H-pyridazine-3-thione (**2**). A mixture of compound **1** (5.06 g, 0.02 mole) and phosphorous pentasulfide (4.44 g, 0.02 mole) in dry pyridine (50 ml) was refluxed for 20 minutes. The cold clear solution was poured into ice-cold water and the solid product obtained was recrystallised



8a-b

a, R=H; b, R=Ph



9a-b

a, R=H; b, R=Ph

from ethanol into red crystals m.p. 254°C, yield 89%. IR: 3160 cm^{-1} (NH), 2230 cm^{-1} (C≡N), 1190 cm^{-1} (C=S).

Anal. Calcd. for $C_{13}H_7N_3O_2S$: C, 57.99; H, 2.62; N, 15.60; S, 11.91
Found: C, 58.12; H, 2.55; N, 15.48; S, 11.90.

Alkylation of 3-cyano-5,6-difur-2'-yl-2H-pyridazine-3-thione. Formation of **3a–d**. *General procedure*: A mixture of compound **2** (0.01 mole), alkylating agent (0.01 mole) and anhydrous sodium acetate (2 g) in ethanol (30 ml) was refluxed for 20–30 minutes. The solid product obtained on cooling and dilution with water was collected, dried and recrystallised from ethanol.

3a: Yellow crystals, yield 90%, m.p. 101°C. IR: 2230 cm^{-1} (C≡N), 1740 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ1.20–1.40 (t, 3H, CH_3), δ4.05–4.35 (q + s, 4H; O—CH_2, S—CH_2), δ6.45–6.70 (m, 4H; $2XH_3$-, H_4-furyl ring), δ7.40, 7.55 (2s, 2H, $2XH_5$-furyl ring).

Anal. Calcd. for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82; S, 9.02
Found: C, 57.55; H, 3.80; N, 11.65; S, 8.96.

3b: Bright yellow crystals, yield 88%, m.p. 204–6°C. IR: 3320, 3120 cm^{-1} (NH_2), 2230 cm^{-1} (C≡N), 1675 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{10}N_4O_3S$: C, 55.21; H, 3.09; N, 17.17; S, 9.82
Found: C, 54.92; H, 3.22; N, 17.30; S, 10.10.

3c: Yellow crystals, yield 75%, m.p. 176°C. IR: 3340 cm^{-1} (NH), 2230 cm^{-1} (C≡N), 1655 cm^{-1} (C=O).

Anal. Calcd. for $C_{21}H_{14}N_4O_3S$: C, 62.68; H, 3.51; N, 13.92; S, 7.97
Found: C, 62.44; H, 3.66; N, 14.15; S, 8.13.

3d: Yellow crystals, yield 90%, m.p. 180–2°C. IR: 2230 cm^{-1} (C≡N), 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{21}H_{12}ClN_3O_3S$: C, 59.79; H, 2.87; Cl, 8.40; N, 9.96; S, 7.60
Found: C, 59.66; H, 3.12; Cl, 8.11; N, 9.80; S, 7.55.

3-Amino-4,5-difur-2'-yl-thieno[2,3-c]pyridazine derivatives (**4a–d**). *General procedure*: A mixture of S-alkylated derivative **3a–d** (0.01 mole) and anhydrous potassium carbonate (3 g) in ethanol was refluxed for 2 hrs. The cold reaction mixture was poured into water and the solid product was collected, washed with water, dried and recrystallised from the proper solvent.

4a: Yellow crystals, yield 75%, m.p. 153°C (ethanol). IR: 3480, 3360 cm^{-1} (NH_2), 1670 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ1.30–1.45 (t, 3H, CH_3), δ4.20–4.40 (q, 2H, CH_2), 5.75 (s, 2H, NH_2), δ6.30–6.55 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.30–7.60 (2s, 2H, $2XH_5$-furyl ring).

Anal. Calcd. for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82; S, 9.02
Found: C, 57.51; H, 3.83; N, 11.68; S, 9.21.

4b: Orange red crystals, yield 73%, m.p. 285–7°C (ethanol/benzene). IR: 3460, 3310 cm^{-1} (NH_2), 1650 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ6.10 (s, 2H, NH_2), δ6.30–6.90 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.60 (s, 2H, $CONH_2$), δ8.10 (s, 2H, $2XH_5$-furyl ring).

Anal. Calcd. for $C_{15}H_{10}N_4O_3S$: C, 55.21; H, 3.09; N, 17.17; S, 9.82
Found: C, 55.32; H, 3.13; N, 17.35; S, 10.12.

4c: Orange crystals, yield 68%, m.p. 264–6°C (acetic acid). IR: 3470, 3370 cm^{-1} (NH), 1630 cm^{-1} (C=O). ^1H NMR (CF_3COOH): δ6.30–7.20 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.40–7.70 (m, 5H, Ar—H), δ8.00, 8.2 (2s, 2H, $2XH_5$-furyl ring).

Anal. Calcd. for $C_{21}H_{14}N_4O_3S$: C, 62.68; H, 3.51; N, 13.92; S, 7.97
Found: C, 62.73; H, 3.62; N, 14.12; S, 8.21.

4d: Red crystals, yield 92%, m.p. 192° (ethanol). IR: 3460, 3120 cm^{-1} (NH_2), 1640 cm^{-1} (C=O). ^1H NMR (CF_3COOH): δ6.40–7.20 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.60–8.20 (m, 6H, 4Ar—H and $2XH_5$-furyl ring).

Anal. Calcd. for $C_{21}H_{12}ClN_3O_3S$: C, 59.79; H, 2.87; Cl, 8.40; N, 9.96; S, 7.60
Found: C, 59.53; H, 3.11; Cl, 8.20; N, 9.74; S, 7.50.

3-Amino-4,5-difur-2'-ylthieno[2,3-c]pyridazine-2-carbohydrazide (**4e**). A mixture of **4a** (2 g) and excess hydrazine hydrate (6 ml) was heated under reflux for one hour. The precipitated solid was collected and recrystallised from acetic acid to give yellow crystals, m.p. 282°C. IR: 3460, 3320 cm^{-1} (NH), 1630

cm^{-1} (C=O). ^1H NMR (CF_3COOH): δ6.30–7.10 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.90, 8.10 (2s, 2H, $2XH_5$-furyl ring).

Anal. Calcd. for $C_{15}H_{11}N_5O_3S$: C, 52.78; H, 3.25; N, 20.52; S, 9.39
Found: C, 52.67; H, 3.38; N, 20.66; S, 9.20.

3-Amino-4,5-difur-2'-ylthieno[2,3-c]pyridazine-2-carbonylazide (**4f**). To a well stirred solution of the carbohydrazide derivative (**4e**) (0.002 mole) in acetic acid (20 ml) was added a solution of sodium nitrite (1 g in 10 ml water) at room temperature. The precipitated solid was collected and dried to give **4f** as yellow powder, m.p. 190°C (dec.). IR: 3470, 3360 cm^{-1} (NH_2), 2160 cm^{-1} (N_3), 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_8N_6O_3S$: C, 51.14; H, 2.29; N, 23.85; S, 9.10
Found: C, 50.88; H, 2.49; N, 23.59; S, 8.90.

4,5-Difur-2'-yl-1H-imidazolo[4',5':4,5]thieno[2,3-c]pyridazin-2(3H)-one (**5**). A sample of the carbonylazide derivative (**4f**) (1 g) was refluxed in xylene (30 ml) for 2 hrs. The product was collected, washed several times with pet. ether (bp 40–60°C) and recrystallised from acetic acid into yellow crystals, yield 66%, m.p. > 300°C. IR: 3120 cm^{-1} (NH), 1710 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ6.20–6.90 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.40 (s, 1H, 3-NH), δ7.95, 8.20 (2s, 2H, $2XH_5$-furyl ring), δ10.6 (s, 1H, 1-NH).

Anal. Calcd. for $C_{15}H_8N_4O_3S$: C, 55.55; H, 2.49; N, 17.28; S, 9.89
Found: C, 55.32; H, 2.46; N, 17.13; S, 9.63.

2-Methyl-8,9-difur-2"-yl-pyridazino[3',4':4,5]thieno[3,2-d]oxazin-4-one (**6**). 3-Amino-2-carbethoxy-4,5-difur-2'-ylthieno[2,3-c]pyridazine (**4a**) (0.01 mole) was refluxed for 2 hrs. with ethanolic sodium hydroxide (20 ml, 4%). The precipitated sodium salt was filtered off, washed with alcohol and dried. The sodium salt was refluxed for 3 hrs. with acetic anhydride (20 ml). The precipitated product was collected and recrystallised from acetic acid into yellow needles, yield 65%, m.p. 235–7°C. IR: 1750 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_9N_3O_4S$: C, 58.12; H, 2.58; N, 11.96; S, 9.13
Found: C, 58.36; H, 2.72; N, 12.12; S, 8.90.

2-Methyl-8,9-difur-2"-yl-pyridazino[3',4':4,5]thieno[3,2-d]pyrimidin-4(3H)-one derivatives (**7a,b**). A mixture of the oxazine derivative (**6**) (0.002 mole) and hydrazine hydrate (0.004 mole) in ethanol or aniline (0.004 mole) in acetic acid was refluxed for 2 hrs. The solid product obtained was filtered off and recrystallised from acetic acid.

7a: Yellow crystals, yield 68%, m.p. > 300°C. IR: 3300, 3200 cm^{-1} (NH_2), 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{11}N_5O_3S$: C, 55.89; H, 3.03; N, 19.17; S, 8.77
Found: C, 56.12; H, 2.98; N, 19.25; S, 8.80

7b: Greenish yellow crystals, yield 58%, m.p. > 300°C. IR: 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{23}H_{14}N_4O_3S$: C, 64.78; H, 3.31; N, 13.14; S, 7.52
Found: C, 64.73; H, 3.42; N, 13.25; S, 7.65.

8,9-Difur-2"-yl-pyridazino[3',4':4,5]thieno[3,2-d]pyrimidine-2(1H), 4(3H)-dione derivatives (**8a,b**). A mixture of **4b** or **4c** (0.002 mole) and urea (0.3 g, 0.005 mole) was refluxed in decalin (20 ml) for 3 hrs. The solid product obtained was filtered off, washed with pet. ether (bp 60–80°C) are recrystallised from ethanol.

8a: Orange powder, yield 55%, m.p. 250°C. IR: 3450, 3140 cm^{-1} (NH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_8N_4O_4S$: C, 54.55; H, 2.29; N, 15.90; S, 9.10
Found: C, 54.46; H, 2.35; N, 16.12; S, 9.22.

8b: Orange powder, yield 63%, m.p. 248–50°C. IR: 3470 cm^{-1} (NH), 1715, 1660 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ6.40–7.30 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.40–8.20 (m, 5H, Ar—H), δ8.30, 8.40 (2s, 2H, $2XH_5$-furyl ring), δ11.50 (s, 1H, NH pyrimidine ring).

Anal. Calcd. for $C_{22}H_{12}N_4O_4S$: C, 61.68; H, 2.82; N, 13.08; S, 7.48
Found: C, 61.53; H, 2.63; N, 13.13; S, 7.65.

8,9-Difur-2"-yl-pyridazino[3',4':4,5]thieno[3,2-d]pyrimidin-4(3H)-one derivatives (**9a,b**). A mixture of **4b** or **4c** (0.003 mole) and triethyl orthoformate (2 ml) in acetic anhydride (10 ml) was heated under reflux for 6 hrs. Upon cooling, the reaction mixture was poured into water and the product formed was filtered and recrystallised from the proper solvent.

TABLE I

Antibacterial activity of the prepared compounds*

Compd. No.	Micrococus luteus	Bacillus cereus	Proteus vulgaris	Serratia rhodnii
1	-	-	-	-
2	-	-	-	11
3a	-	9	11	11
3b	-	7	11	11
3c	-	-	-	-
3d	-	9	11	-
4a	-	7	-	-
4b	-	9	-	-
4c	-	-	-	-
4d	-	7	-	-
4e	-	7	11	-
4f	-	9	11	-
5	-	-	-	-
6	11	9	11	-
7a	11	-	-	-
7b	11	9	-	-
8a	-	9	-	11
8b	-	9	-	-
9a	-	9	-	11
9b	11	9	-	-

(*) Inhibition zones in mm at 0.5% concentration.

9a: Greenish yellow crystals, yield 59%, m.p. > 300°C (acetic acid). IR: 3140 cm^{-1} (NH), 1655 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_8N_4O_3S$: C, 57.14; H, 2.40; N, 16.66; S, 9.53
Found: C, 56.89; H, 2.43; N, 16.72; S, 9.45.

9b: Yellow crystals, yield 65%, m.p. 270°C (EtOH—$CHCl_3$). IR: 1675 cm^{-1} (C=O). ^1H NMR (CF_3COOH): δ6.60–7.20 (m, 4H, $2XH_3$-, H_4-furyl ring), δ7.40–8.10 (m, 5H, Ar—H), δ8.30, 8.40 (2s, 2H, $2XH_5$-furyl ring), δ8.70 (s, 1H, CH-pyrimidine).

Anal. Calcd. for $C_{22}H_{12}N_4O_3S$: C, 64.07; H, 2.93; N, 13.58; S, 7.77
Found: C, 64.25; H, 3.12; N, 13.67; S, 7.62.

Antibacterial activity. All the prepared compounds were screened for antibacterial activity using the disc plate method.[7] Neutrient agar was used as growth media. The bacterial species used were *Micrococus luteus*, *Bacillus cereus*, *Proteus vulgaris* and *Serratia rhodnii*. The diameter of the inhibition zones ranged from 7–11 mm at 0.5% concentration in diethylene glycol and are listed in Table I.

The results revealed that the compounds exhibited pronounced antibacterial activity against at least one of the tested bacteria (except compounds **1**, **3c**, **4c** and **5** which were inactive).

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