SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NEW THIENO[2,3-c]PYRIDAZINES AND RELATED HETEROCYCLES

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ABSTRACT

4-Cyano-6-phenylpyridazine-3(2*H*)-thione **4** was obtained by the reaction of 3-chloro-4-cyano-6-phenylpyridazine 3 with thiourea in ethanol under reflux. Cycloalkylation of compound 4 with ethyl chloroacetate in the presence of sodium ethoxide afforded the novel thieno[2,3-c]pyridazine derivative 6. Hydrazinolysis of compound 6 yielded the corresponding carbohydrazide 9 which on treatment with acetylacetone and ethyl acetoacetate gave the novel thieno[2,3-c]pyridazines 10 and 11. Treatment of 9 with nitrous acid yielded the corresponding carboazide 13, which upon boiling in toluene furnished imidazo[4′,5′:4,5]thieno[2,3-c]pyridazine 15. Pyrimidothienopyridazines 16-18 were achieved by cyclocondensation of compound 9 with some reagents namely, acetic anhydride, formic acid and triethyl orthoformate. The structures of these new compounds were confirmed by elementary analyses and spectral data. The antibacterial activities of the new compounds were also evaluated.

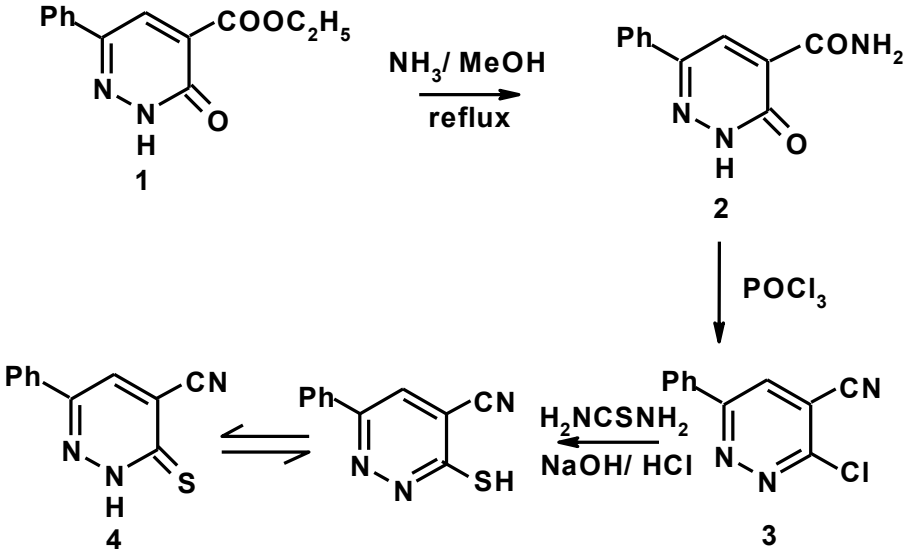
Key words: Pyridazine, Thienopyridazines, Pyrimidothienopyridazines, Antibacterial activity.

INTRODUCTION

Several thienopyridazines are known to possess a broad spectrum of biological activities. Some of them, for example, have been evaluated pharmacologically and used for potent and selective phosphodiesterase IV inhibitor,[1,2] immunosuppressants,[3] antitumor,[4] modules of protein tyrosine phosphatases (PT-Pases),[5] antimicrobials,[6] blood platelet aggregation inhibitors,[7] antibacterial,[8] and antiviral activity.[9] In view of the above observations and as a continuation of our ongoing program directed to the synthesis of heterocyclic systems containing thienopyridazine moiety,[10-12] we report herein the synthesis of some new thieno[2,3-c]pyridazines, imidazothienopyridazine and pyrimidothienopyridazines and their evaluation regarding antibacterial activity by using 4-cyano-6-phenylpyridazine-3(2*H*)-thione 4 as the starting material.

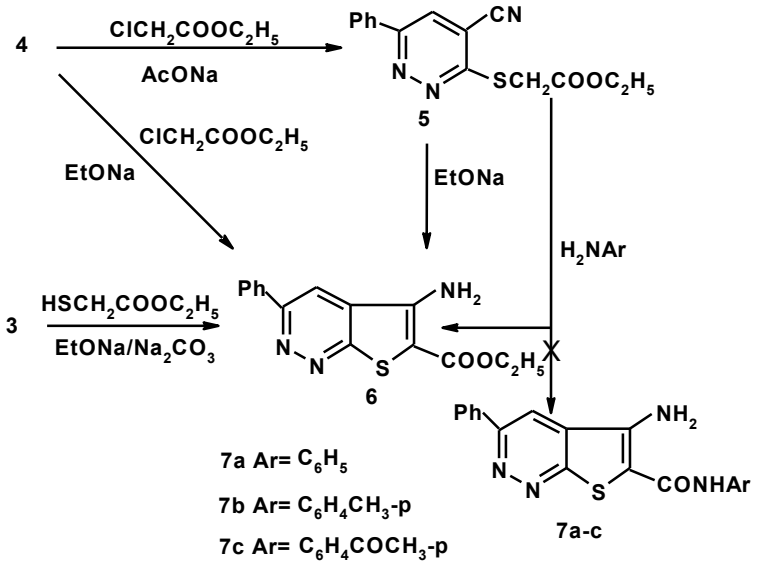
RESULTS AND DISCUSSION

The synthesis of the starting compound 4-cyano-6-phenylpyridazine-3(2*H*)-thione 4 was performed from 4-carbethoxy-6-phenylpyridazinone 1 by successive ammonolysis in methanol to give 4-carboxamide-6-phenylpyridazine-3(2*H*)-one 2. Treatment of the latter compound with phosphorous oxychloride ensured both the dehydration of the carboxamide function and the conversion of pyridazinone into
3-chloro-4-cyano-6-phenylpyridazine 3. Compound 3 was subjected to addition-elimination reaction with thiourea in ethanol under reflux
to afford compound 4 (Scheme 1).
Compounds 1-3 were obtained according to the reported method[13] and the structures are in agreement with the reported data. The structure of the new compound 4 was established on the basis of elemental analysis and spectral data as well as comparison (IR, m.p., m.m.p, TLC). The IR spectrum of compound 4 showed absorption bands at 3470, 2220, and 1230 cm^{-1} due to imino, cyano, and thiocarbonyl groups, respectively. ^{1}H-NMR spectrum (DMSO-d_6) of compound 4 showed a broad singlet at δ 11.1 ppm assigned to the NH and a multiplet at δ 7.4-8.7 ppm assigned to the phenyl protons and pyridazine proton.



scheme 1

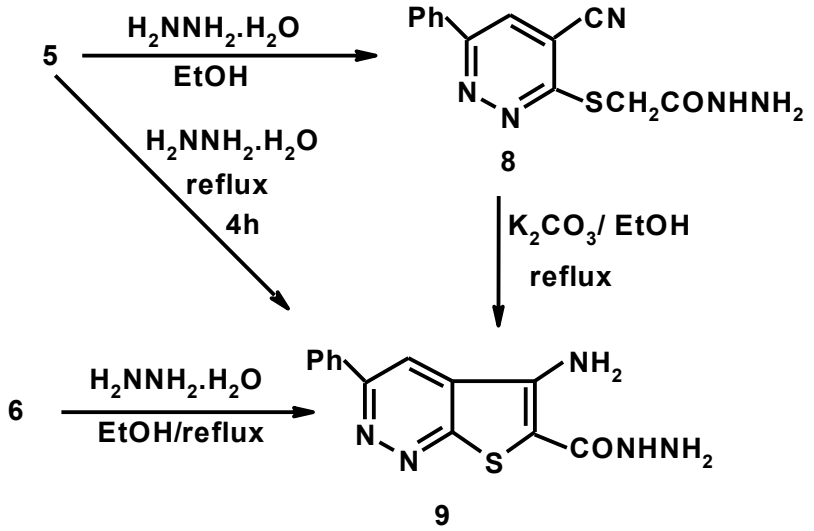
The reaction of compound 4 with ethyl chloroacetate in refluxing ethanol, in the presence of sodium acetate, yielded 3-ethoxycarbonylmethylthiopyridazine derivative 5. Thieno[2,3-c] pyridazine derivative 6 was achieved either by the reaction of compound 3 with ethyl thioglycolate/sodium carbonate, or by the interaction of compound 4 with ethyl chloroacetate in ethanol in the presence of sodium ethoxide. The structure of compound 6 was established by another synthetic route *via* cyclization of compound 5 with sodium ethoxide, or with aniline or aniline derivatives instead of the expected compounds 7a-c (Scheme 2). The structures of compounds 5 and 6 were established by elemental analysis and spectral data. The IR spectrum of compound 5 showed absorption bands at 2220 and 1720 cm^{-1} could be attributed to cyano and ester groups, whilst, that the compound 6 displayed the disappearance of cyano group and presence of the absorption bands at 3430, 3300, and 1670 cm^{-1} due to amino function and carbonyl groups, respectively. The ^{1}H-NMR spectrum of compound 6 in (DMSO-d_6) showed a triplet at δ 1.3 ppm, a quartet at δ 4.3 ppm assigned for ethoxycarbonyl moiety in addition, to the aromatic and amino protons. Also, the structure of compound 6 was supported by the mass spectrum which showed that the molecular ion peak (base peak) at m/z =299 (100 %) which is in agreement with the molecular formula ($C_{15}H_{13}N_3O_2S$).



scheme 2

Treatment of compound 5 with hydrazine hydrate in ethanol at room temperature for 3 h afforded the corresponding 3-methylthiocarbohydrazidepyridazine 8. However, carrying the reaction under reflux gave the novel 6-carbohydrazidethieno[2,3-c]pyridazine derivative 9.

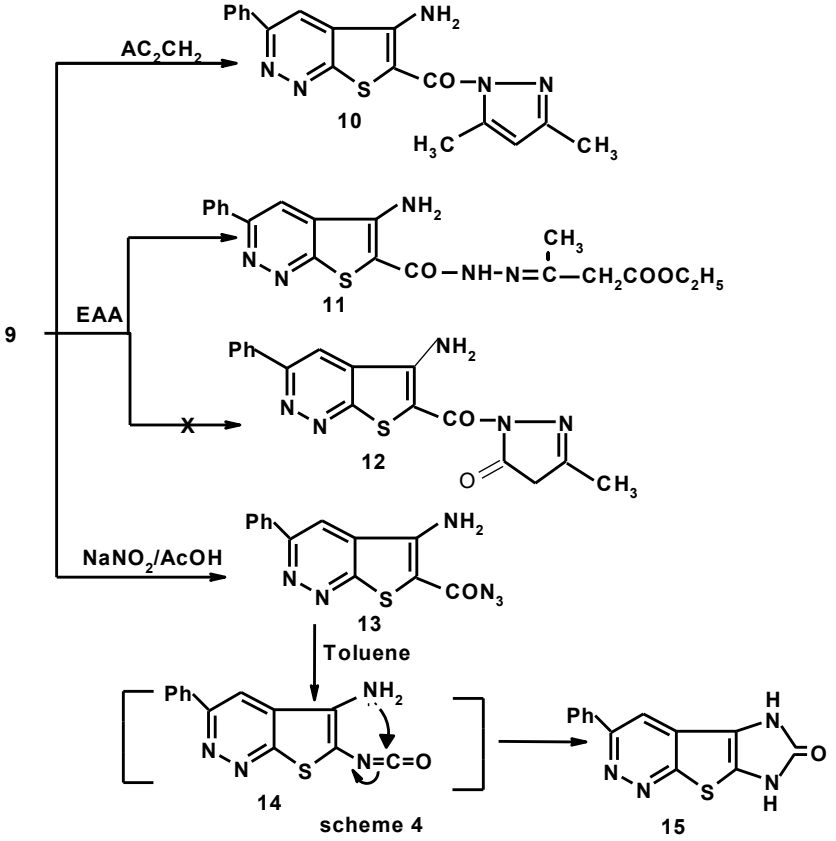
Also, the latter compound was obtained by refluxing 6 with hydrazine hydrate, or by 8 with potassium carbonate in ethanol (Scheme 3). The product 9 formed by the three routes is identical in all respects
(m.p., m.m.p., T.L.C., and IR). The structures of the new compounds 8 and 9 were established on the basis of their elemental analysis and spectral data. The IR spectrum of compound 8 showed absorption bands at 3420, 3280, 3190, 2240, and 1620 cm^{-1} due to NH, amino, cyano, and carbonyl groups, respectively. Meanwhile, compound 9 spectrum revealed the disappearance of cyano group and presence of absorption bands at 3410, 3300, 3200 cm^{-1} for (NH_2), (NH, NH_2) groups and at 1600 cm^{-1} for (CO). Also, the structure of 9 was supported by its mass spectrum which, showed a molecular ion peak at m/z = 285 (62.59%) which is in agreement with its molecular formula ($C_{13}H_{11}N_5OS$).



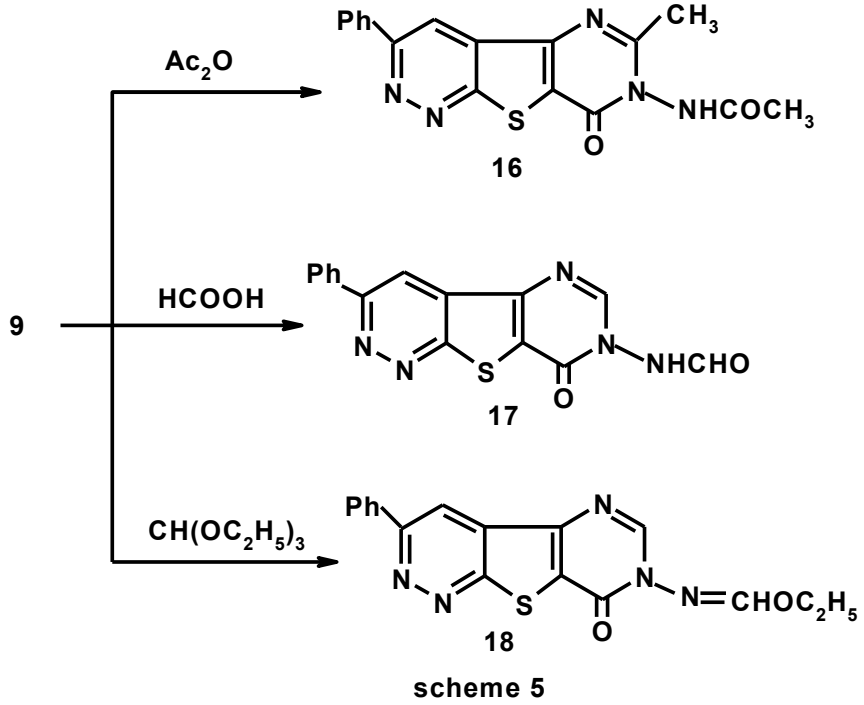
schem 3

6-Carbohydrazide derivative 9 was used as precursor for synthesizing other new thienopyridazines and pyrimidothienopyridazines. Refluxing of compound 9 with acetyl acetone in ethanol yielded a novel pyrazolylthienopyridazine derivative 10. Also, compound 9 was reacted with ethyl acetoacetate in ethanol under reflux to produce the thienopyridazine derivative 11 instead of pyrazolone derivative 12. Treatment of carbohydrazide 9 with nitrous acid at room temperature produced the carboazide derivative 13 which underwent *Curtius rearrangement* followed by intramolecular cyclization upon refluxing in dry toluene to furnish
imidazo [4′,5′ :4,5]thieno[2,3-c]pyridazine 15 *via* the isocyanate intermediate 14 (Scheme 4).
The structures of the new compounds 10, 11, 13 and 15 were confirmed on the basis of their elemental analysis and spectral data.
The IR spectra of compounds10, 11 and 13 revealed absorption bands at 3420-3400, 3290- 3280,1720-1620 cm^{-1} due to amino and carbonyl groups,

respectively, whilst that of compound 15 revealed the disappearance of bands of amino and azido groups and presence of absorption bands at 3200, 1704 cm^{-1} due to (NH) and carbonyl groups, respectively.
The ^{1}H-NMR of compound 10 in (DMSO-d_6) showed two singlets at δ 2.3, 2.6 ppm characteristic for two methyl of pyrazole in addition to the expected signals attributed to amino, pyrazolo and aromatic protons. Also, the structure of 10 was supported by mass spectrum which showed a molecular ion peak at m/z =349 (92.7 %) which is in agreement with its molecular formula($C_{18}H_{15}N_5OS$).



Furthermore, the interaction of compound 9 with some reagents namely, acetic anhydride, formic acid or triethyl orthoformate gave the coressponding pyrimido[4′,5′: 4,5]thieno[2,3-c]pyridazine derivatives 16-18, respectively (Scheme 5). The structures of compounds 16-18 were established based on elemental analysis and spectral data.
The IR spectra of compounds 16 and 17 showed absorption bands at 3300- 3270, 1710 and 1675-1660 cm^{-1} due to imino, carbonyl of acetyl, formyl and carbonyl of pyrimidinone groups, respectively. Also,
the IR spectrumof compound 18 showed absorption band at 1660 cm^{-1} for the (CO, pyrimidinone).



scheme 5

EXPERIMENTAL

Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. The reactions were monitored by thin layer chromatography (TLC) on a silica coated aluminium sheet. IR spectra were recorded on a Shimadzu 470 IR spectrophotometer using KBr pellets. ^{1}H-NMR spectra were measured on a Varian 300 MHZ NMR spectrometer using TMS as internal standard (δ in ppm). The mass spectra were recorded on a Jeol-JMS-600 apparatus. The UV spectrum was recorded on a Shimadzu mini-1240 Spectrophotometer. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer.

4-Cyano-6-phenylpyridazine-3(2H)-thione (4)

A solution of compound (3) (0.01 mole) and thiourea (0.012 mole) in ethanol (20 mL) was heated under reflux for 4 h, the precipitate was boiled with 10% sodium hydroxide (5 mL) for 1 h. The solid salt was dissolved in water and acidified with 2N hydrochloric acid. The solid product was filtered off and recrystallized from ethanol to afford (4) as brown crystals in 89% yield; m.p. 206°C. IR: ύ = 3470 cm^{-1} (NH), 2222 cm^{-1} (C≡N), 1230 cm^{-1} (C=S); UV 324 nm (C=S); ^{1}H-NMR (DMSO-*d*$_6$) : δ 7.4-8.7 (m, 6H, Ar-H and Pyridazine-H), 11.10 (broad, 1H, NH*). Anal.*Calcd. for $C_{11}H_7N_3S$ (213.26); C, 61.95; H, 3.31; N, 19.70; S, 15.03. Found: C, 61.99; H, 3.27; N, 19.73; S, 15.01 %.

4-Cyano-3-ethoxycarbonylmethylthio-6-phenylpyridazine (5)

A mixture of compound (4) (0.01 mole), fused sodium acetate (0.012 mole) and ethyl chloroacetate (0.01 mole) in ethanol (50 mL) was stirred for 2 h. The solid product was filtered off and recrystallized from ethanol to give (5) as white crystals in 67% yield; m.p. 140 °C. IR: ύ = 2220 cm^{-1} (C≡N), 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.3 (t, 3H, CH_3), 4.2-4.3 (m, 4H, SCH_2 and OCH_2), 7.5-8.0 (m, 6H, Ar-H and Pyridazine-H).
Anal.Calcd. for $C_{15}H_{13}N_3O_2S$ (299.35); C, 60.19; H, 4.38; N,14.04; S, 10.71. Found: C, 60.10; H, 4.35; N, 14.11; S, 10.80 %.

5-Amino-3-phenyl-6-ethoxycarbonylthieno[2,3-c]pyridazine (6)

Method A

A mixture of compound (3) (0.01 mole), ethylthioglycolate/sodium carbonate (0.01 mole) or compound (4) (0.01 mole), ethyl chloroacetate (0.01 mole) and sodium ethoxide (0.012 mole) in ethanol (50 mL) was refluxed for 3 h. The solid product was collected and recrystallized from ethanol-chloroform mixture to afford (6) as yellow crystals in 93 % yield: in using (3) as a starting material and 93 % yield: when (4) was used, m.p. 225 °C. IR: ύ = 3430, 3300 cm^{-1} (NH_2), 1670 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) : δ 1.3 (t, 3H, CH_3), 4.3(q, 2H, OCH_2), 7.4-8.2(m, 6H, Ar-H and Pyridazine-H), 9.0 (s, 2H, NH_2); MS: m/z 299 (M^+,100%) , 271 (7.61%) , 253 (69.80%) , 226 (6.00 %) , 77 (15.83%), 51 (13.65%). *Anal*.Calcd. for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.19; H, 4.38; N, 14.04; S, 10.71. Found: C, 59.90; H, 4.50; N, 14.25; S, 10.67 %.

Method B

A mixture of compound (5) (0.01 mole), sodium ethoxide, or aniline or aniline derivatives (0.01 mole) in ethanol (50 mL) was heated under reflux for 2 h. The solid product was collected and recrystallized from ethanol-chloroform mixture to give (6) as yellow crystals, the product was identical in TLC, m.p, IR spectrum to the above method.

4-Cyano -6-phenyl(pyridazin-3-yl-thio)acetichydrazide (8)

A mixture of compound (5) (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (20 mL) was stirred for 3 h. The formed precipitate was collected by filteration and recrystallized from ethanol-chloroform mixture to give (8) as yellow crystals in 91% yield: m.p. 242 °C. IR: ύ= 3400, 3290, 3200 cm^{-1} (NH, NH_2), 2230 cm^{-1} (C≡N),1680 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.1 (s, 2H, SCH_2), 4.5 (s, 2H, NH_2), 7.4-8.1(m, 6H, Ar-H and pyridazine-H) , 9.0 (s, 1H, NH). *Anal*.Calcd. for $C_{13}H_{11}N_5OS$ (285.32); C, 54.73; H, 3.89; N, 24.55; S, 11.24. Found: C, 54.68; H, 3.82; N, 24.62; S, 11.28 %.

5-Amino-3-phenylthieno[2,3-c]pyridazine-6-carbohydrazide (9)
Method A

A mixture of compound (6) or (8) (0.01 mole) and hydrazine hydrate (0.01 mole) or anhydrous potassium carbonate (0.012 mole) in ethanol (50 mL) was refluxed for 3 h, and then allowed to cool. The solid product was collected and recrystallized from ethanol to give (9) as yellow crystals in 93% yield: m.p. 298 °C. IR: ύ = 3400, 3290, 3180 cm^{-1} (NH, NH_2), 1600 cm^{-1} (C=O); MS: m/z 285 ($M^{+\cdot}$,62.59%), 270 (2.36%), 254 (100%), 77 (15.83%), 51 (13.65%). *Anal*.Calcd. for $C_{13}H_{11}N_5OS$ (285.32); C, 54.73; H, 3.89; N, 24.55; S, 11.24 . Found: C, 54.77; H, 3.93; N, 24.48; S, 11.15%.

Method B

Refluxing of compound (5) (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (30 mL) for 4 h. The product, obtained upon recrystallization, was, identical in TLC, m.p. and spectral data to that prepared by the above method.

5-Amino-3-phenyl-thieno[2,3-c]pyridazin-6-yl-(3,5-dimethyl-pyrazol-1-yl)-ketone (10)

A mixture of carbohydrazide (9) (0.01 mole) and acetylacetone (0.01 mole) in ethanol (10 mL) was heated under reflux for 4 h. The precipitate was filtered off and recrystallized from ethanol to give (10) as orange crystals in 86% yield: m.p. 288 °C. IR: ύ = 3420, 3280 cm^{-1} (NH_2), 1680 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 2.3, 2.6 (2s, 6H, 2 CH_3), 6.2 (s, 1H, Pyrazole-H), 7.4-8.1 (m, 6H, Ar-H and pyridazine-H), 9.0 (s, 2H, NH_2); MS: m/z 349 ($M^{+\cdot}$,92.70), 253 (100%), 95 (12.39%). *Anal*.Calcd. for $C_{18}H_{15}N_5OS$ (349.41); C, 61.88; H, 4.33; N, 20.04; S, 9.18 . Found: C, 61.88; H, 4.30; N, 20.01; S, 9.14 %.

5-Amino-3-phenyl-6-ethylacetoacetatecarbohydrazone-thieno[2,3-c] pyridazine (11)

A mixture of carbohydrazide (9) (0.01 mole) and ethyl acetoacetate (0.01 mole) in ethanol (10 mL) was heated under reflux for 3 h. The solid product was collected and recrystallized from ethanol to give (11) as yellow crystals in 82% yield: m.p. 265 °C. IR: ύ = 3410, 3290 cm^{-1} (NH_2), 3190 cm^{-1} (NH), 1720 cm^{-1} (C=O, ester), 1680 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 1.2 (t, 3H, CH_3 of ester), 2.0 (s, 3H, CH_3), 3.4 (s, 2H, CH_2), 4.1 (q, 2H, OCH_2), 6.1 (s, 2H, NH_2), 7.5-8.3 (m, 6H, Ar-H and pyridazine-H), 9.1 (s, 1H, NH). *Anal*.Calcd. for $C_{19}H_{19}N_5O_3S$ (397.45) ; C, 57.42; H, 4.82; N, 17.62; S, 12.08 .Found: C, 57.48; H, 4.85; N, 17.57; S, 12.06 %.

5-Amino-3-phenylthieno[2,3-c]pyridazine-6-carboazide (13)

A sample of carbohydrazide (9) (0.01 mole) in glacial acetic acid (10 mL), solution of sodium nitrite (0.015 mole in 3 mL H_2O) was added dropwise, then allowed to stand for 2 h. The solid product was collected to give (13) as orange crystals in 71% yield: m.p.195 °C. IR: ύ = 3400, 3280 cm^{-1} (NH_2),

2120 cm^{-1} (N_3), 1620 cm^{-1} (C=O); MS: m/z 296 ($M^{+\cdot}$,20.19 ٪), 268 (30.67%), 253 (7.84%), 77 (38.98%), 51 (73.02%), 40 (100%). *Anal*. Calcd. for $C_{13}H_8N_6OS$ (296.31); C, 52.70; H, 2.72; N, 28.36; S, 10.82.
Found: C, 52.60; H, 2.74; N, 28.42; S, 10.91 %.

3-Phenyl-5,7-dihydroimidazo[4',5':4,5]thieno[2,3-c]pyridazine-6-one (15)

Compound of carboazide (13) (0.01 mole) in dry toluene (10 mL) was heated under reflux for 6 h, then allowed to cool. The solid product was collected and recrystallized from ethanol to give (15) as light brown crystals in 70% yield: m.p. >300 ˚C. IR: ύ =3200 cm^{-1} (-NH-CO-NH-), 1704 cm^{-1} (C=O). *Anal*.Calcd. for $C_{13}H_8N_4OS$ (268.29); C, 58.20; H, 3.01; N, 20.88; S, 11.95.
Found: C, 58.27; H, 3.03; N, 20.90; S, 11.90 %.

7-Acetylamino-6-methyl-3-phenylpyrimido[4',5':4,5]thieno[2,3-c] pyridazin-8-one(16)

A mixture of carbohydrazide (9) (0.01 mole) in acetic anhydride (10 mL) was heated under reflux for 3 h, then allowed to cool and poured into water (50 mL).The solid product was collected and recrystallized from ethanol to give (16) as white crystals in 74% yield: m.p. 198 ˚C. IR: ύ = 3300 cm^{-1} (NH), 1710 cm^{-1} (C=O, acetyl), 1675 cm^{-1} (C=O, pyrimidinone); ^{1}H-NMR (DMSO-d_6) δ 2.16 (s, 3H, $COCH_3$), 2.5 (s, 3H, CH_3), 7.4-8.3 (m, 6H, Ar-H and pyridazine-H), 11.3 (s, 1H, NH). *Anal*.Calcd. for $C_{17}H_{13}N_5O_2S$ (351.38); C,58.11; H, 3.73; N,19.93; S, 9.12. Found:C58.06; H,3.82; N, 19.91; S, 9.09 %.

7-Formylamino-3-phenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazin-8-one (17)

A mixture of carbohydrazide (9) (0.01 mole), formic acid (10 mL) was heated under reflux for 3 h, then allowed to cool, and poured into water (50 mL).The formed product was collected and recrystallized from ethanol to give (17) as white crystals in 63 % yield: m.p. 182 ˚C. IR: ύ = 3270 cm^{-1} (NH), at 1710 cm^{-1} (C=O, formyl), 1650 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 7.4-8.4 (m, 6H, Ar-H and pyridazine-H), 8.6 (s, 1H, CHO), 8.8 (s, 1H, NH), 8.9 (s, 1H, pyrimidine-H). *Anal*.Calcd. for $C_{15}H_9N_5O_2S$ (323.33); C, 55.72; H, 2.81; N, 21.66; S, 9.92. Found: C, 55.76; H, 2.75; N, 21.70; S, 9.94%.

7-Ethoxymethyleneamino-3-phenylpyrimido[4',5':4,5]thieno[2,3-c] pyridazin-8-one (18)

A mixture of carbohydrazide (9) (0.01 mole) and triethyl orthoformate (3 mL) in acetic anhydride (10 mL) was refluxed for 3h. The solid product was collected and recrystallized from ethanol to give (18) as white crystals in 74 % yield: m.p. 230˚C. IR: ύ= 1660 cm^{-1} (C=O, pyrimidinone),1630 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6) :δ 1.4 (t, 3H, CH_3), 4.2 (q, 2H, OCH_2), 7.3-8.4 (m, 7H, Ar-H,

Pyridazine-H and pyrimidine-H), 9.1 (s, 1H, CH=N). *Anal*.Calcd. for $C_{17}H_{13}N_5O_2S$ (351.38); C, 58.11; H, 3.73; N, 19.93; S, 9.12. Found: C, 58.06; H, 3.81; N, 19.90; S, 9.07 %.

Antibacterial activity

The compounds 4-6, 8-11, 16 and17 were screened for their antibacterial activity against the bacteria *Staphylococcus xylosus, Bacillus megaterium* (gram-positive bacteria) and *Salmonella typhii* (gram-negative bacteria) following the filter paper disc technique. Ciprofloxacin was used as standard antibacterial agent. The synthesized compounds and the Ciprofloxacin were dissolved in DMSO at 25, 50, 100 (µg /disc.) concentrations in the nutrient agar media. Antibacterial activity was determined by measuring the diameter of inhibition zone after an incubation for 24 h at 37 °C and the activity of each compound was compared with Ciprofloxacin as a positive control. The results are given in Table 1.The antibacterial activity showed that all compounds were active against microorganisms. All compounds were less active in comparison to ciprofloxacin which was taken as standard drug. Further, investigation on the biological activity of these compounds is in the progress.

Table(1) : Antibacterial screening results of the compounds 4-6, 8-11, 16 and17.

Comp.	Concentration (µg /disc.)	*S. xylosus.*	*B. meguterium.*	*S. typhii.*
4	25	-	-	-
	50	-	-	-
	100	-	+	-
5	25	-	+	-
	50	-	+	-
	100	+	+	-
6	25	-	-	-
	50	+	-	-
	100	+ +	+	-
8	25	+	-	-
	50	+	+	-
	100	+	+	-
9	25	-	+	+
	50	-	+	+
	100	-	+	+
10	25	-	-	-
	50	+	+	-
	100	+	+	-
11	25	-	+	-
	50	-	+	-
	100	+	+	+ +
16	25	-	+	-
	50	-	+	-
	100	+	+	-
17	25	-	+	-
	50	-	+	-
	100	-	+	-
Ciprofloxacin		+ + +	+ + +	+ + +

Highly active = + + + (inhibition zone > 27.9 mm)
Moderately active = + + (inhibition zone 18.7- 27.9 mm)
Slightly active = + (inhibition zone 9.4-18.6 mm)
Inactive = - (inhibition zone < 9.3 mm)

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