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Synthesis and Biological Evaluation of New Fused Thiazolo[4,5-*d*] Pyridazine Derivatives

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The synthesis of thiazolo[4,5-*d*]pyridazines and the unknown ring systems, thiazolo[4,5-*d*]-1,2,4-triazolo- and tetrazolo[4,3-*b*]pyridazines as well as thiazolo[4,5-*d*]pyridazino[2,3-*c*]2*H* triazines, has been achieved according to different pathways. Biological testing of the new tricyclic heterocycles revealed that some of these compounds possess remarkable antibacterial activity.

INTRODUCTION

Thiazoles,[1,2] triazoles[3,4] and pyridazines[5,6] are biologically important compounds. Some of these compounds have better antibacterial activity than carbenicillin against gram-negative bacteria,[7] others are used as antimicrobial agents.[8,9] As a wide variety of condensed triazolo[10-13] and triazino[12,14] derivatives also show pharmacological and biological properties, therefore, it was felt interesting to synthesise fused heterocyclic systems incorporating two or three of these biologically active moieties and evaluate their antibacterial activity.

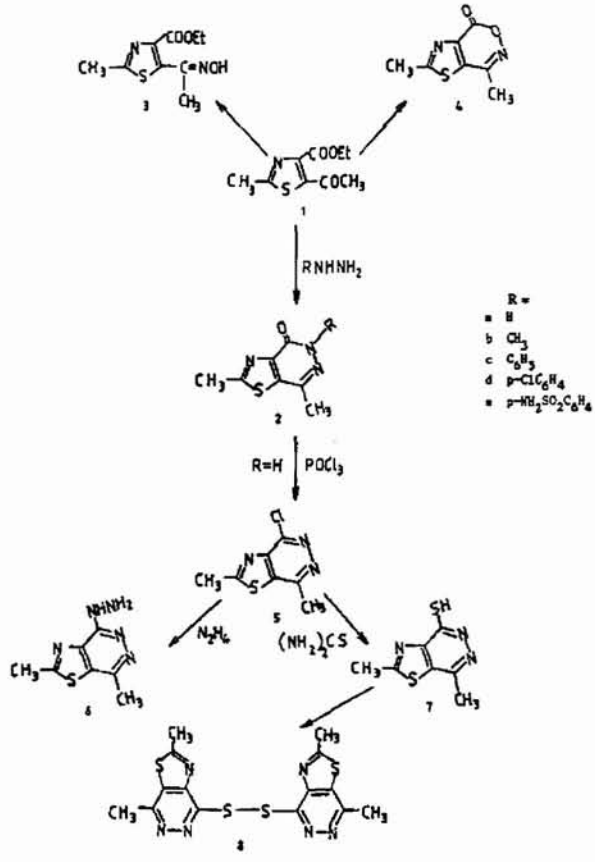
RESULTS AND DISCUSSION

The readily available ethyl 5-acetyl-2-methylthiazole-4-carboxylate **1** served as starting material for the synthesis (Scheme I). Reaction of **1** with hydrazine derivatives afforded the 1-substituted 3,5-dimethyl-7-oxothiazolo[4,5-*d*]pyridazines **2a-e**, while reaction with hydroxylamine hydrochloride **1** gave oxime **3** or 3,5-dimethyl-7-oxothiazolo-[4,5-*d*]-1,2-oxazine **4** depending on the reaction conditions (see Experimental). Consistent with the assigned structure the ^{1}H NMR spectrum of oxime **3** exhibited a triplet and quartet at δ 1.40 and 4.45 for the CH_3 and CH_2 of the ester group, respectively. These signals are lacking in the ^{1}H NMR spectrum of the oxazine derivative **4**. The ^{13}C NMR data of compounds **2** and **4** as summarized in Table 2 agree with the suggested structures.

The MS of the pyridazinone **2a** showed a molecular ion as the base peak while for **2e** the base peak was the [M - $NHSO_2C_6H_4NCO$] species and the molecular ion was only 25%. On the other hand, the mass spectrum of oxazine derivative **4** exhibited the molecular ion peak at *m/z* 182 while the base peak is at *m/z* 59.

Refluxing of **2a** with phosphorus oxychloride gave the

Scheme I



4-chloro derivative **5**, which on reaction with ethanolic hydrazine hydrate at room temperature yielded the 3,5-dimethyl-7-hydrazinothiazolo[4,5-*d*]pyridazine **6** in 92% yield. Reaction of **5** with thiourea gave the thiol derivative **7**, which on treatment with an aqueous solution of sodium hydrogen sulfate and sodium nitrite yielded the disulfide **8**. In agreement with the suggested structure, the ^{13}C NMR spectrum of **7** exhibited the expected number of signals for the aromatic carbons as well as two methyl signals at δ 20.12 and 21.54 (Table 2).

Reaction of the hydrazino compound **6** with acid chlorides afforded the corresponding acyl hyrazides hydrochlorides **9**, which readily cyclized in hot pyridine to the 3-substituted 6,8-dimethylthiazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazines **10** and **11** (Scheme II). The IR spectra of the acyl hydrazides **9** exhibited a secondary carbonyl absorption at 1658-1662 cm^{-1}, which is lacking in the IR spectra of the cyclic derivatives **10** and **11**.

Cyclocondensation of **6** with ethyl bromoacetate gave the 3-(bromomethyl)-1,2,4-triazolo derivative **12**. Its ^1H NMR exhibited a singlet of two protons intensity at δ 4.82 for the CH_2 as well as two methyl singlets at δ 2.40 and 2.72. However, refluxing the hydrazino compound **6** with α-bromoketones in acetic acid afforded the corresponding 3-substituted 7,9-dimethylthiazolo [4,5-*d*]pyridazino[2,3-*c*]-2*H*-1,2,4-triazines **15a-c**. In agreement with the suggested structure, the ^1H NMR spectra of the triazines **15a** and **15b** showed, besides the CH_3 and aromatic protons, an exchangeable NH signal at δ 12.56-12.90. The structure of **15a** was further confirmed by its MS analyses. A molecular ion peak at *m/z* 295 was detected, while the base peak is at *m/z* 181.

In 1969 Polts et al.[15] reported that the reaction of an excess of oxalic acid with 1-hydrazinophthalazine at 160 °C to give a 50% yield of *s*-triazolo[3,4-*a*]phthalazine, presumably arising from the decarboxylation of the originally formed *s*-triazolo[3,4-*a*]phthalazine-3-carboxylic acid. Zimmer et al.[16] isolated the 2*H*-*as*-triazolo[3,4-*a*]phthalazine-3,4-dione in 90% yield instead of the expected ethyl *s*-triazolo[3,4-*a*]phthalazine-3-carboxylate from the reaction of hydralazine with excess ethyl oxalate. However, in our case, when we refluxed **6** with ethyl oxalate, the product isolated was **13** or **14** depending on the reaction conditions (see Experimental) as evidenced by analytical and spectral data (Table 1).

Finally, when a solution of **6** in acetic acid was allowed to react with sodium nitrite the product was found to be the tetrazolo derivative **16**, a reaction similar to what's reported by Gatta et al.[13]

ANTIMICROBIAL ACTIVITY

Antimicrobial testing of compounds **2-6**, **10-13** and **15** was carried out and it was found (Table 3) that against *S. aureus* compound **15a** showed maximum activity (+++) (MIC = 25 μg/mL), compound **12** showed moderate activity (++) (MIC = 50 μg/mL), while compounds **5**, **6** and **15c** exhibited slight activity (+) (MIC = 75 μg/mL). Against *E. Coli* compound **15c** showed the maximum activity, while compounds **12** and **15a** exhibited moderate activlty and compound **5** showed the slight activity. Against *C. Albicans* compound **3** and **15c** revealed maximum inhibition (+++), compounds **12**, **15a** and **15b** showed moderate inhibition (++) and compound **2b**, **2c**, **5** and **6** were slightly active (+). However all other compounds were inactive towards the dif-

Scheme II

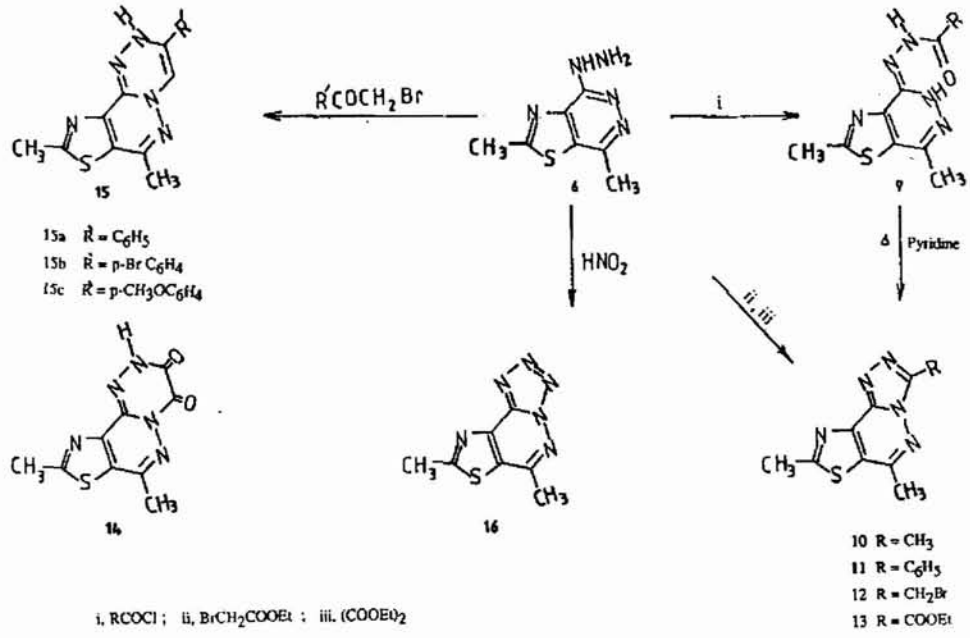


Table 1. Physical and Analytical Data

Compound	R or R′	Yield [%]	M.P. [°C]	Formula	Analysis Calcd./% C	H	N	S	Found/% C	H	N	S
2a	H	86	254	$C_7H_7N_3OS$	46.41	3.87	23.20	17.68	46.23	3.62	23.05	17.75
2b	CH_3	65	68	$C_8H_9N_3OS$	49.23	4.62	21.54	16.41	49.15	4.42	21.35	16.36
2c	C_6H_5	72	184	$C_{13}H_{11}N_3OS$	60.70	4.28	16.34	12.45	61.00	4.32	16.33	12.40
2d	p-ClC_6H_4	78	204	$C_{13}H_{10}ClN_3OS$	53.52	3.43	14.41	10.98	53.32	3.26	14.51	11.10
2e	p-$NH_2SO_2C_6H_4$	84	249	$C_{13}H_{12}N_4O_3S_2$	46.43	3.57	16.67	19.05	46.25	3.68	16.58	19.21
3		78	76	$C_9H_{12}N_2O_3S$	47.37	5.26	12.28	14.04	47.40	5.40	12.24	14.00
4		68	162	$C_7H_6N_2O_2S$	46.15	3.30	15.38	17.58	46.23	3.26	15.42	17.65
5		82	146	$C_7H_6ClN_3S$	42.11	3.01	21.05	16.04	41.99	3.02	21.15	16.22
6		85	92	$C_7H_9N_5S$	43.08	4.62	35.90	16.41	43.10	4.72	35.76	16.28
7		72	>300	$C_7H_7N_3S_2$	42.64	3.55	21.32	32.49	42.75	3.60	21.41	32.51
8		78	>300	$C_{14}H_{12}N_6S_4$	42.86	3.06	21.42	32.65	42.93	3.11	21.28	32.76
9a	CH_3	82	202	$C_9H_{12}ClN_5OS$	39.49	4.39	25.59	11.70	39.60	4.42	25.68	11.82
9b	C_6H_5	86	146	$C_{14}H_{14}ClN_5OS$	50.07	4.17	20.86	9.53	50.14	4.12	20.90	9.55
10	CH_3	60	138	$C_9H_9N_5S$	49.31	4.11	31.96	14.61	49.52	3.95	32.05	14.71
11	C_6H_5	62	215	$C_{14}H_{11}N_5S$	59.79	3.91	24.91	11.38	59.95	3.75	24.75	11.42
12	CH_2Br	68	146	$C_9H_8BrN_5S$	36.24	2.68	23.49	10.74	36.33	2.88	23.50	10.71
13	COOEt	65	242	$C_{11}H_{11}N_5O_2S$	47.65	3.97	25.27	11.55	47.77	4.00	25.40	11.70
14		62	>300	$C_9H_7N_5O_2S$	43.37	2.81	28.11	12.85	43.40	2.85	27.98	12.80
15a	C_6H_5	72	248	$C_{15}H_{13}N_5S$	61.02	4.41	23.73	10.85	61.15	4.32	23.85	10.95
15b	p-BrC_6H_4	68	196	$C_{15}H_{12}BrN_5S$	48.13	3.21	18.72	8.56	48.32	3.25	18.80	8.65
15c	p-$MeOC_6H_4$	70	252	$C_{16}H_{15}N_5OS$	59.08	4.62	21.54	9.85	59.24	4.42	21.38	9.90
16		58	144	$C_7H_6N_6S$	40.78	2.91	40.78	15.53	40.90	3.11	40.82	15.52

ferent strains of bacteria. Quantitative assays were done on active compounds only.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained on a Magna FT 550 spectrophotometer using potassium bromide pellets. ^{1}H NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer in the solvents as indicated. Chemical shifts are reported in ppm from TMS as internal standard and are given in δ units. ^{13}C NMR spectra were recorded on Bruker DPX-400-FT spectrometer.

Table 2. ^{13}C NMR Spectral Data of Thiazolo[4,5-*d*]pyridazine Derivatives[a]

Compound	Aromatic *C*	CH_3	CO
2a	138.94, 139.47, 147.53, 156.24	20.47, 19.80	170.98
2c	122.52, 126.30, 126.96, 138.64, 140.35, 144.32, 148.02, 155.25	20.32, 21.54	175.05
2d	126.80, 127.72, 132.42, 131.88, 139.35, 139.89, 147.57, 154.61	19.46, 20.62	171.27
2e	126.18, 126.85, 138.56, 140.27, 143.44, 144.19, 147.99, 155.10	20.17, 21.27	174.47
4	136.94, 140.9, 149.55, 159.43	19.01, 20.15	173.52
5	138.93, 147.50, 147.80, 155.22, 164.47	20.50, 21.85	
7	136.56, 145.82, 148.55, 155.75, 158.65	20.12. 21.54	
15a	122.83, 127.30, 128.20, 129.63, 136.75, 137.22, 138.45, 145.40, 149.86, 154.21, 168.63	17.85, 18.70	

[a] Solution in DMSO-d_6/$CDCl_3$, δ in ppm.

Table 3. Antimicrobial Activities of Synthesized Compounds (+++ for maximum activity, MIC[a] 25: ++ for moderate activity, MIC 50; + for slight activity, MIC 75 and - for inactive)

Organism	2a	2b	2c	3	4	5	6	10	11	12	13	15a	15b	15c
S. aureus (Gram-positive)	-	-	-	-	-	+	+	-	-	++	-	+++	-	+
E. coli (Gram-negative)	-	-	-	-	-	+	-	-	-	++	-	++	-	+++
C. albicans (Fungi)	-	+	+	+++	-	+	+	-	-	++	-	++	++	+++

[a] Minimal inhibitory concentration (*MIC in μg/mL*).

MS were obtained on a Kratos MS 30. Elemental analyses were performed by Microanalyses unit, King Abdulaziz University, Jeddah, S.A. Ethyl 5-acetyl-2-methylthiazole-4-carboxylate was obtained from Maybridge Chemical Company Limited, UK.

1-Substituted 3,5-dimethyl-7-oxothiazolo[4,5-*d*]pyridazines (2a-e) (Table 1)

A solution of ethyl 5-acetyl-2-methylthiazole-4-carboxylate **1** (0.43 g, 0.002 mL) in C_2H_5OH (25 mL) was refluxed with the appropriate hydrazine for 2 h. The pyridazines which separated after concentration of the reaction mixture were filtered off, washed with C_2H_5OH, and recrystallized from C_2H_5OH as needles.

2a: IR (KBr, ν_{max}, cm^{-1}) 1655 (CO), 3293 (NH); ^1H NMR (DMSO-d_6) δ 2.50 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 12.82 (s, 1H, NH); MS *m/z* (relative intensity) 181 (M^+, 100), 153 (M-CO, 28), 125 (17), 110 (12), 97 (5), 84 (16), 66 (22).

2b: IR (KBr, ν_{max}, cm^{-1}) 1658 (CO), ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.15 (s, 3H, CH_3).

2c: IR (KBr, ν_{max}, cm^{-1}) 1660 (CO), ^1H NMR (DMSO-d_6) δ 2.55 (s, 3H, CH_3), 2.80 (s, 3H, CH_3); 7.1-7.3 (m, 5H, C_6H_5).

2e: IR (KBr, ν_{max}, cm^{-1}) 1653 (CO), 3314 and 3181 (NH_2); ^1H NMR (DMSO-d_6) δ 2.65 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 7.35-8.16 (m, 6H, Ar + NH_2), MS *m/z* (relative intensity) 336 (M^+, 25), 308 (M-CO, 32), 256 (M-SO_2NH_2, 12), 228 (I8), 184 ($N_2C_6H_4SO_2NH_2$, 20), 180 (M-$NH_2C_6H_4SO_2NH_2$, 10), 170 ($^+NC_6H_4SO_2NH_2$, 18), 156 ($C_6H_4SO_2NH_2$, 36), 141 (43), 139 (100), 124 (7), 113 (13), 111 (42), 97 (8), 85 (10), 80 (12), 75 (36), 69 (15), 50 (28).

Ethyl 5-acetyl-2-methylthiazole-4-carboxylate oxime (3)

A solution of **1** (0.43 g, 0.002 mL) in C_2H_5OH (20 mL) was refluxed with hydroxylamine hydrochloride (0.15 g, 0.0022 mol) and NaOAc (0.18 g, 0.0022 mol) for 3 h. The oxime which separated after dilution with water was recrystallized from diluted C_2H_5OH as needles; IR (KBr, ν_{max}, cm^{-1}) 1740 (CO), 3277 (OH); ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 6Hz, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.45 (q, J = 6Hz, 2H, CH_2).

3,5-Dimethyl-7-oxothiazolo[4,5-*d*]-1,2-oxazine (4)

A solution of **1** (0.43 g, 0.002 mol) in pyridine (10 mL) was refluxed with hydroxylamine hydrochloride (0.15 g, 0.0022 mol) for 6 h. The oxazinone **4** separated on dilution with water was recrystallized from C_2H_5OH as needles; IR (KBr, ν_{max}, cm^{-1}) 1745 (CO); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 2.70 (s, 3H, CH_3); MS *m/z* (relative intensity) 182 (M^+, 50), 141 (M-CH_3CN, 41), 125 (8), 113 (12), 112 (23), 100 (13), 97 (4), 87 (10), 82 (10), 70 (24), 59 (100), 57 (24), 53 (14), 45 (13).

7-Chloro-3,5-dimethylthiazolo[4,5-*d*]pyridazine (5)

Compound **2a** (0.91 g, 0.005 mol) was suspended in phosphorus oxychloride (10 mL) and the mixture was refluxed for 1 h. The excess of phosphorus oxychloride was distilled under reduced pressure and the residual syrup was poured into finely crushed ice (50 g), extracted with ether and the solvent was removed to give pale yellow solid of the chloro derivative **5** which was recrystallized from CH_3OH as needles; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H, CH_3), 2.68 (s, 3H, CH_3).

3,5-Dimethyl-7-hydrazinothiazolo[4,5-*d*]pyridazine (6)

A solution of the 4-chloro derivative **5** (1 g, 0.005 mol) and 94% hydrazine hydrate (1 g) in absolute C_2H_5OH (50 mL) was stirred at room temperature for 2 h. The solid which separated was filtered and recrystallized from CH_3OH as needles; IR (KBr, ν_{max}, cm^{-1}) 3174 and 3319 ($NHNH_2$), ^1H NMR (DMSO-d_6) δ 8.65-9.25 (broad s, 3H, NH and NH_2), 2.46 (s, 3H, CH_3), 2.76 (s, 3H, CH_3).

3,5-Dimethylthiazolo[4,5-*d*]pyridazine-7-thiol (7)

A solution of **5** (1 g, 0.005 mol) in CH_3COCH_3 (25

mL) was refluxed with thiourea (0.76 g, 0.010 mol) for 1 h. The reaction mixture was then cooled to 0 °C, Na_2CO_3 (10 mL, 0.5 M) was added slowly with temperature kept below 5 °C and the mixture stirred overnight. The precipitate was filtered off and the filtrate neutralized with 5% (v/v) HCl. The product which separated out was collected, washed with water, and recrystallized from DMSO as pale yellow needles; IR (KBr, ν_{max}, cm^{-1}) 2605 (SH); ^1H NMR (DMSO-d_6) δ 2.50 (s, 3H, CH_3), 2.68 (s, 3H, CH_3).

Bis(3,5-dimthylthiazolo[4,5-*d*]pyridazin-7-yl) disulfide (8)

To a suspension mixture of **7** (0.39 g, 0.002 mol) and $NaHSO_4$ (2 g) in water (15 mL), $NaNO_2$ (2 g) was gradually added (30 min) with stirring at 20 °C. The disulfide which separated (78% yield) was recrystallized from DMSO as pale yellow needles; ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 2.72 (s, 3H, CH_3).

3-Substituted 6,8-dimethylthiazolo[4,5-*d*]-1,2,4-triazolo-[4,3-*b*]pyridazines (10) and (11)

The hydrazino derivative **6** (0.49 g, 0.0025 mol) was heated on a water bath with the appropriate acid chloride (0.003 mol) for 1 h. The acylhydrazides **9** that separated out in the form of hydrochlorides were recrystallized from C_2H_5OH as needles (Table 1). Cyclization to the triazolo derivatives **10** and **11** was performed by refluxing these acylhydrazides (0.001 mol) in dry pyridine (8 mL) for one hour. The reaction mixture was then poured into 10% Na_2CO_3 solution and the solid which separated was recrystallized from CH_3OH as needles.

9a: IR (KBr, ν_{max}, cm^{-1}) 1662 (CO), 3265 (NH).

9b: IR (KBr, ν_{max}, cm^{-1}) 1558 (CO), 3279 (NH).

10: ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.70 (s, 3H, CH_3).

11: ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 7.3-7.6 (m, 5H, C_6H_5).

3-Bromomethyl-6,8-dimethylthiazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazines (12)

A solution of **6** (0.49 g, 0.0025 mol) in C_2H_5OH (20 mL) was refluxed with ethyl bromoacetate (0.43 g, 0.0026 mol) for 2 h. The reaction mixture was then concentrated to yield white solid which was recrystallized from C_2H_5OH as needles; ^1H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.82 (s, 2H, CH_2).

Ethyl 6,8-dimethylthiazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]-pyridazine-3-carboxylate (13)

A mixture of **6** (0.49 g, 0.0025 mol) and excess ethyl oxalate (10 mL) was refluxed for 3 h and cooled. The solid which separated was collected and recrystallized from DMF as pale yellow needles; IR (KBr, ν_{max}, cm^{-1}) 1728 (CO), ^1H NMR (DMSO-d_6) δ 1.42 (t, J = 6Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.40 (q, J = 6Hz, 2H, CH_2).

2,9-Dimethylthiazolo[4,5-*d*]pyridazino-[2,3-*c*]-2*H*-1,2,4-triazine-3,4-dione (14)

A mixture of **6** (0.49 g, 0.0025 mol), NaOAc (1.0 g) and ethyl oxalate (0.38 g, 0.0027 mol) in C_2H_5OH (30 mL) was refluxed for 8 h. The reaction mixture was then poured into ice - cold water and the solid separated out was recrystallized from DMF as needles; IR (KBr, ν_{max}, cm^{-1}) 1689 (CO), 1742 (CO), 3179 (NH); ^1H NMR (DMSO-d_6) δ 2.46 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 8.01 (broad s, 1H, NH).

3-Substituted 7,9-dimethylthiazolo[4,5-*d*]pyridazino[2,3-*c*]-2*H*-1,2,4-triazines (15)

A solution of **6** (0.49 g, 0.0025 mol) in glacial AcOH (10 mL) was refluxed with the appropriate α-bromoketone (0.0026 mol) for 2 h and poured into ice - cold water. The solid which separated was collected and recrystallized from C_2H_5OH as needles.

15a (R′ = C_6H_5): ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.45-7.62 (m, 5H, C_6H_5), 12.90 (s, 1H, NH); MS *m/z* (relative intensity) 295 (M^+, 22), 293 (M-2H, 10), 282 (M-CH, 8), 267 (M-N_2, 12), 205 (10), 191 (12), 181 (100), 153 (25), 125 (20), 111 (18), 96 (8), 84 (22), 66 (25).

15b (R′ = p-BrC_6H_4): ^1H NMR (DMSO-d_6) δ 2.42 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.35-7.75 (m, 4H, ArH), 12.56 (s, 1H, NH).

6,8-Dimethylthiazolo[4,5-*d*]-1,2,3,4-tetrazolo[4,3-*b*]pyridazine (16)

A stirred solution of **6** (0.49 g, 0.0025 mol) in glacial AcOH (10 mL) was gradually treated with 25% aqueous $NaNO_2$ (15 mL). The tetrazolo derivative which separated as white solid was recrystallized from C_2H_5OH as needles; ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 2.72 (s, 3H, CH_3).

BIOLOGICAL TESTING

Compounds **2-6**, **10-13** and **15** were screened for their antibacterial and antifungal activity following agar-diffusion method,[17] using Gram-positive bacteria Staphylococcus aureus and Gram-negative bacteria Escherichia coli. The antifungal testing was carried out against candida albicans.

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Key Words

Thiazoles; Triazoles; Pyridazines.

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