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The Use of 4-(3,4-Dichlorophenyl)-4-Oxo-2-(4-Antipyrinyl)-Butanoic Acid in the Preparation of Some New Heterocyclic Compounds With Expected Biological Activity

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Abstract: Reaction of 4-oxo-4-(3,4-dichlorophenyl)-2-butenoic acid (**1**) with antipyrin (**2**) gave the corresponding butanoic acid **3**. Reaction of **3** with hydrazines gave the pyridazinone derivatives **5a,b**. Compounds **5a,b** were used to prepare the corresponding dithio derivatives. Reaction of **5a** with $POCl_3$ unexpectedly gave the chloropyridazine derivative **7**, which is used to prepare the corresponding thio derivative. The hitherto unknown reactions of this chloro derivative with 2-amino-3-carbethoxy-4,5-dimethylthiophene and 2-amino-3-carbethoxy tetrahydrobenzothiophene have now been described. The behaviour of the chloro derivative toward hydrazine hydrate, sodium azide and anthranilic acid was also studied. Some of the new compounds showed antimicrobial and antifungal activities .

Keywords: Substituted pyridazinones, chloropyridazine, substituted thiophenes

Introduction

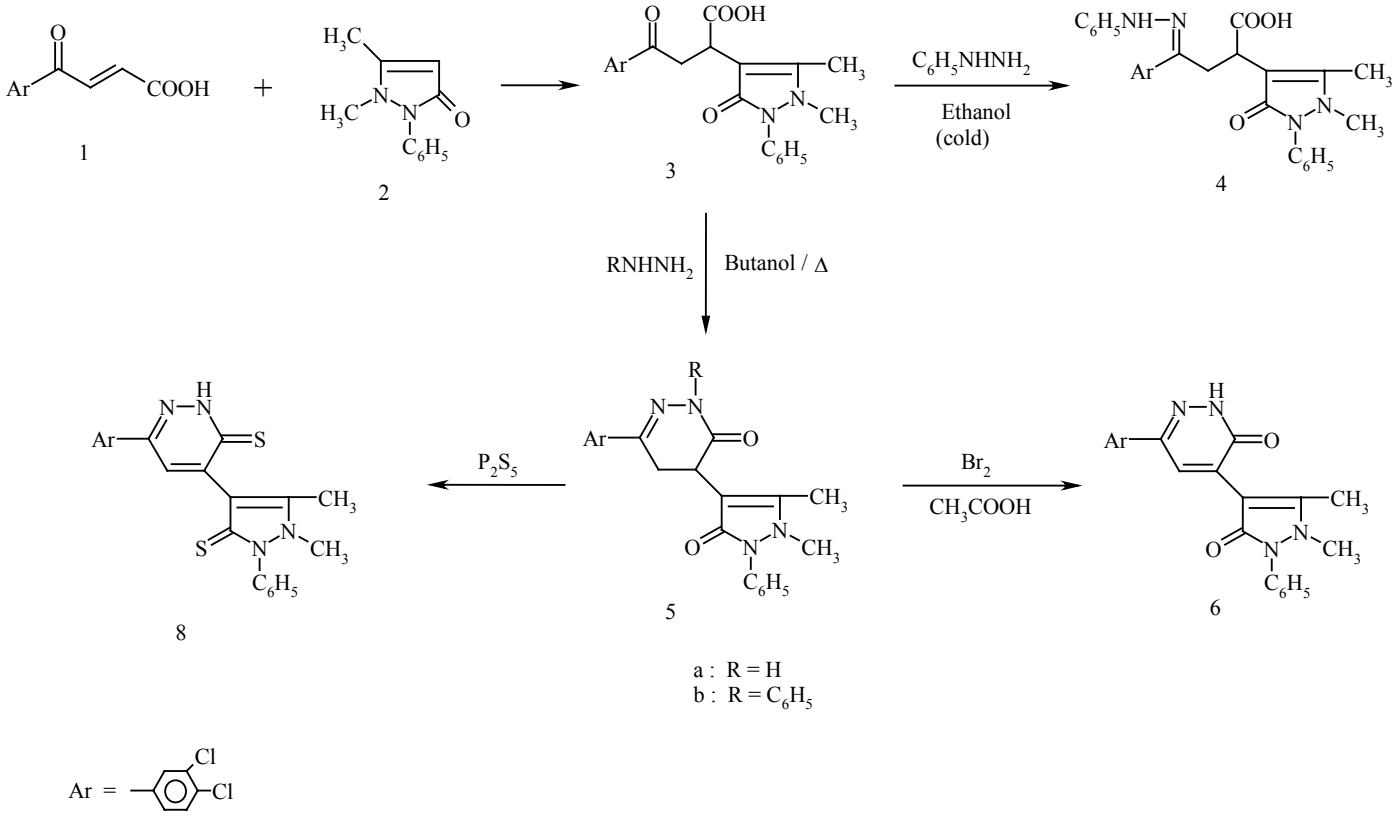
Antipyrin derivatives are reported to exhibit analgesic and anti-inflammatory effects [1-3], antiviral [4], antibacterial [5] and herbicidal [6] activities and have also been used as hair colour additives [7] and to potentiate the local anesthetic effect of lidocaine [8]. This prompted us to synthesize a new

series of heterocyclic compounds containing the antipyrinyl moiety. The antimicrobial activities of several of the compounds were screened. The various compounds prepared are outlined in Schemes 1 and 2.

Results and Discussion

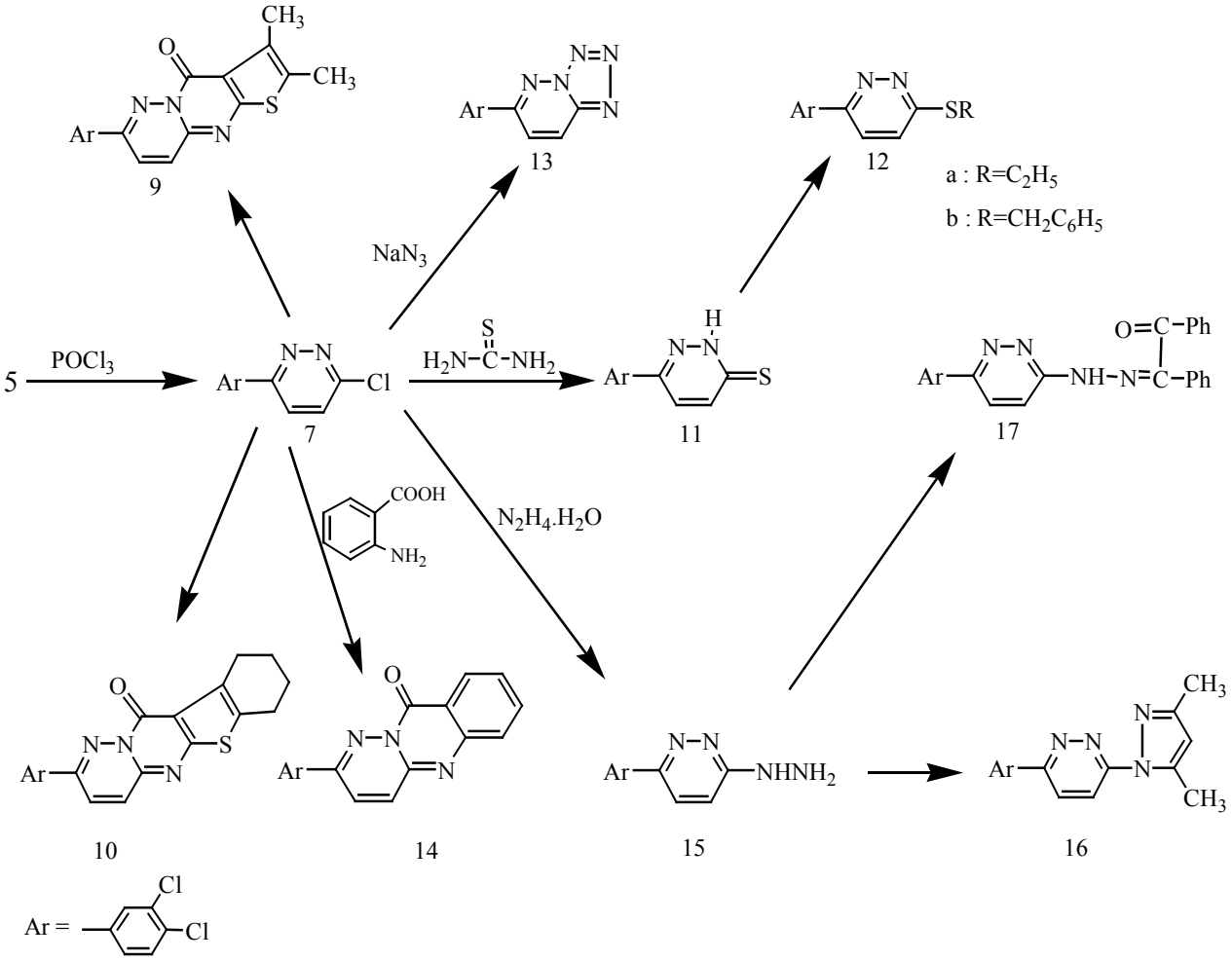
The reaction of 4-oxo-4-(3,4-dichlorophenyl)-2-butenoic acid (**1**) with antipyrin (**2**) in dry benzene gave 4-(3,4-dichlorophenyl)-4-oxo-2-(4-antipyrinyl)butanoic acid (**3,** Scheme 1). The reaction of the acid **3** with phenylhydrazine in ethanol under cooling for 15 days gave 4-(3,4-dichlorophenyl)-4-phenylhydrazono-2-(4-antipyrinyl)butanoic acid (**4**)**.** However, upon reaction of the acid **3** with hydrazine hydrate and phenylhydrazine in boiling butanol the derivatives 6-(3,4-dichlorophenyl)-4-(4-antipyrinyl)-4,5-dihydropyridazin-3(2H)-one (**5a**) and 6-(3,4-dichlorophenyl)-2-phenyl-4-(4-antipyrinyl)-4,5-dihyropyridazin-3(2H)-one (**5b**) were obtained, respectively. Compound **5a** undergoes dehydrogenation upon treatment with bromine/acetic acid mixture to give **6.** This is in accordance with a previously reported result [9].

Scheme 1



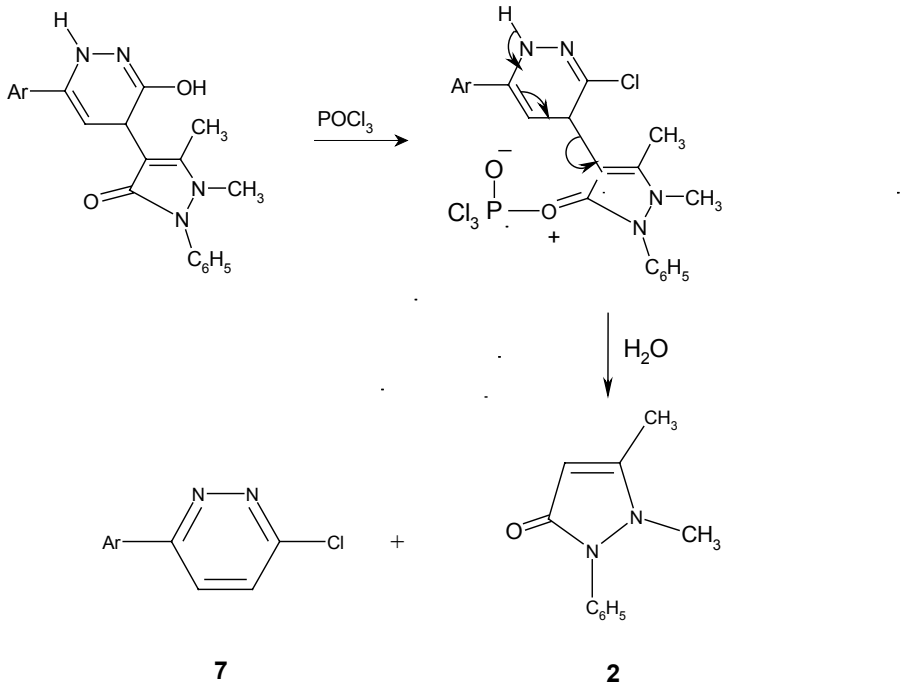
Surprisingly, when the reaction of **5a** with phosphorus oxychloride was carried out for 3 hr., we unexpectedly obtained 6-(3,4-dichlorophenyl)-3-chloropyridazine (**7,** Scheme 2). The proposed structure of compound **7** was supported by the identity of its m.p. [10] with that of an authentic sample prepared by the reaction of the corresponding 4-oxo-4-(3,4-dichlorophenyl)-2-butenoic acid with hydrazine hydrate and treating the resulting pyridazinone with $POCl_3$.

Scheme 2



The reaction presumably proceeds through protonation of the two carbonyl groups to give an intermediate which subsequently loses the antipyrinyl ring which rearranges to give **2**. The pyridazinone moiety was also rearranged and converted into **7** by substitution of the hydroxyl group with chlorine according to the mechanism shown in Scheme 3.

Scheme 3



7 **2**

The prepared compounds **5a** and **7** were then used to prepare new sulfur-containing compounds. Thus, treatment of pyridazine **5a** with phosphorus pentasulfide in dry xylene gave 6-(3,4-dichlorophenyl)-4-(1,5-dimethyl-2-phenyl-3-thioxo-2,3-dihydro-1H-pyrazol-4-yl)-3(2H)pyridazine-thione (**8**). In this reaction, dithioketone formation together with dehydrogenation take place. The hitherto unknown reaction of chloropyridazine **7** with 2-amino-3-carbethoxy-4,5-dimethylthiophene affording the three fused ring compound 7-(3,4-dichlorophenyl)-2,3-dimethyl-4H-thieno-[2',3':4,5]-pyrimido-[1,2-b] pyridazin-4-one (**9**) was also studied. The reaction is assumed to proceed through nucleophilic N attack at C_3 ,and departure of the chlorine followed by cyclization..

Similarly, **7** reacted with 2-amino-3-carbethoxy tetrahydrobenzothiophene to afford a compound containing four fused rings: 2-(3,4-dichlorophenyl)7,8,9,10-tetrahydro-11H-[1]-benzothieno-[2',3': 4,5] pyrimido-1,2-b]-pyridazin-11-one (**10**).

The behaviour of the chloropyridazine derivative **7** towards thiourea has also been studied. Thus, treatment of **7** with thiourea in dry xylene gave the 6-(3,4-dichlorophenyl)-3(2H)-pyridazine thione (**11**)**.** The proposed structure of the thione **11** is supported by its reaction with dimethyl sulfate and benzyl chloride in dry acetone in the presence of anhydrous K_2CO_3 to give 6-(3,4-dichlorophenyl)-3-(ethylsulfanyl)pyridazine (**12a**) and 6-(3,4-dichlorophenyl)-3-(benzylsulfanyl)-pyridazine (**12b**), respectively.

The chloropyridazine derivative **7** has also been used as the key starting material for the preparation of some other new heterocyclic compounds. Thus, **7** reacts with sodium azide, anthranilic acid or hydrazine hydrate to give 6-(3,4-dichlorophenyl) [1,2,3,4] tetrazolo [1,5-b] pyridazine (**13**), 2-(3,4-dichlorophenyl)-10H-pyridazino-(6,1-b)-quinazolin-10-one (**14**) and 6-(3,4-dichlorophenyl)-3-

hydrazinopyridazine (**15**), respectively. Reaction of the hydrazino derivative **15** with acetylacetone in methanol gave 6-(3,4-dichlorophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazine (**16**), while reaction of **15** with benzil in boiling methanol gave the condensation product 1,2-diphenyl-1,2-ethanedione-1-{N-[6-(3,4-dichlorophenyl)-3-pyridazinyl]hydrazone} (**17**).

The IR spectrum of **13** showed absorption bands at 1040 and 1085 cm^{-1}, characteristic of the tetrazole ring, and at 1590 cm^{-1} attributable to $\upsilon_{C=N}$. Similarly the IR spectrum of **14** exhibited characteristic absorption bands for $\nu_{C=O}$ at 1710 and $\nu_{C=N}$ at 1620 cm^{-1}, while that of **15** showed the bands of $\nu_{C=N}$ at 1610 cm^{-1}.

Biological Screening

The antimicrobial activity of the prepared compounds **3, 4, 6, 8, 10, 12a, 13** and **17** was tested by the disk diffusion method [11]. The results of antimicrobial activity are listed in Table 1. From the data it is clear that compounds **3**, **10** and **12a** possess high activity, while compounds **4, 6, 8, 13** and **17** possess moderate activity against Gram positive strains. As far as Gram negative microorganisms are concerned, compounds **6, 10, 12a** and **17** showed high activity while compounds **3, 4, 8** and **13** display moderate activity. Compounds **6** and **17** also exerted high activity while compounds **3, 4, 8, 10, 12a** and **13** moderate activity against fungi.

Table 1. Antimicrobial activity of some compounds[a]

Compound No.	Gram positive bacteria		Gram negative bacteria		Fungi
	Staphylococcus aureus (NCTC-7447)	Bacillus cereus (ATCC-14579)	Serratia marcescens (IMRU-70)	Proteus merabilis (NCTC-289)	Aspergillus fungytus (PP-29)
3	+++	+++	+++	++	++
4	++	++	++	++	++
6	+++	++	+++	+++	+++
8	++	++	++	++	++
10	+++	+++	+++	+++	++
12a	+++	+++	+++	+++	++
13	+++	++	+++	++	++
17	+++	++	+++	+++	+++

[a] Solvent: DMF, C = 250 μg ml^{-1}; Ratings: ++ = moderate activity (diameter 0.6-1.4 cm), +++ = high activity (diameter 1.15-3.0 cm); Reference substances: ampicillin for Gram positive and Gram negative bacteria, mycostatin for fungi.

Experimental

General

All melting points are uncorrected, IR spectra (KBr) were recorded on a Unicam SP 1200 spectrophotometer using KBr wafer technique and are expressed as υ (cm-1). Nmr spectra were recorded on a Jeol 100 FT instrument using tetramethylsilane as internal standard and are expressed in δ (ppm) units. Mass spectra were obtained with an GCMS-QP 100 EX mass spectrometer. Analytical data for the prepared compounds is summarized in Table 2.

Synthesis of 4-(3,4-dichlorophenyl)-4-oxo-2-(4-antipyrinyl) butanoic acid (**3**)**.**

To a solution of **1** (0.01 mol) in dry benzene (20 mL), antipyrin **2** (0.01 mol) was added and the reaction mixture was refluxed for 10 hrs. The solid that separated on cooling was filtered off and recrystallized to give **3** (65% yield); IR: 1730 (acid C=O), 1688 (ketone C=O); ^{1}H-NMR: 8.12-7.20 (8H, m, Ar-H), 4.03-3.17 (3H, m, CH_2CH), 2.26 (6H, s, 2 CH_3) and 12.42 (1H, s, COOH); MS: m/z 432 (M^+, 100%).

Synthesis of 4-(3,4-dichlorophenyl)-4-phenylhydrazono-2-(4-antipyrinyl)butanoic acid (**4**).

Phenylhydrazine (0.01 mol) was added to a solution of **3** (0.01 mol) in ethanol (50 mL) and the reaction mixture was left 15 days at room temperature. The solid that separated was filtered off and recrystallized to give **4**; (85 % yield); IR: 1719 (acid C=O), 1683 (ketone C=O), 1601 (C=N).

Synthesis of 6-(3,4-dichlorophenyl)-4-(4-antipyrinyl)-4,5-dihydropyridazin-3(2H)-one (**5a**) *and 6-(3,4-dichlorophenyl)-2-phenyl-4-(4-antipyrinyl)4,5-dihydropyridazin-3(2H)-one* (**5b**).

Hydrazine hydrate or phenylhydrazine (0.01 mol) were added to a solution of **3** (0.01 mol) in butanol (50 mL), and the resulting mixtures were refluxed for 5-10 hrs. The solids that separated were filtered off and recrystallized to give **5a** (82 % yield); IR: 1676 (C=O), 1630 (C=N); ^{1}H-NMR: 7.95-7.29 (8H, m, Ar-H), 3.75-3.05 (3H, m, -CH_2-CH-), 2.2 (6H, s, 2CH_3) and 11.15 (1H, s, NH); MS: m/z 428 (M^+, 100%) or **5b** (65 % yield); IR: 1670 (C=O), 1596 (C=N); ^{1}H-NMR 7.7-7.2 (13H, m, Ar-H), 3.75-3.00 (3H, m, CH_2-CH), 2.2 (6H, s, 2 CH_3).

Synthesis of 6-(3,4-dichlorophenyl)-4-(4-antipyrinyl)pyridazin-3(2H)-one (**6**).

A stirred solution of **5a** (0.01 mol) in glacial acetic acid (20 mL) was treated dropwise with bromine (0.02 mol) at 60-70^{o}C. The solution was further stirred for 2 hrs, then cooled in ice. The precipitated product was filtered off, washed with pet. ether (b.p. 40-60^{o}C) and stirred with

concentrated ammonium hydroxide for 50 minutes. The resulting solid product was filtered off and recrystallized to give **6** (55% yield); IR: 1719 (C=O), 1591 (C=N); MS: m/z 426 (M^+, 100 %)

Synthesis of 6-(3,4-dichlorophenyl)-3-chloropyridazine (**7**)**.**

A mixture of **5a** (0.01 mol) and $POCl_3$ (10 ml) was refluxed for 3 hrs, cooled and treated with crushed ice. The solid obtained was filtered off and recrystallized to give **7**; (60% yield); IR: 1600 (C=N).

Preparation of an authentic sample of **7.**

Hydrazine hydrate (0.01 mol) was added to a solution of **1** (0.01 mol) in absolute ethanol (50 mL), and the reaction mixture was refluxed for 5 hrs. The solid that separated on cooling was recrystallized from ethanol to give the corresponding pyridazinone. A mixture of the obtained pyridazinone (0.01 mol) and $POCl_3$ (10 mL) was refluxed for 3 hrs, cooled, treated with crushed ice. The solid obtained was filtered off and crystallized from pet. ether (b.p. 80-100^{o}C) to give **7**, identified by m.p. and mixed m.p. determinations [10].

Synthesis of 6-(3,4-dichlorophenyl)-4-(1,5-dimethyl-2-phenyl-3-thioxo-2,3-dihydro-1H-pyrazol-4-yl)-3(2H)pyridazine thione (**8**).

A solution of **5a** (0.01 mol), P_2S_5 (0.03 mol) in dry xylene (50 mL) was boiled under reflux for 6 hrs. The reaction mixture was filtered while hot and the filtrate concentrated. The product which separated on cooling was filtered off and recrystallized to give **8** (50% yield); IR: 1598 (C=N), 1475 (N-C=S), 1384 (C=S).

Synthesis of 7-(3,4-dichlorophenyl)-2,3-dimethyl-4H-thieno-[2',3':4,5] pyrimido-[1,2-b]-pyridazin-4-one (**9**) *and 2-(3,4-dichlorophenyl)-7,8,9,10-tetrahydro-11H-[1]-benzothieno-[2',3':4,5]-pyrimido-[1,2-b]-pyridazin-11-one* (**10**).

To a solution of **7** (0.01 mol) in absolute ethanol (50 mL), 2-amino-3-carbethoxy-4,5-dimethylthiophene or 2-amino-3-carbe-thoxy tetrahydrobenzothiophene (0.01 mol) were added and the reaction mixture was refluxed for 5 hrs. The solids that separated on cooling were recrystallized to give **9** (85% yield); IR: 1695 (C=O), 1622 (C=N); MS: m/z 375 (M^+, 100 %) and **10** (87% yield); IR: 1711 (C=O), 1622 (C=N); MS: m/z 402 (M^+, 0 %), 361(M-C_3H_4, 60 %), respectively.

Synthesis of 6-(3,4-dichlorophenyl)-3(2H)pyridazine thione (**11**)**.**

Thiourea (0.01 mol) was added to a solution of **7** (0.01 mol) in butanol (50 mL), and the reaction mixture refluxed for 5 hrs. The solid that separated on cooling was washed with water and recrystallized to give **11** (80 % yield); IR: 1600 (C=N), 1470 (N-C=S), 1380 (C=S); ^{1}H-NMR 7.8-7.3 (5H, m, Ar-H) and 3.1 (1H, s, NH).

Synthesis of 6-(3,4-dichlorophenyl)-3-(ethylsulfanyl)pyridazine (**12a**) *and 6-(3,4-dichlorophenyl)-3-(benzylsulfanyl)pyridazine* (**12b**)**.**

A mixture of **11** (0.01 mol), anhydrous potassium carbonate (0.03 mol), diethyl sulfate or benzyl chloride (0.03 mol) and dry acetone (100 mL) was refluxed for 40 hrs. After filtration while hot and removing excess solvent, the product was recrystallized to give **12a** (35 % yield); IR: 1620 (C=N) and **12b** (40 % yield); IR: 1610 (C=N).

Synthesis of 6-(3,4-dichlorophenyl) [1,2,3,4] tetrazolo [1,5-b] pyridazine (**13**)**.**

A mixture of **7** (1 gm), sodium azide (2 gm), water (5 mL) and dimethylformamide (20 mL) was refluxed for 2 hrs. The solid obtained upon dilution with water was filtered off and recrystallized to give 13 (45 % yield); IR: 1590 (C=N), 1040 and 1085 (tetrazole ring); ^{1}H-NMR: 8.22-7.10 (5H, m, Ar-H).

Synthesis of 2-(3,4-dichlorophenyl)-10H-pyridazino (6,1-b)quinazolin-10-one (**14**)**.**

A mixture of **7** (0.01 mol) and anthranilic acid (0.012 mol) was heated in an oil bath at 150^{o}C for 3 hrs, cooled and triturated with ethanol. The solid obtained was filtered off and recrystallized to give **14** (60 % yield); IR: 1710 (C=O), 1620 (C=N).

Synthesis of 6-(3,4-dichlorophenyl)-3-hydrazinopyridazine (**15**)**.**

To a solution of **7** (0.01 mol) in absolute ethanol (50 mL), hydrazine hydrate (0.01 mol) was added and the reaction mixture was refluxed for 3 hrs. The solid that separated on cooling was recrystallized to give **15** (65 % yield); IR: 1610 (C=N)

Synthesis of 6-(3,4-dichlorophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)pyridazine (**16**) *and 1,2-diphenyl-1,2-ethanedione-1-{N-[6-(3,4-dichlorophenyl)-3-pyridazonyl]- hydrazone}* (**17**).

To a solution of **15** (0.01 mol) in absolute methanol (50 mL) acetylacetone and/or benzil (0.01 mol) were added and the reaction mixtures were refluxed for 15 hrs. The solids that separated on

cooling were recrystallized to give **16** (75 % yield); IR: 1589 (C=N); ^{1}H-NMR: 8.22-7.10 (5H, m, Ar-H), 2.2 (6H, s, $2CH_3$), 2.8 (1H, s, CH); MS:m/z 318 (M^+, 100 %) and **17** (70 % yield); IR: 1649 (C=O), 1581 (C=N), 3309 (NH); ^{1}H-NMR: 7.8-7.10 (15H, m, Ar-H), 3.5 (1H, s, NH).

Table 2

Comp. No.	M.P. (^{o}C) (cryst. solvent)	Molecular formula (mol. mass)	Analysis % Calc. / Found			
			C	H	N	S
3	213 (ethanol)	$C_{21}H_{18}Cl_2N_2O_4$ (433.28)	58.21 58.19	4.19 3.98	6.47 6.44	
4	148 (ethanol)	$C_{27}H_{24}Cl_2N_4O_3$ (523.41)	61.96 61.89	4.62 4.48	10.70 10.58	
5a	255 (methanol)	$C_{21}H_{18}Cl_2N_4O_2$ (429.30)	58.75 58.47	4.23 3.99	13.05 12.84	
5b	185 (pet. ether b.p. 80-100^{o}C)	$C_{27}H_{22}Cl_2N_4O_2$ (505.39)	64.17 64.04	4.39 4.05	11.09 10.92	
6	227 (acetic acid)	$C_{21}H_{16}Cl_2N_4O_2$ (427.28)	59.03 59.30	3.77 3.58	13.11 12.83	
7	182 (pet. ether b.p. 80-100^{o}C)	$C_{10}H_5Cl_3N_2$ (259.52)	46.28 46.16	1.94 1.64	10.79 10.58	
8	238 (benzene)	$C_{21}H_{16}Cl_2N_4S_2$ (459.42)	54.90 54.96	3.51 3.29	12.20 12.41	13.96 14.1
9	313 (ethanol)	$C_{17}H_{11}Cl_2N_3OS$ (376.26)	54.27 54.31	2.95 3.17	11.17 10.99	8.52 8.75
10	325 (ethanol)	$C_{19}H_{13}Cl_2N_3OS$ (402.30)	56.73 56.41	3.26 2.97	10.45 10.41	7.97 7.77
11	203 (ethanol)	$C_{10}H_6Cl_2N_2S$ (257.14)	46.71 46.94	2.35 2.30	10.89 10.62	12.47 12.72
12a	124 (pet. ether b.p. 80-100^{o}C)	$C_{12}H_{10}Cl_2N_2S$ (285.19)	50.54 50.78	3.53 3.63	9.82 10.12	11.24 11.06

12b	155 (pet. ether b.p. 80-100°C)	$C_{17}H_{12}Cl_2N_2S$ (347.26)	58.80 58.67	3.48 3.58	8.07 7.93	9.23 9.50
13	202 (benzene)	$C_{10}H_5Cl_2N_5$ (266.09)	45.14 45.11	1.89 1.70	26.32 26.12	
14	325 (acetic acid)	$C_{17}H_9Cl_2N_3O$ (342.18)	59.67 59.51	2.65 2.50	12.28 12.42	
15	135 (methanol)	$C_{10}H_8Cl_2N_4$ (255.10)	47.08 47.30	3.16 3.40	21.96 22.12	
16	166 (methanol)	$C_{15}H_{12}Cl_2N_4$ (319.19)	56.44 56.69	3.79 3.98	17.55 17.39	
17	172 (pet. ether b.p. 80-100°C)	$C_{24}H_{16}Cl_2N_4O$ (447.31)	64.44 64.16	3.61 3.38	12.53 12.78	

Biological testing

Whatman No1 filter paper disks were sterilized by autoclaving for one hr. at 140°C. The sterile disks were impregnated with the test compounds. Agar plates were uniformly surface inoculated with fresh broth culture of *Staphylococcus aureus* and *Bacilus cereus* (as examples of Gram positive strains), *Serratia marcescens* and *Proteus merabilis* (as Gram negative strains) and *Aspergillus fungytus* (as fungus). The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5°C for 1 hr to permit good diffusion and then transferred to an incubator at 28°C for 24 hr. The inhibition zones were then measured.

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Sample availability: Available from MDPI.