Research Article

Synthesis and Antimicrobial Activities of Some New Heterocyclic Compounds Based on 6-Chloropyridazine-3(2H)-thione

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Three tricyclic ring system, pyridazino[6,1-b]quinazolin-10-ones, benzimidazolo-pyridazine thione, and 1,2,4-benzotriazino-pyridazinethione along with imidazo-[1,2-b]-pyridazinethione, 1,2,4-triazolo[4,3-b]pyridazine-thione derivatives were synthesized starting from 6-chloropyridazin-3-(2H)-thione. Some disulfide and sulfide derivatives were also prepared. The antimicrobial activity of the synthesized compounds was tested. Some of these compounds possess a highly response against gram-positive and gram-negative bacteria as well as fungi.

1. Introduction

The chemistry of pyridazines and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. Pyridazines have been reported to possess antimicrobial [1–3], antituberculosis [4–6], antifungal [7], anticancer [8], antihypertensive [9], herbicidal [10], anti-inflammatory [11] activities, and protein tyrosine phosphatase 1B (PTP1B) inhibitors [12]. They also have an immense potential in agricultural science as plant growth regulators and crop protection agents [13]. The incorporation of two moieties increases biological activity of both and thus it was of value to synthesize some new heterocyclic derivatives having two moieties in the same molecules. Several derivatives of pyridazine incorporating 1,2,4-triazole, imidazole, isoxazole, and triazine rings have been shown to display a wide spectrum in biological and therapeutic areas [14–18]. Prompted by these observations and in continuation to authors' work on the synthesis of new pyridazine compounds [19, 20], authors report herein the use of 6-chloropyridazin-3(2H)-thione (**1**) for the synthesis of new pyridazine compounds with the aim to evaluate their antimicrobial activities.

2. Experimental

Uncorrected melting points were determined on Gallenkamp Electric Melting point Apparatus. IR spectra (KBr Discs) were recorded on a FT/IR-400 Spectrophotometer (Perkin Elmer). ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Varian instrument. Chemical shifts were reported as δ values relative to tetramethylsilane (TMS) as internal reference. Elemental analyses for C, H, N, and S were performed on a Perkin-Elmer 240 microanalyser in the Faculty of Science, Cairo University.

2.1. Reaction of 6-Chloropyridazin-3(2H)-thione (1) with Anthranilic Acid Derivatives, o-Aminophenol, and o-Chlorophenylhydrazine: Formation of 2-Thioxo-1,2,10-trihydro-pyridazino[6,1-b]quinazolin-10-ones (2a–c), Benzimidazolo[2,3-a]pyridazine-3(2H)-thione (3), and 1, 2,4-Benzotriazino[3,4-a]pyridazine-3(2H)-thione (4)

General Procedure. To a solution of compound (**1**) (0.01 mole) in absolute ethanol (30 mL), equimolar amounts of anthranilic acid derivatives (namely, anthranilic acid,

SCHEME 1

3,5-dibromoanthranilic acid, and 5-bromo-anthranilic acid), *o*-aminophenol, and *o*-chlorophenylhydrazine were added and the reaction mixture was refluxed for 7-8 h. The solid product, obtained upon cooling, was filtered off, dried, and crystallized from an appropriate solvent to give compounds (**2a-c**), (**3**), and (**4**), respectively, shown in Scheme 1 (Tables 2 and 3).

2.2. Reaction of (1) with Phenylalanine: Formation of Imidazo [1,2-*b*]pyridazine-3(2*H*)-thione Derivative (5). A mixture of **1** (0.01 mole) and phenylalanine (0.01 mole) in butanol (20 mL) was heated under reflux for 6 h. The solvent was concentrated under vacuum and allowed to cool. The separated solid was filtered off and recrystallized from ethanol to afford (**5**), shown in Scheme 2 (Tables 2 and 3).

2.3. Reaction of (1) with Thiosemicarbazide and Benzoylhydrazines: Formation of 1,2,4-triazolo[4,3-*b*]pyridazinethione Derivatives (6) and (7a, b). A solution of **1** (0.01 mole) in

ethanol (30 mL) was treated with thiosemicarbazide or benzoylhydrazines (0.01 mole for each) and refluxed for 6 h. The solution was concentrated and cooled, the solid, so separated, was collected and recrystallized from suitable solvent to yield **6** and **7a, b** (Tables 2 and 3).

2.4. Reaction of (1) with Acetophenonehydrazone Derivatives: Formation of Compounds (8a, b). A mixture of (**1**) (0.01 mol) and acetophenonehydrazone and/or 3-nitroacetophenonehydrazone (0.01 mol), was fused on oil bath at 180°C for 2 h. The solid mass obtained upon air cooling was refluxed with ethanol (20 mL) for 2 hr. The precipitate obtained upon cooling was collected and crystallized from methanol into (**8a, b**) (Tables 2 and 3).

2.5. Reaction of (1) with *p*-Toluenesulfonyl Hydrazine: Formation of (9). A mixture of compound (**1**), (0.01 mol) and *p*-toluenesulfonylhydrazine (0.01 mol) in butanol (30 mL) was

SCHEME 2

heated under reflux for 6 h. The reaction mixture was left to cool at room temperature and the solid formed was collected and crystallized from ethanol to give **9** (Tables 2 and 3).

2.6. Formation of 2,4-Dinitrophenyl-6-chloropyridazylsulfide (10). Compound **1** (0.01 mole) was stirred at room temperature for 1 h with an equimolar amount of 2,4-dinitrobenzenesulfonyl chloride in acetic acid (25 mL). The reaction mixture was then concentrated by evaporation and the product was crystallized from methanol to produce **10** (Tables 2 and 3).

2.7. Formation of Bis(6-chloropyridazyl)disulfide (11). A solution of **1** (0.01 mole) was left at room temperature for 4 h in acetic acid (15 mL) and sodium nitrite (0.01 mol), then poured in cold water (20 mL). The obtained solid was collected and

crystallized from mixture of petroleum ether 60–80 and benzene, to give **11** (Tables 2 and 3).

2.8. Reaction of (1) with Thiophenol or 3,6-Dichloropyridazine: Formation of Phenyl pyridazyl-thione disulfide (12) and Bis(6-chloropyridazyl)sulfide (13). A mixture of compound **1**, (0.01 mole) and thiophenol or 3,6-dichloropyridazine (0.01 mole for each) was refluxed in ethanol (30 mL) containing sodium metal (0.01 mol), for 8 h. The reaction mixture was left to cool; the solid produced was collected and crystallized from proper solvent to yield **12** and **13** (Tables 2 and 3).

3. Results and Discussion

6-Chloropyridazin-3(2H)-thione (**1**) has been used as the key starting material for the preparation of some new

TABLE 1: Antimicrobial activity of synthetic compounds.

Compd. no.	Gram +ve Bacteria		Gram -ve bacteria		Fungi	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>P. aurignosa</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
2a	24	30	22	20	19	14
2b	18	20	10	10	10	13
2c	18	10	11	10	16	12
3	20	23	17	17	20	15
4	25	27	11	12	19	14
5	18	19	10	18	18	15
6	21	23	16	12	18	14
7a	12	20	19	17	16	12
7b	11	16	11	18	19	13
8a	15	13	14	11	22	16
8b	19	22	10	12	19	15
9	26	29	22	20	23	18
10	17	16	15	13	18	12
11	19	19	22	20	16	15
12	14	19	18	17	24	17
13	14	11	13	15	19	10
Ampicillin	22	26	20	19	—	—
Micostatin	—	—	—	—	22	16

SCHEME 3

heterocyclic compounds. Thus, (1) reacts with bifunctional nucleophile like anthranilic acid, 2-aminophenol, and 2-chlorophenylhydrazine to afford a tricyclic ring system as 2-thioxo-1,2,10-trihydropyridazino[6,1-b]quinazolin-10-ones (**2a-c**), benzimidazolopyridazine thione (**3**), and 1,2,4-benzotriazinopyridazinethione (**4**) derivatives, respectively (Scheme 1). The IR spectrum of (**2a-c**) showed characteristic absorption bands for (NH) at 3410–3380, (CO) at 1750–1616

and (C=N) at 1620–1580 cm^{-1} , while that of (**3**) and (**4**) showed the bands of (NH) at 3370–3317 and (C=N) at 1610–1590 cm^{-1} (Tables 1 and 2).

Imidazo[1,2-b]pyridazinethione derivative (**5**) was prepared by treatment compound (1) with phenylalanine in refluxing butanol (Scheme 2). The IR spectrum of **5** revealed absorption bands at 3310 (NH), 1660 (CO), and 1605 cm^{-1} (C=N). In the ^1H NMR of (**5**), the two doublet signals

TABLE 2: Physical properties of the prepared compounds (2–13).

Compd. no.	m.p. °C	Yield (%)	Solvent of cryst.	Mol. formula (M.wt)	Elemental analysis Calcd./Found			
					C	H	N	S
2a	182–184	37	Ethanol	C ₁₁ H ₇ N ₃ OS	57.61	3.10	18.35	13.99
				229.26	57.63	3.08	18.33	13.98
2b	255–257	41	Methanol	C ₁₁ H ₅ Br ₂ N ₃ OS	34.16	1.33	10.89	8.30
				387.05	34.14	1.30	10.86	8.28
2c	232–234	45	Ethanol	C ₁₁ H ₆ BrN ₃ OS	42.91	1.98	13.68	10.42
				308.15	42.88	1.96	13.64	10.40
3	168–170	49	Methanol	C ₁₀ H ₇ N ₃ S	59.70	3.56	20.92	15.96
				201.25	59.68	3.51	20.88	15.93
4	285–287	39	Acetic acid	C ₁₀ H ₈ N ₄ S	55.56	3.92	25.95	14.92
				216.26	55.54	3.73	25.91	14.82
5	282–283	61	Ethanol	C ₁₃ H ₁₁ N ₃ OS	60.58	4.78	16.38	12.49
				257.06	60.68	4.31	16.33	12.46
6	279–280	58	Ethanol	C ₅ H ₅ N ₅ S	35.94	3.07	41.92	19.20
				167.19	35.92	3.01	41.89	19.18
7a	261–263	52	Ethanol	C ₁₁ H ₇ ClN ₄ S	50.33	2.71	21.37	12.24
				262.72	50.29	2.69	21.33	12.20
7b	242–243	63	Ethanol	C ₁₁ H ₈ N ₄ S	57.85	3.55	24.56	14.07
				228.27	57.88	3.53	24.54	14.04
8a	271–273	35	Methanol	C ₁₂ H ₁₂ N ₄ S	59.02	4.99	22.97	13.10
				244.31	58.99	4.95	22.93	13.12
8b	246–248	44	Methanol	C ₁₂ H ₁₁ N ₅ O ₂ S	49.78	3.86	24.23	11.12
				289.31	49.82	3.83	24.21	11.08
9	205–207	49	Ethanol	C ₁₁ H ₁₀ N ₄ OS ₂	47.52	3.57	20.17	23.09
				278.35	47.47	3.62	20.13	23.04
10	239–240	73	Methanol	C ₁₀ H ₅ ClN ₄ O ₄ S ₂	34.86	1.62	16.29	18.63
				344.75	34.84	1.46	16.25	18.60
11	221–223	85	ether 60–80/Benzene	C ₈ H ₄ Cl ₂ N ₄ S ₂	33.04	1.42	19.25	22.09
				291.17	33.00	1.38	19.24	22.02
12	234–236	73	Ethanol	C ₁₀ H ₈ N ₂ S ₃	47.64	3.25	11.14	38.15
				252.37	47.59	3.20	11.10	38.11
13	186–88	71	Methanol	C ₈ H ₄ Cl ₂ N ₄ S	37.10	1.59	21.65	12.40
				259.11	37.08	1.56	21.62	12.37

appeared at 2.95 and 3.15 ppm for (–CH₂) group, while NH and Ar–H peaks were observed at 6.83 and 7.41–7.96 ppm, respectively.

Treatment of 6-chloro-pyridazinethione (1) with thiosemicarbazide or benzoylhydrazines in boiling ethanol and by fusion with acetophenone hydrazones afforded 1,2,4-triazolo[4,3-b]pyridazinethione derivatives (6), (7a, b), and (8a, b), respectively (Scheme 2). The IR spectra of these triazolopyridazine derivatives showed absorption bands at 3420–3349 cm^{–1} for NH; furthermore, compound (6) exhibited a characteristic band for amino group. The ¹H NMR spectrum of compound (6) displayed two exchangeable (NH₂) protons as a singlet signal at 6.29 ppm (Table 2). On the other hand, compound (1) reacted with *p*-toluenesulfonyl hydrazine to give compound (9).

Finally, disulfide derivatives were prepared. Stirring a solution of pyridazine-3-thione (1) and 2,4-dinitrobenzenesulfonyl chloride in acetic acid at room temperature afforded 2,4-dinitrophenyl-6-chloropyridazyl disulfide (10) (Scheme 3). The ¹H NMR of this disulfide exhibited signals at δ 7.9 and 8.1 ppm as doublet signals for two hydrogen of pyridazine ring, and at δ 8.58–8.62 and 9.08 ppm as multiplet and single signals for 2H and 1H, respectively for ((NO₂)₂C₆H₃–). Oxidation of pyridazine-3-thione (1) with sodium nitrite in acetic acid gave the bis(6-chloropyridazyl)disulfide (11) in good yield. Elemental analysis, infrared, and ¹H NMR data were consistent with the assigned structure. Compound (1) reacted with thiophenol or 3,6-dichloropyridazine in refluxing ethanolic sodium ethoxide to afford phenyl pyridazylthione disulfide (12) and bis(6-chloropyridazyl)sulfide

TABLE 3: Spectral data of compounds (2–13).

Comp.	IR cm ⁻¹	¹ H NMR ppm	¹³ C-NMR ppm
2a	3380 (NH), 1750 (CO), 1610 (C=N), 1459 (N–C=S), 1405 (C=S).	6.1 (s, 1H, NH, exchangeable with D ₂ O), 6.9–7.6 (m, 6Ar H)	126.72 (C ₆ , C ₉), 127.45 (C ₈), 130.12 (C ₄), 130.48 (C ₃), 134.76 (C ₇), 154 (C ₂), 162 (C=O).
2b	3410 (NH), 1620 (CO), 1595 (C=N), 1451 (N–C=S), 1411 (C=S).	6.4 (s, 1H, NH, exchangeable with D ₂ O), 7.4–7.9 (m, 4H Ar H)	114 (C ₆), 123 (C ₈), 131.2 (C ₄), 131.6 (C ₃), 134.9 (C ₉), 139.9 (C ₇), 154 (C ₂), 162 (C=O).
2c	3385 (NH), 1616 (CO), 1580 (C=N), 1432 (N–C=S), 1418 (C=S).	6.6 (s, 1H, NH, exchangeable with D ₂ O), 7.1–7.8 (m, 5H, Ar H)	122 (C ₈), 125 (C ₆), 131 (C ₄), 131.8 (C ₃), 133 (C ₉), 138 (C ₇), 153.4 (C ₂), 162.3 (C=O).
3	3370 (NH), 1610 (C=N), 1438 (N–C=S), 1401 (C=S).	6.7 (s, 1H, NH, exchangeable with D ₂ O), 6.8–7.6 (m, 6H, Ar H).	110.3 (C ₇), 112.1 (C ₁₀), 121.2 (C ₄), 123 (C ₈), 123 (C ₉), 125.2 (C ₅), 180.6 (C ₃).
4	3420 (NH), 3390 (NH), 1610 (C=N), 1432 (N–C=S), 1416 (C=S).	6.3 (s, 1H, NH, exchangeable with D ₂ O), 6.8 (s, 1H, NH, exchangeable with D ₂ O), 6.9–7.6 (m, 6H, Ar H).	116.8 (C ₅ & C ₈ benzotriazine), 120.4 (C ₆ & C ₇ , benzotriazine), 132.4 (C ₄ , pyridazine), 134.1-(C ₅ , pyridazine), 151 (C ₆), 154.1 (C ₃).
5	3310 (NH), 1660 (CO), 1605 (C=N), 1440 (N–C=S), 1413 (C=S).	2.95 (d, 1H, –CH ₂), 3.15 (d, 1H, –CH ₂), 3.85 (d, 1H, –CH), 6.83 (s, 1H, NH, exchangeable with D ₂ O), 7.41–7.96 (m, 7H, Ar H).	40.1 (CH ₂), 72.4 (C ₄ , imidazole), 125.1, 127.3, 128 (Ph–C), 130 (C ₅ , pyridazine), 131.3 (C ₄ , pyridazine), 152.3 (C ₆ , pyridazine), 154.2 (C ₃ , pyridazine), 174.2 (C=O).
6	3427-3409 (NH ₂), 3316 (NH), 1580 (C=N), 1444 (NC=S), 1408 (C=S).	6.29 (s, 2H, NH ₂ , exchangeable with D ₂ O), 6.45 (s, 1H, NH), 6.81–6.93 (m, 2H, Ar H).	122.1 (C ₄ , pyridazine), 125.3 (C ₅ , pyridazine), 137.9 (C ₃ , triazole), 141.6 (C ₆ , pyridazine), 179.3 (C ₃ , p-yrizidine).
7a	3357 (NH), 1600 (C=N), 1425 (N–C=S), 1405 (C=S).	6.52 (s, 1H, NH, exchangeable with D ₂ O), 6.81–7.84 (m, 6H, Ar H).	119.9 (C ₄ , pyridazine), 122.2 (C ₅ , pyridazine), 126.1 (C ₁ , phenyl), 126.7 (C ₂ & C ₆ , phenyl), 129.1 (C ₃ & C ₅ , phenyl), 132.4 (C–Cl), 179.1 (C ₃ , pyridazine).
7b	3349 (NH), 1606 (C=N), 1432 (N–C=S), 1418 (C=S).	6.48 (s, 1H, NH, exchangeable with D ₂ O), 6.76–7.59 (m, 7H, Ar H).	120.1 (C ₄ , pyridazine), 122.5 (C ₅ , pyridazine), 127.2 (C ₂ & C ₆ , phenyl) 129.2 (C ₃ & C ₅ , phenyl), 130.6 (C ₁ , phenyl), 130.9 (C ₄ , phenyl), 139.8 (C ₃ , triazole), 180.1 (C ₃ , pyridazine)
8a	3420 (NH), 3391 (NH), 1610 (C=N), 1429 (N–C=S), 1408 (C=S).	2.14 (s, 3H, CH ₃), 6.42 (s, 1H, NH, exchangeable with D ₂ O), 6.9–7.7 (m, 7H, Ar H), 10.14 (s, 1H, NH, exchangeable with D ₂ O).	25.4 (CH ₃), 81.5 (C ₃ , triazole), 126 (C ₄ , phenyl), 126.9 (C ₂ & C ₆ , phenyl), 128 (C ₃ & C ₅ , phenyl), 129.8 (C ₄ , pyridazine), 134.2 (C ₅ , pyridazine), 141.2 (C ₁ , phenyl), 150.1 (C ₃ , pyridazine).
8b	3406 (NH), 3360 (NH), 1590 (C=N), 1437 (N–C=S), 1410 (C=S).	2.23 (s, 3H, CH ₃), 6.56 (s, 1H, NH, D ₂ O-exchangeable), 6.8–7.7 (m, 6H, Ar H), 10.67 (s, 1H, NH, exchangeable with D ₂ O).	25.8 (CH ₃), 83.2 (C ₃ , triazole), 122 (C ₄ , phenyl), 123.5 (C ₂ , phenyl), 129.1 (C ₅ , phenyl), 129.8 (C ₄ , pyridazine), 131.2 (C ₄ , pyridazine), 133.2 (C ₆ , phenyl), 136.2 (C ₅ , pyridazine), 143.2 (C ₁ , phenyl), 148.2 (C–NO ₂), 152.3 (C ₃ , pyridazine).
9	3360 (NH), 1572 (C=N), 1417 (C=S), 1345 (S=O).	2.99 (s, 3H, CH ₃), 6.5 (s, 1H, NH, exchangeable with D ₂ O), 6.89–7.92 (m, 6H, Ar H).	22.1 (CH ₃), 123.3 (C ₁ , phenyl), 128.1 (C ₃ & C ₅ , phenyl), 129.2 (C ₅ , pyridazine), 129.8 (C ₄ , pyridazine), 130.4 (C ₂ & C ₆ , phenyl), 132.6 (C ₄ , phenyl), 154.1 (C ₃ , pyridazine).
10	1605 (C=N), 1530-1380 (NO ₂), 1340 (C–S–).	7.9 (d, 1H, CH), 8.1 (d, 1H, CH), 8.58–8.62 (m, 2H, (NO ₂) ₂ C ₆ H ₃ –), 9.08 (s, 1H, (NO ₂) ₂ C ₆ H ₃ –),	123.6 (C ₅ , pyridazine), 124.8 (C ₃ , phenyl), 129.1 (C ₅ , phenyl), 129.3 (C ₄ , pyridazine), 143.2 (C ₄ , phenyl), 145.9 (C ₂ , phenyl), 152.2 (C–Cl), 178.2 (C ₆ , pyridazine).
11	1620 (C=N)	7.9 (d, 2H, 2CH), 8.0 (d, 2H, 2CH)	124.2 (2C ₅), 125.4 (2C ₄), 152.2 (2C–Cl), 178.1 (2C ₆).
12	3340 (NH), 1600 (C=N), 1273 (C–S–).	6.35 (s, 1H, NH, exchangeable with D ₂ O), 6.81–7.98 (m, 7H, Ar H).	120.3 (C ₄ & C ₅ , pyridazine), 122.5 (C ₄ , phenyl), 127.1 (C ₂ & C ₆ , phenyl), 128.2 (C ₃ & C ₅ , phenyl), 134.2 (C ₁ , phenyl), 177.2 (2C–S).
13	1580 (C=N).	7.99 (d, 2H, 2CH), 8.87 (d, 2H, 2CH).	122.1 (2C ₅), 126.3 (2C ₄), 152.6 (2C–Cl), 178 (2C–S).

(13), respectively (Scheme 3). Elemental analysis, infrared, ^1H NMR, and ^{13}C NMR data of (12) and (13) are given in Tables 2 and 3.

3.1. Antimicrobial Activity. The antimicrobial activity of the synthesized compounds has been evaluated by filter paper disc method [21]. The synthesized compounds have been tested for their antibacterial activity against *Staphylococcus aureus* ATCC6538P, *Bacillus subtilis* ATCC6633, *Pseudomonas aurignosa* ATCC9027, and *Echerichia coli* ATCC8739 and antifungal activity against *Candida albicans* ATCC2091, *Aspergillus niger*, at a concentration of 500 $\mu\text{g/mL}$ in DMF. Nutrient agar and potato dextrose agars were used to culture the bacteria and fungi, respectively. The plates were inoculated by the bacteria or fungi and incubated for 24 h at 37°C for bacteria and for 72 h at 27°C for fungi and then the inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters. Ampicillin and mycostatin, at a concentration 500 $\mu\text{g/mL}$, were used as standard against bacteria and fungi, respectively. Test results are shown in Table 1. From the data, it is clear that compounds (2a), (4) and (9) possess high activity, while compounds (3), (6), (8b), and (11) possess moderate activity against gram-positive strains. As far as gram-negative microorganisms are concerned, compounds (2a), (9), and (11) showed high activity while compounds (3), (7a), and (12) display moderate activity. Compounds (9) and (12) also exerted high activity while compounds (2a), (3), (4), and (8b) have moderate activity against fungi.

4. Conclusion

6-Chloropyridazin-3(2H)-thione (1) has been shown to be a useful building block for the synthesis of some dropyridazino[6,1-b]quinazolin-10-ones, 1,2,4-benzotriazinopyridazinethione, imidazo[1,2-b]pyridazinethione, 1,2,4-triazolo[4,3-b]pyridazinethione, and disulfide. The structure of all newly synthesized compounds was established from their spectral data and elemental analysis. Some of these compounds possess a highly response against gram-positive and gram-negative bacteria as well as fungi.

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