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STUDY ON THE CHARACTERIZATION OF NEW HETEROCYCLIC COMPOUNDS

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ABSTRACT

Three tricyclic ring system, pyridazino[6,1-b]quinazolin-10-ones, benzimidazolo-pyridazine thione, and 1,2,4-benzotriazino-pyridazinethione combined with imidazo-[1,2-b] -pyridazinethione, 1,2,4-triazolo[4,3-b]pyridazine-thione derivatives were produced beginning from 6-chloropyridazin3-(2H)-thione. Some disulfide and sulphide derivatives were also produced. The antibacterial activity of the produced compounds was investigated. Some of these chemicals feature a strong reaction against gram-positive and gram-negative bacteria as well as fungus.

Keywords: *Pyridazino, Chemical, bacteria, Chloropyridazin*

1. INTRODUCTION

The chemistry of pyridazines and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological significance. Pyridazines have been shown to have antibacterial, antituberculosis, antifungal, anticancer, antihypertensive, herbicidal, anti-inflammatory, and protein tyrosine phosphatase 1B (PTP1B) inhibitory properties, as well as antituberculosis, antifungal, and anticancer properties. Plant growth regulators and crop protection agents are two applications in agricultural science where they have tremendous promise. Due to the fact that the inclusion of two moieties boosts the biological activity of both, it was worthwhile to synthesis some novel heterocyclic derivatives that included two moieties in the same molecule to test their effectiveness. It has been shown that pyridazine derivatives integrating 1,2,4-triazole, imidazole, isoxazole, and triazine rings have a broad range of activity in a variety of biological and medicinal applications. These observations prompted the authors to report on the use of 6-chloropyridazin-3(2H)-thione (1) to synthesise new pyridazine compounds, which is a continuation of their previous work on the synthesis of new p yridazine compounds. The authors hope to evaluate the antimicrobial activities of these new pyridazine compounds.

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2. EXPERIMENTAL METHOD

The melting points of the samples were determined using the Gallenkamp Electric Melting Point Apparatus. Infrared spectra (KBr Disces) were obtained using an FT/IR-400 Spectrophotometer (Perkin Elmer). A Varian equipment was used to collect 1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra, which were then analysed. Chemical shifts were expressed as δ values relative to tetramethylsilane (TMS), which served as an internal reference. On a Perkin-Elmer 240 micro-analyser located at the Faculty of Science at Cairo University, elemental analyses for C, H, N, and S were done on the elements C, H, N, and S.

2.1 6-Chloropyridazin-3(2H)-thione (1) reacts with anthranilic acid derivatives, o-Aminophenol, and o-Chlorophenylhydrazine in the presence of anthranilic acid derivatives.

Formation of 2-Thioxo-1,2,10-trihydropyridazino[6,1-b]quinazolin-10-ones (2a–c), Benzimidazolo[2,3-a]quinozolin-10-ones (2a–c), and Benzimidazolo[2,3-a]quinozolin-10-ones (2a–c).

Pyridazine-3(2H)-thione (3), as well as 1,2,4-Benzotriazino[3,4-a] and 1,2,4-Benzotriazino[3,4-a] pyridazine-3(2H)-thione is a pyridazine derivative (4)

GENERAL PROCEDURE

A solution of compound (1) (0.01 mole) in absolute ethanol (30 mL) was prepared by adding equimolar amounts of anthranilic acid derivatives (namely, anthranilic acid, 3,5-dibromoanthranilic acid, and 5-bromo-anthranilic acid), o-aminophenol, and o-chlorophenylhydrazone to a solution of compound (1) (0.01 mole) in absolute The solid product produced after cooling was filtered out, dried, and crystalized from a suitable solvent to provide the compounds (2a–c), (3), and (4), which are depicted in Scheme 1 as a result of this procedure (Tables 2 and 3).

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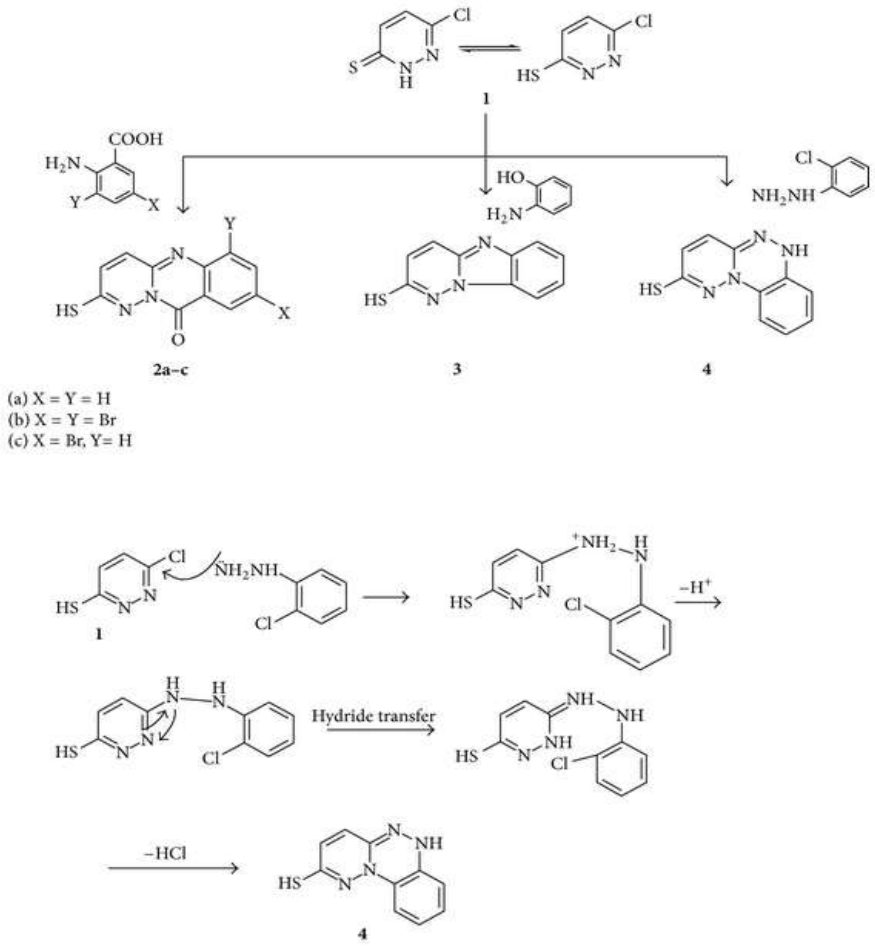

Schematic 1

2.2 Reaction of (1) with Phenylalanine: Formation of Imidazo [1,2-b]pyridazine-3(2H)-thione Derivative (5)

In a 20 mL butanol solution, a combination of 1 (0.01 mole) and phenylalanine (0.01 mole) was heated under reflux for 6 hours. The solvent was concentrated under vacuum and allowed to cool before being reconstituted. A portion of the separated material was filtered out and recrystallized from ethanol to yield (5), as seen in Schematic 2. (Tables 2 and 3).

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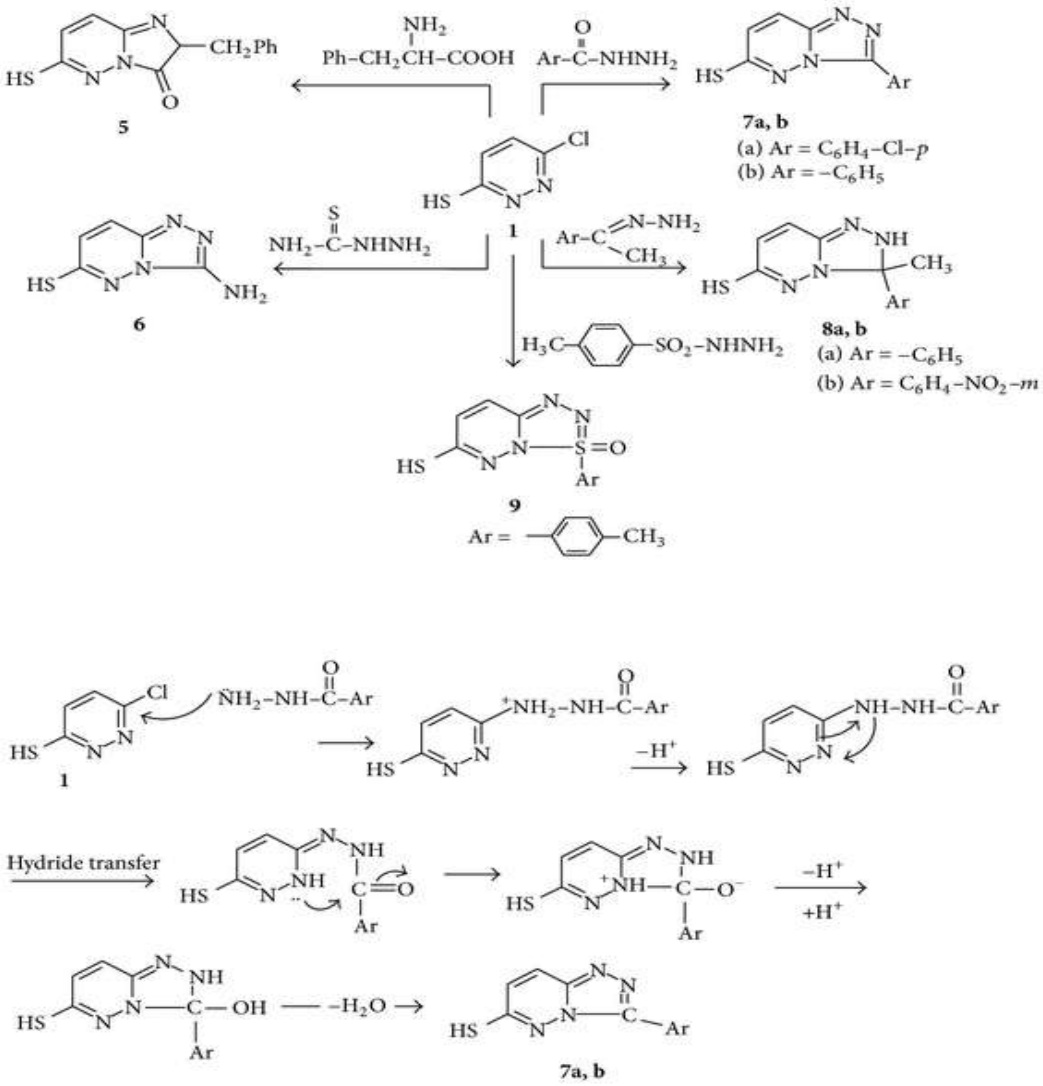

Schematic 2

2.3. Formation of 1,2,4-triazolo[4,3-b]pyridazinethione Derivatives (6) and (7a, b) by reacting (1) with Thiosemicarbazide and Benzoylhydrazines.

A solution of 1 (0.01 mole) in ethanol (30 mL) was refluxed for 6 hours after being treated with thiosemicarbazide or benzoylhydrazines (0.01 mole for each). The solution was concentrated and cooled, and the solid was recovered and recrystallized from a suitable solvent to produce 6 and 7a, b. (Tables 2 and 3).

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2.4. Acetophenonehydrazone Derivatives Reaction with (1): Compound Formation (8a, b)

(1) (0.01 mol) and acetophenonehydrazone and/or 3-nitroacetophenonehydrazone (0.01 mol) were fused for 2 hours in an oil bath at 180°C. The solid mass produced after air cooling was refluxed for 2 hours with ethanol (20 mL). After cooling, the precipitate was recovered and crystallised from methanol into (8a, b) (Tables 2 and 3).

2.5. Formation of (1) by reacting it with p-Toluenesulfonyl Hydrazine (9)

Compound (1) (0.01 mol) and p-toluenesulfonylhydrazine (0.01 mol) were heated in butanol (30 mL) under reflux for 6 hours. The reaction mixture was allowed to cool to ambient temperature, and the resulting solid was collected and crystallised from ethanol to yield 9 (Tables 2 and 3).

2.6 Dinitrophenyl-6-chloropyridazyldisulfide formation (10)

Compound 1 (0.01 mole) was mixed in acetic acid (25 mL) for 1 hour at room temperature with an equimolar quantity of 2,4-dinitrobenzensulfenyl chloride. The product was crystallised from methanol after the reaction mixture was concentrated by evaporation (Tables 2 and 3).

2.7. Bis (6-chloropyridazyl) disulfide formation (11)

(1) (0.01 mole) was dissolved in acetic acid (15 mL) and sodium nitrite (0.01 mol) at room temperature for 4 hours, then emptied into cold water (20 mL). A combination of petroleum ether 60–80 and benzene was used to collect and crystallize the obtained solid, yielding (11). (Tables 2 and 3).

3. RESULTS AND DISCUSSION

The main starting material for the production of certain novel heterocyclic compounds has been 6-chloropyridazin-3(2H)-thione (1). Thus, (1) interacts with bifunctional nucleophiles such as anthranilic acid, 2-aminophenol, and 2-chlorophenylhydrazine to provide 2-thioxo-1,2,10-trihydropyridazino[6,1-b]quinazolin-10-ones (2a–c), benzimidazolopyridazine thione (3), and 1,2,4-benzotriazinopyridazin (Scheme 1). The absorption bands for (NH) at 3410–3380, (CO) at 1750–1616, and (C=N) at 1620–1580 cm1 were visible in the IR spectra of (2a–c), whereas the bands for (NH) at 3370–3317 and (C=N) at 1610–1590 cm1 were visible in the IR spectrum of (3) and (4). (Tables 1 and 2).

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TABLE 1 Antimicrobial activity of synthetic compounds

Compd. no.	Gram +ve Bacteria		Gram −ve bacteria		Fungi	
	S. aureus	*B. subtilis*	*P. aurignosa*	*E. coli*	*C. albicans*	*A. niger*
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

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	$C_{11}H_7N_3OS$	57.61	3.10	18.35	13.99
				229.26	57.63	3.08	18.33	13.98
2b	255–257	41	Methanol	$C_{11}H_5Br_2N_3OS$	34.16	1.33	10.89	8.30
				387.05	34.14	1.30	10.86	8.28
2c	232–234	45	Ethanol	$C_{11}H_6BrN_3OS$	42.91	1.98	13.68	10.42
				308.15	42.88	1.96	13.64	10.40
3	168–170	49	Methanol	$C_{10}H_7N_3S$	59.70	3.56	20.92	15.96
				201.25	59.68	3.51	20.88	15.93
4	285–287	39	Acetic acid	$C_{10}H_8N_4S$	55.56	3.92	25.95	14.92
				216.26	55.54	3.73	25.91	14.82
5	282-283	61	Ethanol	$C_{13}H_{11}N_3OS$	60.58	4.78	16.38	12.49
				257.06	60.68	4.31	16.33	12.46
6	279-280	58	Ethanol	$C_5H_5N_5S$	35.94	3.07	41.92	19.20
				167.19	35.92	3.01	41.89	19.18
7a	261–263	52	Ethanol	$C_{11}H_7ClN_4S$	50.33	2.71	21.37	12.24
				262.72	50.29	2.69	21.33	12.20

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7b	242-243	63	Ethanol	$C_{11}H_8N_4S$	57.85	3.55	24.56	14.07
				228.27	57.88	3.53	24.54	14.04
8a	271–273	35	Methanol	$C_{12}H_{12}N_4S$	59.02	4.99	22.97	13.10
				244.31	58.99	4.95	22.93	13.12
8b	246–248	44	Methanol	$C_{12}H_{11}N_5O_2S$	49.78	3.86	24.23	11.12
				289.31	49.82	3.83	24.21	11.08
9	205–207	49	Ethanol	$C_{11}H_{10}N_4OS_2$	47.52	3.57	20.17	23.09
				278.35	47.47	3.62	20.13	23.04
10	239-240	73	Methanol	$C_{10}H_5ClN_4O_4S_2$	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	$C_8H_4Cl_2N_4S_2$	33.04	1.42	19.25	22.09
				291.17	33.00	1.38	19.24	22.02
12	234–236	73	Ethanol	$C_{10}H_8N_2S_3$	47.64	3.25	11.14	38.15
				252.37	47.59	3.20	11.10	38.11
13	186–88	71	Methanol	$C_8H_4Cl_2N_4S$	37.10	1.59	21.65	12.40
				259.11	37.08	1.56	21.62	12.37

Table 3 Spectral data of compounds (**2**–**13**).

Comp.	IR cm^{-1}	^1H 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_2O), 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_2O), 7.4–7.9 (m, 4H Ar H)	114 (C_6), 123 (C_8), 131.2 (C_4), 131.6 (C_3), 1349 (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_2O), 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_2O), 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_2O), 6.8 (s, 1H, NH, exchangeable with D_2O), 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_2O), 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_2O), 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-yridazine).
7a	3357 (NH), 1600 (C=N), 1425 (N–C=S), 1405 (C=S).	6.52 (s, 1H, NH, exchangeable with D_2O), 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_2O), 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_2O), 6.9–7.7 (m, 7H, Ar H), 10.14 (s, 1H, NH, exchangeable with D_2O).	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_2O-exchangeable), 6.8–7.7 (m, 6H, Ar H), 10.67 (s, 1H, NH, exchangeable with D_2O).	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_2O), 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, $(NO_2)_2C_6H_3$–), 9.08 (s, 1H, $(NO_2)_2C_6H_3$–),	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_2O), 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).

Preparation of imidazo[1,2-b]pyridazinethione derivative (5) with phenylalanine in refluxing butanol (Scheme 2). Absorption bands at 3310 (NH), 1660 (CO), and 1605 cm1 (C=N) were found in 5. The (–CH2) doublet signals emerged at 2.95 and 3.15 ppm, whereas the NH and Ar–H peaks appeared at 6.83 and 7.41–7.96 ppm, respectively.

The 1,2,4-triazolo[4,3-b]pyridazinethione derivatives (6), (7a, b), and (8a, b) were obtained by treating 6-chloro-pyrizadinethione (1) with thiosemicarbazide or benzoylhydrazines in boiling ethanol (Scheme 2). On the other hand, compound (6) revealed a typical band for amino group absorption at 3420–3349 cm1. Compound (6) showed a single signal of two exchangeable (NH2) protons at 6.29 ppm (Table 2). Compound (1) interacted with p-toluenesulfonyl hydrazine to form (9).

Then disulfide derivatives were made. 2.4.4 Dinitrophenyl-6-chloropyridazyl (10) was obtained by stirring pyridazine-3-thione (1) and dinitrobenzenesulfenyl chloride in acetic acid (Scheme 3). The 1H NMR of this disulfide showed doublet signals for two hydrogens of the pyridazine ring at 7.9 and 8.1 ppm, and multiplite and single signals for 2H and 1H at 8.58–8.62 and 9.08 ppm, respectively. The acetic acid oxidation of pyridazine-3-thione (1) yielded the bis(6-chloropyridazyl)disulfide (11). Elemental analysis, infrared, and 1H NMR data matched the structure provided. (2) and (3) were formed by reacting (1) with thiophenol or 3,6-Dichloropyridazine, respectively.

4. CONCLUSION

6-Chloropyridazin-3(2H)-thione (1) has been demonstrated to be a valuable building block for certain dropyridazino[6,1-b]quinazolin-10-ones, imidazo[1,2-b]pyridazinethione, and disulfide. All freshly synthesised compounds' structures were determined by spectral and elemental analyses. Some of these chemicals are very reactive against bacteria, fungus, and viruses.

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