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SYNTHESIS, FUNGICIDAL AND ANTIBACTERIAL ACTIVITY OF NEW PYRIDAZINE DERIVATIVES

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Abstract – Compounds **1** - **3** were obtained in the reaction of 3,6-dichloro-pyridazines with phenylacetonitriles in the biphasic system - DMSO / 50% NaOH. The chlorine atom was replaced with cycloalkylamino (**4** - **13)** and hydrazinyl (**23, 24)** moiety. These last compounds were condensed with aldehydes (**25** - **34)**. Pyridazynylphenylacetonitriles were converted into amides **14** - **18** and thioamides **19** - **22**. In compounds **2**, **3** the chlorine atom was replaced with thiophenyl (**37**, **38**) and in compound **1** with thioethyl and thiophenyl (**35**, **36**) functional groups. In the reactions of compounds **1**, **2** with ammonium polysulfide thioamides with thiol group (**39**, **40)** and chlorine atom (**41**, **42**) were obtained. Compounds **1** – **17**, **19** – **43** were screened for antibacterial and fungicidal activities.

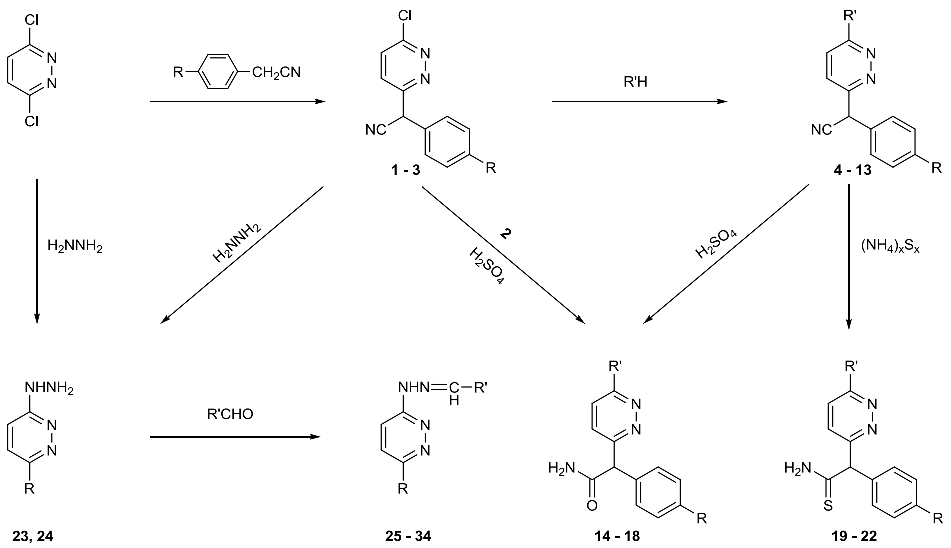
INTRODUCTION

Organic compounds with pyridazine moiety exhibit wide pharmacological activity. Many compounds act as antiphlogistic and antirheumatic agents like naphthylpyridinylpyridazine[1] and bis-4-methoxy-3,5-diphenylpyridazine[2,3] derivatives. Rohet et al.[4] showed that 6-oxo-3,5-diphenylpyridazines analgetic and antiphlogistic effects are stronger than for acetylsalicylic acid and indomethacine with simultaneous absence of ulcerogenesis. Pyridazine phenylpiperazinyl derivative, beyond its own activity, strengthened morphine analgesis.[5] Some pyridazine derivatives possess antiepileptic activity[6-8] and are useful in Alzhimer's disease theraphy.[9,10] Reported antineoplastic,[11-13] antiviral,[14-15] antibacterial,[16-18] and fungicidal[19] activities deserve attention. Due to these facts essential is the search for new pyridazine derivatives, investigation of their activity and synthetic methods.

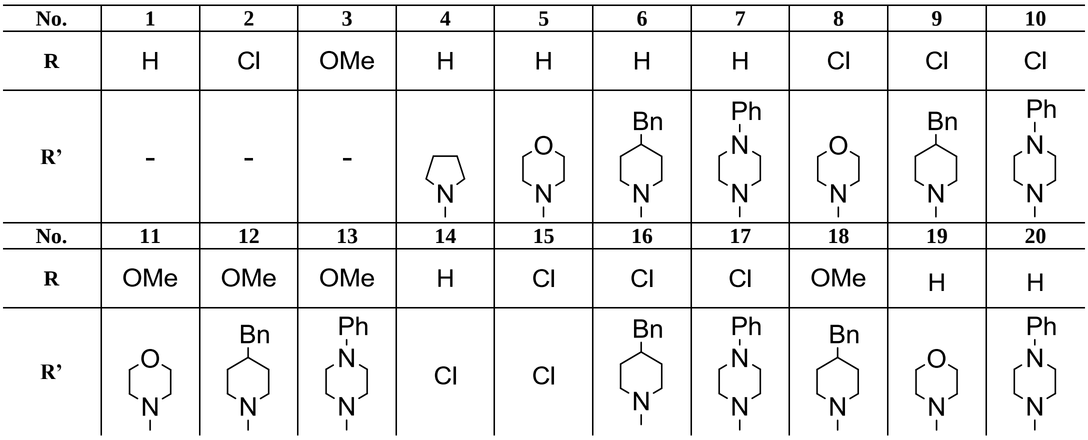
RESULTS AND DISCUSSION

The present work is the continuation of diazine derivatives investigations[20,21] and relates to pyridazynylphenylacetonitriles chemistry. Our method of obtaining 2-(6-chloropyridazin-3-yl)-2-phenylacetonitrile (**1**) has relative advantages comparing to previously reported syntheses,[22-24] which involve sodium amide and anhydrous environment. Compounds **1** - **3** were obtained in the reactions of 3,6-dichloropyridazine with phenylacetonitrile, 4-chloro- and 4-methoxyphenylacetonitrile in the biphasic system DMSO / 50% NaOH. Thus obtained compounds **1** - **3** reacted with amines: pyrrolidine, morpholine, 4-benzylpiperidine and 4-phenylpiperidine forming 6-aminopyridazineacetonitriles **4** - **13**. Some of thus obtained pyridazineacetonitriles were treated with concentrated H_2SO_4 giving appropriate amides **14** - **18** and with ammonium polysulfide – thioamides (**19** - **22**). Next we obtained pyridazinylhydrazones **25** - **34** in the reactions of hydrazinylpyridazines **23**, **24** with some aldehydes (Scheme 1).

Other pyridazine derivatives, which contain sulfur in their structure are sulfides **35** - **38**, obtained in reaction of chloropyridazines **1** - **3** with sodium thiolate and for **35** – sodium ethanethiol. 2-[6-(Ethylthio)pyridazin-3-yl]-2-phenylacetonitrile in reaction with ammonium polysulfide gives



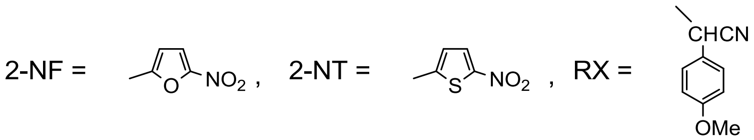
Scheme 1 (Continued)



No.	1	2	3	4	5	6	7	8	9	10
R	H	Cl	OMe	H	H	H	H	Cl	Cl	Cl
R'	-	-	-	N	O N	Bn N	Ph N N	O N	Bn N	Ph N N
No.	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
R	OMe	OMe	OMe	H	Cl	Cl	Cl	OMe	H	H
R'	O N	Bn N	Ph N N	Cl	Cl	Bn N	Ph N N	Bn N	O N	Ph N N

No.	21	22	23	24	25	26	27
R	Cl	Cl	Cl	RX	Cl	Cl	Cl
R'	O N	Bn N	-	-	Ph	4BrPh	$4NO_2Ph$

No.	28	29	30	31	32	33	34
R	Cl	Cl	RX	RX	RX	RX	RX
R'	2-NF	2-NT	Ph	4BrPh	$4NO_2Ph$	2-NF	2-NT

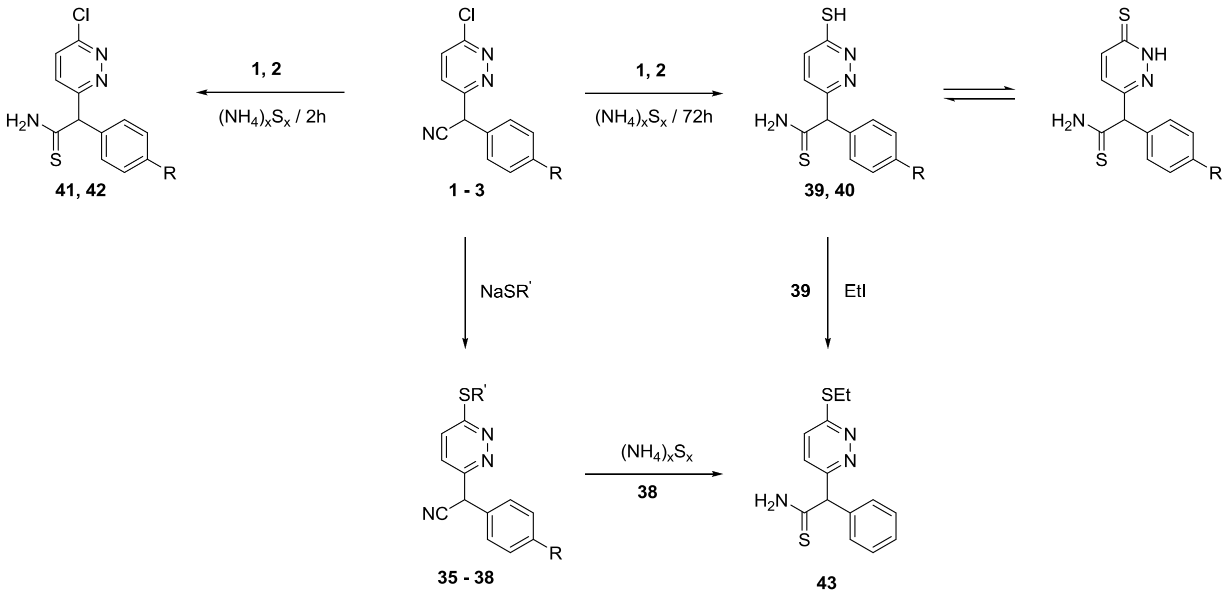


Scheme 1

thioamide **43**. The same compound can be synthesized via alkylation of thioamide **39**, which contains free mercapto group, with ethyl iodide. In comparison with the previous works, which report antibacterial activity of thioamides,[25,26] compounds **1 - 3** were transformed into thioamides in reaction with ammonium polysulfide solution.In this work method of gaining thioamides **39 - 42** allows control over sulfurilation degree of products (Scheme 2). Good yields of thioamides were obtained, in which chlorine atom in pyridazine ring was intact under the reaction conditions. Compound **39** was obtained by Yamada and co-workers[23] in different conditions and exhibited gastric antisecretary activity.

MICROBIOLOGY

Antimicrobial activity of the chemical agents against three recommended reference strains: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and clinical strain *Candida albicans* were examined. The susceptibility of the microorganisms to the agents was determined by the broth microdilution assay according to the procedures outlined by the National



No.	35	36	37	38	39	40	41	42
R	H	H	Cl	OMe	H	Cl	H	Cl
R'	Et	Ph	Ph	Ph	-	-	-	-

Scheme 2

Committee for Clinical Laboratory Standards.[27] The stock solutions of the agents were prepared by dissolving the chemicals in DMSO. The final concentration of the agents in 200 µL of Mueller – Hinton broth (or Sabouraud's medium for *C. albicans*) ranged over 0.125 – 256 µg/mL. In order to prepare bacterial suspension, overnight culture of bacteria in 3 % Trypticase Soy Broth (or Sabouraud's medium for *C. albicans*) was diluted in sterile saline to the final concentration of approximately 107 CFU/mL of bacteria. Aliquots (5 µL) of bacterial suspension were added to each agent solution. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of the agent that completely inhibited growth of the bacteria after 24 hours incubation in 37 °C. The final results were the average values from two independent experiments. Gentamycine was used as the reference substance (Table 1).

Table 1. Antibacterial and fungicidal activity of tested compounds 1 – 17, 19 - 43.

No	MIC [µg/mL]			
	S.aureus	*E.coli*	*P.aeruginosae*	*C.albicans*
1-17, 20, 22, 24-38, 41, 42	>256	>256	>256	>256
19	128	>256	>256	>256
21	128	>256	>256	>256
23	128	128	128	>256
39	64	>256	>256	128
40	32	>256	>256	>256
43	>256	>256	>256	128
Gentamycine	0.5	0.5	2	

In summary, the tested derivatives exhibited diversified activity against aerobic bacteria and *C. albicans*. The results indicated that only five of synthesized compounds possessed antibacterial activity against *S. aureus* (**19**, **21**, **23**, **39** and **40**), with the most active compound **40** (MIC = 32 μg/mL) . Only compound **23** showed activity against *E. coli*, but in relative high concentration (MIC = 128 μg/mL). The highest activity against *C. albicans* showed derivatives **39**, **40** (MIC = 128 μg/mL).

EXPERIMENTAL

All melting points were obtained with Boetius apparatus and are uncorrected. The IR spectra were taken using Thermo Mattson Satellite spectrophotometer and the ^{1}H NMR were taken with a Varian Gemini 200 MHz apparatus. The results of elemental analyses for C, H, N and S were in agreement with the calculated values within +/- 0.3% range.

General procedure for the synthesis of compounds 1-3.

3,6-Dichloropyridazine (7.45 g, 0.05 mol) was dissolved in DMSO (20 mL) and then 2-phenylacetonitrile (5.85 g, 0.05 mol) (for **1**), 2-(4-chlorophenyl)acetonitrile (7.58 g, 0.05 mol) (for **2**) or 2-(4-methoxyphenyl)acetonitrile (7.36 g, 0.05 mol) (for **3**) and 50 % aqueous NaOH (10 mL) were added. The mixture was stirred and heated at 60^{o}C for 2 h. Next ice (150 g) was added and the mixture was acidified with concentrated HCl. The precipitated solid was filtered off, washed with water and crystallized from the appropriate solvent.

2-(6-Chloropyridazin-3-yl)-2-phenylacetonitrile (1)

The crude product was crystallized from MeOH to give a white solid (7.46 g, 65 %), mp 128-129°C; ^{1}H NMR ($CDCl_3$) δ 5.52 (1H, s), 7.35 (5H, m), 7.55 (2H, s); IR (KBr) ν_{max} 3052, 2935, 2257, 1410, 1149, 1066, 862, 697 cm^{-1}; Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.63; H, 3,49; N, 18.26.

2-(4-Chlorophenyl)-2-(6-chloropyridazin-3-yl)acetonitrile (2)

The crude product was crystallized from MeOH to give a white solid (9.24 g, 70 %), mp 144-146°C; ^{1}H NMR ($CDCl_3$) δ 5.65 (1H, s), 7.40 (4H, m), 7.56 (2H, s); IR (KBr) ν_{max} 3057, 2935, 2250, 1570, 1490, 1412, 1152, 1097, 824 cm^{-1}; Anal. Calcd for $C_{12}H_7Cl_2N_3$: C, 54.57; H, 2.67; N, 15.91. Found: C, 54.41; H, 2.66; N, 15.87.

2-(6-Chloropyridazin-3-yl)-2-(4-methoxyphenyl)acetonitrile (3)

The crude product was crystallized from MeOH to give a white solid (7.79 g, 60 %), mp 129-132°C; ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 5.62 (1H, s), 6.90 (1H, s), 6.95 (1H, s), 7.36 (1H, s), 7.40 (1H, s), 7.54 (2H, s); IR (KBr) ν_{max} 3041, 2923, 2251, 1610, 1512, 1409, 1253, 1178, 1150, 1027, 821 cm^{-1}; Anal. Calcd for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88; N, 16.18. Found: C, 59.98; H, 3.87; N, 16.14.

General procedure for the synthesis of compounds 4-13.

6-Chloropyridazine derivative (**1-3**) (5 mmol) and suitable amine (13 mmol) were dissolved in 1,4-dioxane (15 mL) and refluxed for 2 h. Then the solution was evaporated in vacuo, ice (30 g) was added to the residue and the mixture was extracted with $CHCl_3$ (3x50 mL) and dried with $MgSO_4$. Solution was concentrated and the solid formed was crystallized from the appropriate solvent.

2-Phenyl-2-[6-(pyrrolidin-1-yl)pyridazin-3-yl]acetonitrile (4)

Reaction with pyrrolidine. Product **4** was crystallized from EtOH to give a white solid (yield 47 %), mp 176-177°C; ^{1}H NMR ($CDCl_3$) δ 2.10 (4H, m), 3.55 (4H, m), 5.51 (1H, s), 6.60 (1H, d, *J* = 9.5 Hz), 7.15 (6H, m); IR (KBr) ν_{max} 3035, 2919, 2864, 2240, 1594, 1542, 1475, 1455, 1030, 741, 700 cm^{-1}; Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.51; H, 6.08; N, 21.14.

2-(6-Morpholinopyridazin-3-yl)-2-phenylacetonitrile (5)

Reaction with morpholine. Product **5** was crystallized from EtOH to give a white solid (yield 63 %), mp 141-143°C; ^{1}H NMR ($CDCl_3$) δ 3.65 (4H, m), 3.85 (4H, m), 5.56 (1H, s), 6.90 (1H, d, *J* = 9.4 Hz), 7.25 (6H, m); IR (KBr) ν_{max} 3057, 2968, 2857, 2246, 1601, 1544, 1439, 1269, 1242, 1116, 1029, 845, 735, 699 cm^{-1}; Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.35; H, 5.73; N, 19.93.

2-[6-(4-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-phenylacetonitrile (6)

Reaction with 4-benzylpiperidine. Product **6** was crystallized from MeOH to give a white solid (yield 45 %), mp 176-177°C; ^{1}H NMR ($CDCl_3$) δ 1.30 (2H, m), 1.85 (3H, m), 2.58 (2H, m), 2.95 (2H, m), 4.40 (2H, d, *J* = 13.0 Hz), 5.52 (1H, s), 6.90 (1H, d, *J* = 9.6 Hz), 7.10-7.51 (11H, m); IR (KBr) ν_{max} 3064, 2944, 2915, 2846, 2245, 1599, 1444, 1256, 756, 697 cm^{-1}; Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57; N, 15.21. Found: C, 77.99; H, 6.55; N, 15.17.

2-Phenyl-2-[6-(4-phenylpiperazin-1-yl)pyridazin-3-yl]acetonitrile (7)

Reaction with phenylpiperazine. Product **7** was crystallized from MeOH to give a white solid (yield 35 %), mp 174-177°C; ^{1}H NMR ($CDCl_3$) δ 3.35 (4H, m), 3.90 (4H, m), 5.54 (1H, s), 7.02-7.51 (12H, m); IR (KBr) ν_{max} 3059, 2846, 2245, 1599, 1495, 1444, 1236, 948, 756, 697 cm^{-1}; Anal. Calcd for $C_{22}H_{21}N_5$: C, 74.34; H, 5.96; N, 19.70. Found: C, 74.15; H, 5.94; N, 19.64.

2-(4-Chlorophenyl)-2-(6-morpholinopyridazin-3-yl)acetonitrile (8)

Reaction with morpholine. Product **8** was crystallized from IPA to give a white solid (yield 51 %), mp 102-104°C; ^{1}H NMR ($CDCl_3$) δ 3.65 (4H, m), 3.85 (4H, m), 5.56 (1H, s), 6.93 (1H, d, *J* = 9.5 Hz), 7.20-7.53 (5H, m); IR (KBr) ν_{max} 3055, 2920, 2854, 2250, 1595, 1544, 1490, 1269, 1117, 1094, 942, 848, 827 cm^{-1}; Anal. Calcd for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 60.88; H, 4.78; N, 17.75.

2-[6-(4-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4-chlorophenyl)acetonitrile (9)

Reaction with 4-benzylpiperidine. Product **9** was crystallized from MeOH to give a white solid (yield 44 %), mp 172-175°C; ^{1}H NMR ($CDCl_3$) δ 1.30 (2H, m), 1.80 (3H, m), 2.55 (2H, m), 2.90 (2H, m), 4.40 (2H, d, *J* = 11.7 Hz), 5.47 (1H, s), 6.89 (1H, d, *J* = 9.5 Hz), 7.10-7.51 (10H, m); IR (KBr) ν_{max} 3061, 2915, 2853, 2253, 1590, 1541, 1492, 1445, 1257, 1095, 753, 704 cm^{-1}; Anal. Calcd for $C_{24}H_{23}ClN_4$: C, 71.54; H, 5.75; N, 13.91. Found: C, 71.33; H, 5.73; N, 13.87.

2-(4-Chlorophenyl)-2-[6-(4-phenylpiperazin-1-yl)pyridazin-3-yl]acetonitrile (10)

Reaction with phenylpiperazine. Product **10** was crystallized from IPA to give a white solid (yield 47 %), mp 142-146°C; ^{1}H NMR ($CDCl_3$) δ 3.55 (4H, s), 3.90 (4H, s), 5.51 (1H, s), 6.98 (1H, d, *J* = 9.3 Hz), 7.26-7.46 (10H, m); IR (KBr) ν_{max} 3062, 2846, 2247, 1600, 1494, 1444, 1241, 1157, 1096, 948, 755 cm^{-1}; Anal. Calcd for $C_{22}H_{20}ClN_5$: C, 67.77; H, 5.17; N, 17.96. Found: C, 67.63; H, 5.16; N, 17.92.

2-(4-Methoxyphenyl)-2-(6-morpholinopyridazin-3-yl)acetonitrile (11)

Reaction with morpholine. Product **11** was crystallized from MeOH to give a white solid (yield 37 %), mp 114-116°C; ^{1}H NMR ($CDCl_3$) δ 3.65 (4H, m), 3.85 (7H, m), 5.50 (1H, s), 6.90-7.45 (6H, m); IR (KBr) ν_{max} 3060, 2960, 2855, 2247, 1606, 1510, 1446, 1255, 1177, 1119, 1030, 938, 830 cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.62; H, 5.83; N, 17.99.

2-[6-(4-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4-methoxyphenyl)acetonitrile (12)

Reaction with 4-benzylpiperidine. Product **12** was crystallized from MeOH to give a white solid (yield 40 %), mp 155-158°C; ^{1}H NMR ($CDCl_3$) δ 1.30 (2H, m), 1.70 (3H, m), 2.60 (2H, m), 2.90 (2H, m), 3.80 (3H, s), 4.40 (2H, d, *J* = 13.0 Hz), 5.48 (1H, s), 6.20-6.90 (5H, m), 7.10-7.45 (6H, m); IR (KBr) ν_{max} 3062, 2917, 2838, 2249, 1591, 1511, 1444, 1257, 1177, 1033, 752, 704 cm^{-1}; Anal. Calcd for $C_{25}H_{26}N_4O$: C, 75.35; H, 6.58; N, 14.06. Found: C, 75.24; H, 6.56; N, 14.02.

2-(4-Methoxyphenyl)-2-[6-(4-phenylpiperazin-1-yl)pyridazin-3-yl]acetonitrile (13)

Reaction with phenylpiperazine. Product **13** was crystallized from MeOH to give a white solid (yield 43 %), mp 123-125°C; ^{1}H NMR ($CDCl_3$) δ 3.27 (4H, m), 3.80 (3H, s), 3.84 (4H, m), 5.48 (1H, s), 6.84-7.41 (11H, m); IR (KBr) ν_{max} 3070, 2960, 2841, 2247, 1599, 1511, 1442, 1255, 1235, 1030, 984, 759 cm^{-1}; Anal. Calcd for $C_{23}H_{23}N_5O$: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.49; H, 5.99; N, 18.13.

General procedure for the synthesis of compounds 14-18.

2-(6-Chloropyridazin-3-yl)-2-phenylacetonitrile (0.345 g, 1.5 mmol) (for **14**), 2-(4-chlorophenyl)-2-(6-chloropyridazin-3-yl)acetonitrile (0.396 g, 1.5 mmol) (for **15**), 2-[6-(4-benzylpiperidin-1-yl) pyridazin-3-yl]-2-(4-chlorophenyl)acetonitrile (0.604 g, 1.5 mmol) (for **16**), 2-(4-chlorophenyl)-2-[6-(4-phenylpiperazin-1-yl)pyridazin-3-yl]acetonitrile (0.584 g, 1.5 mmol) (for **17**) or 2-[6-(4-benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4-methoxyphenyl)acetonitrile (0.597 g, 1.5 mmol) (for **18**) was dissolved in concentrated H_2SO_4 (5 mL) and left for 24 h at rt. Next ice (10 g) was added and the mixture was alkalized with ammonia. The precipitated solid was filtered off and crystallized.

2-(6-Chloropyridazin-3-yl)-2-phenylacetamide (14)

The crude product was crystallized from MeOH/H_2O (1:1) to give a white solid (0.152 g, 41 %), mp 79-83°C; ^{1}H NMR ($CDCl_3$) δ 5.44 (1H, s); 6.09 (1H, s), 6.82 (1H, s), 7.20-7.50 (6H, m), 7.65 (1H, d, *J* =

8.9 Hz); IR (KBr) ν_{max} 3320, 3199, 1669, 1624, 1410, 1152, 702 cm^{-1}; Anal. Calcd for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.06; H, 4.05; N, 16.93.

2-(4-Chlorophenyl)-2-(6-chloropyridazin-3-yl)acetamide (15)

The crude product was crystallized from MeOH to give a white solid (0.211 g, 50 %), mp 169-172°C; ^1H NMR ($CDCl_3$) δ 3.25 (2H, s), 5.40 (1H, s), 7.36-7.46 (4H, m), 7.66-7.85 (2H, m); IR (KBr) ν_{max} 3363, 3195, 1628, 1487, 1415, 1158, 820, 648 cm^{-1}; Anal. Calcd for $C_{12}H_9Cl_2N_3O$: C, 51.09; H, 3.22; N, 14.89. Found: C, 50.97; H, 3.21; N, 14.85.

2-[6-(4-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4-chlorophenyl)acetamide (16)

The crude product was crystallized from MeOH/H_2O (1:1) to give a white solid (0.435 g, 69 %), mp 215-219°C; ^1H NMR ($CDCl_3$) δ 1.30 (2H, m), 1.70 (3H, m), 2.50 (2H, m), 3.20 (2H, m), 3.40 (2H, bs), 4.22 (2H, d, *J* = 12.9 Hz), 5.16 (1H, s), 7.09-8.00 (11H, m); IR (KBr) ν_{max} 3412, 2922, 1684, 1640, 1599, 1216, 1174, 1121, 1034, 1010, 696, 605 cm^{-1}; Anal. Calcd for $C_{24}H_{25}ClN_4O$: C, 68.48; H, 5.99; N, 13.31. Found: C, 68.31; H, 5.97; N, 13.28.

2-(4-Chlorophenyl)-2-[6-(4-phenylpiperazin-1-yl)pyridazin-3-yl]acetamide (17)

The crude product was crystallized from MeOH to give a white solid (0.287 g, 47 %), mp 102-105°C; ^1H NMR ($CDCl_3$) δ 3.50 (4H, s), 3.80 (4H, s), 5.10 (1H, s), 5.84 (1H, bs), 6.80-7.50 (12 H, m); IR (KBr) ν_{max} 3375, 3183, 2847, 1678, 1597, 1492, 1445, 1386, 1231, 759 cm^{-1}; Anal. Calcd for $C_{22}H_{22}ClN_5O$: C, 64.78; H, 5.44; N, 17.17. Found: C, 64.63; H, 5.43; N, 17.12.

2-[6-(4-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4-methoxyphenyl)acetamide (18)

The crude product was crystallized from MeOH to give a white solid (62 mg, 10 %), mp 243-247°C; ^1H NMR (DMSO-d_6) δ 1.20 (2H, m), 1.60 (3H, m), 2.50 (2H, m), 2.90 (2H, m), 3.40 (2H, bs), 3.72 (3H, s), 4.25 (2H, d, *J* = 12.8 Hz), 5.07 (1H, s), 6.75-7.85 (9H, m); IR (KBr) ν_{max} 3425, 3196, 2920, 2851, 1679, 1642, 1602, 1492, 1450, 1182, 1032, 1010, 621 cm^{-1}; Anal. Calcd for $C_{25}H_{28}N_4O_2$: C, 72.09; H, 6.78; N, 13.45. Found: C, 71.89; H, 6.76; N, 13.41.

General procedure for the synthesis of compounds 19-22.

Compound (**5**, **7**, **8**, **9**) (5 mmol) was dissolved in pyridine (10 mL) and yellow ammonium polysulfide solution (3 mL) was added. The mixture was stirred at rt for 12 h and next ice (10 g) was added. The precipitated solid was filtered off and crystallized from the appropriate solvent.

2-(6-Morpholinopyridazin-3-yl)-2-phenylethanethioamide (19)

The crude product was crystallized from benzene to give a yellow solid (0.990 g, 63 %), mp 128-130°C; ^1H NMR ($CDCl_3$) δ 3.60 (4H, m), 3.90 (4H, m), 5.62 (1H, s), 6.90 (1H, d, *J* = 9.5 Hz), 7.20-7.60 (6H, m), 7.83 (1H, bs), 9.70 (1H, bs); IR (KBr) ν_{max} 3271, 3096, 2964, 2852, 1592, 1444, 1252, 1124, 934, 699 cm^{-1}; Anal. Calcd for $C_{16}H_{18}N_4OS$: C, 61.12; H, 5.77; N, 17.82; S, 10.20. Found: C, 60.98; H, 5.75; N, 17.77; S, 10.17.

2-Phenyl-2-[6-(4-phenylpiperazin-1-yl)pyridazin-3-yl]ethanethioamide (20)

The crude product was crystallized from EtOH to give a white solid (0.934 g, 48 %), mp 177-179°C; ^{1}H NMR ($CDCl_3$) δ 3.30 (4H, m), 3.80 (4H,m), 5.61 (1H, s), 6.95 (4H, m), 7.30 (6H, m), 7.55 (2H, m), 7.88 (1H, bs), 9.76 (1H, bs); IR (KBr) ν_{max} 3262, 3060, 2849, 1591, 1543, 1485, 1448, 1258, 1229, 1030, 708, 696 cm^{-1}; Anal. Calcd for $C_{22}H_{23}N_5S$: C, 67.84; H, 5.95; N, 17.98; S, 8.23. Found: C, 67.72; H, 5.93; N, 17.93; S, 8.20.

2-(4-Chlorophenyl)-2-(6-morpholinopyridazin-3-yl)ethanethioamide (21)

The crude product was crystallized from benzene/petr. ether to give a yellow solid (1.05 g, 60 %), mp 66-67°C; ^{1}H NMR ($CDCl_3$) δ 3.60 (4H, m), 3.85 (4H, m), 5.56 (1H, s), 6.90 (1H, d, *J* = 9.4 Hz), 7.45 (1H, d, *J* = 9.4 Hz), 7.20-7.40 (4H, m), 8.02 (1H, bs), 9.75 (1H, bs); IR (KBr) ν_{max} 3288, 3169, 2962, 2853, 1594, 1545, 1489, 1442, 1254, 1116, 682 cm^{-1}; Anal. Calcd for $C_{16}H_{17}ClN_4OS$: C, 55.09; H, 4.91; N, 16.06; S, 9.19. Found: C, 54.93; H, 4.89; N, 16.02; S. 9.17.

2-[6-(4-Benzylpiperidin-1-yl)pyridazin-3-yl]-2-(4-chlorophenyl)ethanethioamide (22)

The crude product was crystallized from benzene/petr. ether to give a beige solid (1.42 g, 65 %), mp 83-84°C; ^{1}H NMR ($CDCl_3$) δ 0.89 (1H, m), 1.60 (2H, m), 1.80 2H, m), 2.60 (2H, m), 2.90 (2H, m), 4.35 (2H, d, *J* = 6.7 Hz), 5.50 (1H, s), 6.90 (1H, d, *J* = 9.5 Hz), 7.34 (9H, m), 7.50 (1H, d, *J* = 9.5 Hz), 7.85 (1H, bs), 9.98 (1H, bs); IR (KBr) ν_{max} 3280, 3163, 3025, 2924, 2847, 1594, 1543, 1488, 1445, 1251, 743, 700 cm^{-1}; Anal. Calcd for $C_{24}H_{25}ClN_4S$: C, 65.96; H, 5.77; N, 12.82; S, 7.34. Found: C, 65.79; H, 5.75; N, 12.79; S, 7.32.

(6-Chloro-pyridazin-3-yl)hydrazine (23)

3,6-Dichloropyridazine (4.50 g, 30 mmol) was dissolved in dioxane (20 mL) and then triethylamine (4.2 mL, 30 mmol) and hydrazine (1.6 mL, 33 mmol) were added. The mixture was refluxed for 2 h. The mixture was concentrated in vacuo and ice (20 g) was added to the residue. The precipitated solid was filtered off and crystallized from IPA to give a white solid (3.18 g, 73 %), mp 123-126°C; ^{1}H NMR (DMSO-d_6) δ 4.40 (2H, bs), 7.10 (1H, d, *J* = 9.4 Hz), 7.40 (1H, d, *J* = 9.4 Hz), 8.20 (1H, bs); IR (KBr) ν_{max} 3255, 3030, 2925, 1600, 1452, 1154, 833, 641 cm^{-1}; Anal. Calcd for $C_4H_5ClN_4$: C, 33.23; H, 3.49; N, 38.76. Found: C, 33.15; H, 3.48; N, 38.66.

(6-Hydrazino-pyridazin-3-yl)-(4-methoxyphenyl)-acetonitrile (24)

Compound **3** (1.3 g, 5 mmol) was dissolved in EtOH (20 mL) and hydrazine monohydrate (3 mL, 61 mmol) was added. The mixture was refluxed for 3 h. Next the mixture was concentrated in vacuo and MeOH (3 mL) was added. After cooling down the precipitated solid was filtered off and crystallized from MeOH to give a white solid (0.64 g, 50 %), mp 153-157°C; ^{1}H NMR (DMSO-d_6) δ 3.73 (3H, s), 4.30 (2H, s), 5.79 (1H, s), 6.85-7.40 (6H, m), 8.10 (1H, s); IR (KBr) ν_{max} 3307, 3236, 3017, 2931, 2250, 1608, 1513, 1430, 1262, 1178, 1101, 1033, 825, 641 cm^{-1}; Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43.

Found: C, 61.01; H, 5.11; N, 27.38.

General procedure for the synthesis of compounds 25-34.

Compound **23** or **24** (2 mmol) was dissolved in EtOH (30 mL) and then suitable aldehyde (2.5 mmol) was added. The mixture was refluxed for 1 h. After cooling down water (20 mL) was added, and precipitated solid was filtered off and crystallized from the appropriate solvent.

3-(2-Benzylidenehydrazinyl)-6-chloropyridazine (25)

Reaction with benzaldehyde. Product **25** was crystallized from dioxane to give a white solid (yield 53 %), mp 254-256°C; ^{1}H NMR (DMSO-d_6) δ 7.37-7.72 (7H, m), 8.13 (1H, s); 11.72 (1H, s); IR (KBr) ν_{max} 3024, 2921, 2847, 1614, 1593, 1530, 1413, 1135, 1064, 751,687 cm^{-1}; Anal. Calcd for $C_{11}H_9ClN_4$: C, 56.78; H, 3.90; N, 24.08. Found: C, 56.63; H, 3.88; N, 24.01.

3-[2-(4-Bromobenzylidene)hydrazinyl]-6-chloropyridazine (26)

Reaction with 4-bromobenzaldehyde. Product **26** was crystallized from dioxane to give a white solid (yield 62 %), mp 278-279°C; ^{1}H NMR (DMSO-d_6) δ 7.54-7.70 (6H, m), 8.09 (1H, s), 11.80 (1H, s); IR (KBr) ν_{max} 3204, 2921, 1616, 1600, 1530, 1485, 1416, 1397, 1130, 1070, 831, 812 cm^{-1}; Anal. Calcd for $C_{11}H_8BrClN_4$: C, 42.40; H, 2.59; N, 17.98. Found: C, 42.30; H, 2.58; N, 17.93.

3-Chloro-6-[2-(4-nitrobenzylidene)hydrazinyl]pyridazine (27)

Reaction with 4-nitrobenzaldehyde. Product **27** was crystallized from dioxane to give a lateritious solid (yield 52 %), mp 277-279°C; ^{1}H NMR (DMSO-d_6) δ 7.60-8.25 (7H, m), 12.09 (1H, s); IR (KBr) ν_{max} 2925, 2845, 1621, 1527, 1429, 1395, 1345, 1139, 1105, 1074, 851, 839, 746, 685 cm^{-1}; Anal. Calcd for $C_{11}H_8ClN_5O_2$: C, 47.58; H, 2.90; N, 25.22. Found: C, 47.48; H, 2.89; N, 25.16.

3-Chloro-6-{2-[(5-nitrofuran-2-yl)methylene]hydrazinyl}pyridazine (28)

Reaction with 5-nitrofuran-2-carbaldehyde. Product **28** was crystallized from MeOH to give a yellow solid (yield 90 %), mp 276-278°C; ^{1}H NMR (DMSO-d_6) δ 7.20 (1H, d, *J* = 4.2 Hz), 7.60-8.10 (3H, m), 8.06 (1H, s), 12.28 (1H, s); IR (KBr) ν_{max} 3135, 2922, 2850, 1594, 1471, 1417, 1387, 1353, 1257, 1138, 1028, 809 cm^{-1}; Anal. Calcd for $C_9H_6ClN_5O_3$: C, 40.39; H, 2.26; N, 26.17. Found: C, 40.29; H, 2.25; N, 26.11.

3-Chloro-6-{2-[(5-nitrothiophen-2-yl)methylene]hydrazinyl}pyridazine (29)

Reaction with 5-nitrothiophene-2-carbaldehyde. Product **29** was crystallized from DMF/H_2O (1:1) to give an orange solid (yield 69 %), mp 303-305°C; ^{1}H NMR (DMSO-d_6) δ 7.46 (1H, d, *J* = 3.0 Hz), 8.10 (1H, d, *J* = 3.0 Hz), 7.63 (1H, d, *J* = 9.0 Hz), 7.73 (1H, d, *J* = 9.0 Hz), 8.28 (1H, s), 12.27 (1H, s); IR (KBr) ν_{max} 3100, 2917, 2819, 1610, 1573, 1436, 1419, 1330, 1286, 1221, 1140, 812, 732 cm^{-1}; Anal. Calcd for $C_9H_6ClN_5O_2S$: C, 38.10; H, 2.13; N, 24.69; S, 11.30. Found: C, 38.02; H, 2.12; N, 24.62; S, 11.27.

2-[6-(2-Benzylidenehydrazinyl)pyridazin-3-yl]-2-(4-methoxyphenyl)acetonitrile (30)

Reaction with benzaldehyde. Product **30** was crystallized from dioxane to give a white solid (yield

54 %), mp 263-265°C; ^{1}H NMR (DMSO-d_6) δ 3.74 (3H s), 5.91 (1H, s), 6.90-7.80 (11H, m), 8.13 (1H, s), 11.65 (1H, s); IR (KBr) ν_{max} 3189, 2919, 2849, 2248, 1615, 1540, 1513, 1428, 1257, 1137, 1031, 824, 693 cm^{-1}; Anal. Calcd for $C_{20}H_{17}N_5O$: C, 69.96; H, 4.99; N, 20.40. Found: C, 69.99; H, 4.97; N, 20.35.

2-{6-[2-(4-Bromobenzylidene)hydrazinyl]pyridazin-3-yl}-2-(4-methoxyphenyl)acetonitrile (31)

Reaction with 4-bromobenzaldehyde. Product **31** was crystallized from dioxane to give a white solid (yield 61 %), mp 256-259°C; ^{1}H NMR (DMSO-d_6) δ 3.75 (3H s), 5.93 (1H, s) 7.00-7.63 (10H m), 8.10 (1H, s), 11.75 (1H, s); IR (KBr) ν_{max} 3186, 2934, 2837, 2249, 1603, 1540, 1510, 1487, 1428, 1255, 1139, 1033, 827 cm^{-1}; Anal. Calcd for $C_{20}H_{16}BrN_5O$: C, 56.89; H, 3.82; N, 16.58. Found: C, 56.74; H, 3.80; N, 16.54.

2-(4-Methoxyphenyl)-2-{6-[2-(4-nitrobenzylidene)hydrazinyl]pyridazin-3-yl}acetonitrile (32)

Reaction with 4-nitrobenzaldehyde. Product **32** was crystallized from dioxane to give a lateritious solid (yield 40 %), mp 273-275°C; ^{1}H NMR (DMSO-d_6) δ 3.74 (3H, s), 5.94 (1H, s), 6.85-8.30 (11H, m), 12.05 (1H, s); IR (KBr) ν_{max} 3195, 2841, 2249, 1611, 1573, 1541, 1524, 1429, 1341, 1256, 1143, 1032, 857, 827 cm^{-1}; Anal. Calcd for $C_{20}H_{16}N_6O_3$: C, 61.85; H, 4.15; N, 21.64. Found: C, 61.72; H, 4.13; N, 21.59.

2-(4-Methoxyphenyl)-2-{6-{2-[(5-nitrofuran-2-yl)methylene]hydrazinyl}pyridazin-3-yl}acetonitrile (33)

Reaction with 5-nitrofuran-2-carbaldehyde. Product **33** was crystallized from MeOH to give a lateritious solid (yield 56 %), mp 224-227°C; ^{1}H NMR (DMSO-d_6) δ 3.74 (3H, s), 5.96 (1H, s), 6.90-7.80 (8H, m), 8.10 (1H, s), 12.25 (1H, s); IR (KBr) ν_{max} 3123, 2936, 2838, 2247, 1583, 1512, 1477, 1431, 1351, 1307, 1252, 1020, 810 cm^{-1}; Anal. Calcd for $C_{18}H_{14}N_6O_4$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.02; H, 3.72; N, 22.16.

2-(4-Methoxyphenyl)-2-{6-{2-[(5-nitrothiophen-2-yl)methylene]hydrazinyl}pyridazin-3-yl}aceto-nitrile (34)

Reaction with 5-nitrothiophene-2-carbaldehyde. Product **34** was crystallized from dioxane to give a lateritious solid (yield 62 %), mp 206-208°C; ^{1}H NMR (DMSO-d_6) δ 3.33 (3H, s), 5.97 (1H, s), 6.95-8.10 (8H, m), 8.29 (1H, s), 12.25 (1H, s); IR (KBr) ν_{max} 3106, 2933, 2838, 2248, 1607, 1510, 1434, 1333, 1254, 1033, 816, 732 cm^{-1}; Anal. Calcd for $C_{18}H_{14}N_6O_3S$: C, 54.81; H, 3.58; N, 21.31; S, 8.13. Found: C, 54.72; H, 3.57; N, 21.26; S, 8.10.

2-[6-(Ethylthio)pyridazin-3-yl]-2-phenylacetonitrile (35)

To a round bottomed flask (100 mL) containing solution of 0.888 mL (0.745 g, 12 mmol) EtSH in 20 mL of anhydrous dioxane 0.276 g (12 mmol) of sodium was added and gently heated until all of sodium was reacted (ca. 1.5h). Clear solution was then cooled to rt and the solution of 1.378 g (6 mmol) of 2-(6-chloropyridazin-3-yl)-2-phenylacetonitrile in 20 mL of anhydrous dioxane was dropped into within 5 min. After heating 3.5 h in reflux the mixture was concentrated in vacuo and 30 mL of ice-cold water was added. Precipitated solid was collected and crystallized from MeOH to give a beige solid (0.991 g, 65 %), mp 157-158°C; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, t, *J* = 7.3 Hz), 3.35 (2H, q, *J* = 7.3 Hz), 5.57 (1H, s), 7.25-7.55 (7H, m); IR (KBr) ν_{max} 3063, 3039, 2978, 2934, 2248, 1576, 1415, 1153, 1052, 854, 697 cm^{-1}; Anal. Calcd for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.71; H, 5.11; N, 16.41; S, 12.53.

General procedure for the synthesis of compounds 36-38.

To a round bottomed flask containing 20 mL of anhydrous dioxane and 12 mmol of appropriate thiol,12 mmol of sodium was added and then heated for 15 min. in reflux. After cooling, solution of 4-chloropyridazinephenylacetonitrile (6 mmol) in 20 mL of anhydrous 1,4-dioxane was dropped into. After heating in reflux for 3.5 h the mixture was concentrated in vacuo and 30 mL of water was added. The crude product was collected and crystallized from MeOH.

2-Phenyl-2-[6-(phenylthio)pyridazin-3-yl]acetonitrile (36)

Reaction with 2-(6-chloropyridazin-3-yl)-2-phenylacetonitrile. A white solid (0.45 g, 25 %), mp 111-113°C; ^{1}H NMR ($CDCl_3$) δ 5.60 (1H, s), 7.00 (1H, d, *J* = 9.1 Hz), 7.20 - 7.70 (11H, m); IR (KBr) ν_{max} 3032, 2931, 2250, 1406, 1149, 1067, 748, 699 cm^{-1}; Anal. Calcd for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.32; N, 13,85; S, 10.57. Found: C, 71.11; H, 4.30; N, 13.81; S, 10.54.

2-(4-Chlorophenyl)-2-[6-(phenylthio)pyridazin-3-yl]acetonitrile (37)

Reaction with 2-(4-chlorophenyl)-2-(6-chloropyridazin-3-yl)acetonitrile. A white solid (1.05 g, 52 %), mp 163-165°C; ^{1}H NMR ($CDCl_3$) δ 5.58 (1H, s), 7.00 (1H, d, *J* = 9.1 Hz), 7.23 - 7.64 (10H, m); IR (KBr) ν_{max} 3063, 2879, 2247, 1570, 1493, 1408, 1149, 1094, 819, 746, 687 cm^{-1}; Anal. Calcd for $C_{18}H_{12}ClN_3S$: C, 64.00; H, 3.58; N, 12.44; S, 9.49. Found: C, 63.87; H, 3.57; N, 12.41; S, 9.46.

2-(4-Methoxyphenyl)-2-[6-(phenylthio)pyridazin-3-yl]acetonitrile (38)

Reaction with 2-(6-chloropyridazin-3-yl)-2-(4-methoxyphenyl)acetonitrile. A white solid (1.00 g, 50 %), mp 135-137°C; ^{1}H NMR ($CDCl_3$) δ 3.80 (3H, s), 5.55 (1H, s), 6.68 - 7.66 (11H, m); IR (KBr) ν_{max} 3067, 3028, 2933, 2830, 2248, 1511, 1407, 1252, 1172, 1010, 819, 745, 688 cm^{-1}; Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.32; H, 4.51; N, 12.57; S, 9.59.

General procedure for the synthesis of compounds 39, 40.

Compound **1** (0.92 g, 4 mmol) or compound **2** (1.05 g, 4 mmol) was dissolved in pyridine (5 mL, 61 mmol), MeOH (2 mL) and yellow solution of ammonium polysulfide (3 mL) were added. The mixture was stirred at rt for 72 h. Next ice (50 g) was added and the precipitated solid was filtered off. The filtrate was acidified with concentrated acetic acid. The precipitated solid was filtered off and crystallized from appropriate solvent.

2-(6-Mercaptopyridazin-3-yl)-2-phenylethanethioamide (39)

The crude product was crystallized from benzene to give a yellow solid (0.68 g, 65 %), mp 156-157°C; ^{1}H NMR (DMSO-d_6) δ 5.39 (1H, s), 7.10 (1H, d, J = 9.4 Hz), 7.30 – 7.60 (6H, m), 9.63 (1H, bs), 9.83 (1H, bs), 14.10 (1H, bs); IR (KBr) ν_{max} 3412, 3275, 3181, 3146, 3074, 2995, 2922, 2884, 1620, 1572, 1416, 1402, 1232, 1089, 1028, 698, 634, 551 cm^{-1}; Anal. Calcd for $C_{12}H_{11}N_3S_2$: C, 55.14; H, 4.24; N, 16.08; S, 24.54. Found: C, 55.03; H, 4.23; N, 16.03; S, 24.49.

2-(4-Chlorophenyl)-2-(6-mercaptopyridazin-3-yl)ethanethioamide (40)

The crude product was crystallized from MeOH to give a yellow solid (0.99 g, 85 %), mp 179-181°C; ^{1}H NMR ($CDCl_3$) δ 5.41 (1H, s), 7.15 (1H, d, J = 9.2 Hz), 7.45 – 7.55 (5H, m), 9.65 (1H, bs), 9.98 (1H, bs), 14.58 (1H, bs); IR (KBr) ν_{max} 3309, 3136, 3054, 2993, 2922, 2854, 1624, 1563, 1488, 1407, 1086, 1027, 810, 679 cm^{-1}; Anal. Calcd for $C_{12}H_{10}ClN_3S_2$: C, 48.72; H, 3.41; N, 14.21; S, 21.68. Found: C, 48.62; H, 3.39; N, 14.17; S, 21.62.

General procedure for the synthesis of compounds 41, 42.

Compound **1** (0.92 g, 4 mmol) or compound **2** (1.05 g, 4 mmol) was dissolved in pyridine (5 mL, 61 mmol), MeOH (2 mL) and yellow solution of ammonium polysulfide (2.5 mL) were added. The mixture was stirred at rt for 2 h. Next ice (50 g) was added, the precipitated solid after 12 h was filtered off and crystallized.

2-(6-Chloropyridazin-3-yl)-2-phenylethanethioamide (41)

The crude product was crystallized from MeOH to give a yellow solid (0.89 g, 85 %), mp 192-195°C; ^{1}H NMR ($CDCl_3$) δ 5.83 (1H,s), 7.30 – 7.55 (7H, m), 7.92 (1H, bs), 8.82 (1H, bs); IR (KBr) ν_{max} 3302, 3153, 3046, 1621, 1418, 1148, 855, 719, 697 cm^{-1}; Anal. Calcd for $C_{12}H_{10}ClN_3S$: C, 54.65; H, 3.82; N, 15.93; S, 12.16. Found: C, 54.53; H, 3.80; N, 15.89; S, 12.13.

2-(4-Chlorophenyl)-2-(6-chloropyridazin-3-yl)ethanethioamide (42)

The crude product was crystallized from cyclohexane to give a yellow solid (0.53 g, 45 %), mp 112-113°C; ^{1}H NMR ($CDCl_3$) δ 5.91 (1H, s), 7.33 – 7.58 (6H, m), 7.94 (1H, bs), 9.07 (1H, bs); IR (KBr) ν_{max} 3303, 3160, 2925, 2851, 1617, 1491, 1415, 1149, 1092, 916, 810 cm^{-1}; Anal. Calcd for $C_{12}H_9Cl_2N_3S$: C, 48.33; H, 3.04; N, 14.09; S, 10.75. Found: C, 48.21; H, 3.03; N, 14.05; S, 10.72.

2-[6-(Ethylthio)pyridazin-3-yl]-2-phenylethanethioamide (43)

Method A

Compound **35** (0.255 g, 1 mmol) was dissolved in pyridine (3 mL, 37 mmol) and dioxane (5 mL). Next yellow solution of ammonium polysulfide was added and the mixture was stirred at rt for 12 h. After this time the mixture was concentrated in vacuo and ice (10 g) was added to the residue. Water was decanted and MeOH (3 mL) was added to the oily residue. Water was added and the solid formed was filtered off and crystallized from MeOH to give a yellow solid (0.202 g, 70 %), mp 121-122°C; ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, J = 7.3 Hz), 3.36 (2H, q, J = 7.3 Hz), 5.69 (1H, s), 7.20 – 7.60 (7H, m), 7.95 (1H, bs), 9.38

(1H, bs); IR (KBr) ν_{max} 3305, 3156, 3062, 3029, 2971, 2932, 1618, 1429, 1412, 1219, 1160, 717, 700 cm^{-1}; Anal. Calcd for $C_{14}H_{15}N_3S_2$: C, 58.10; H, 5.22; N, 14.52; S, 22.16. Found: C, 57.99; H, 5.20; N, 14.49; S, 22.10.

Method B

Compound **39** (0.65 g, 2.5 mmol) was dissolved in a methanolic KOH solution (0.14 g, 2.5 mmol)/10 mL and then MeI (0.28 mL, 4.5 mmol) was added. The mixture was stirred at rt for 12 h. Next solvent was evaporated and ice (10 g) was added. The precipitate was filtered off and crystallized from MeOH to give a yellow solid (0.41 g, 57 %).

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