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Microwave assisted synthesis of novel nonfused and fused heterocyclic systems derivatives having plant growth stimulant activity based on 3-chloro-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine

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Abstract : The microwave-assisted and conventional synthesis of novel nonfused and fused heterocyclic systems derivatives based on 3-chloro-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine were carried out to determine the usefulness and the range of application of MWI procedure. The synthesized compounds have shown the pronounced plant growth stimulate properties and can be of interest for the search of new plants growth stimulators. Eight compounds having high activity (higher than 70% compared with heteroauxin) are selected for deeper study and further field trials.

Keywords : Microwave-assisted synthesis; Heterocyclization; Pyrazolyl-pyridazine; (1H-pyrazol-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine; Plant growth stimulators.

INTRODUCTION

On the basis of pyrazole and pyridazine heterocycles a large number of compounds are synthesized, which widely used not only in medical practice, but also in agriculture as means of plants protection[1]. Among the pyrazole derivatives there are effective insecticides (acetoprole, chlorantraniliprole, cyantraniliprole, dimetilan, ethiprole, fipronil, isolan, pyraclofos, pyrafluprole, pyriprole, pyrolan, rizazole, tebufenpyrad, tolfenpyrad, vaniliprole) and fungicides (bixafen, fenpyrazamine, fluxapyroxad, furametpyr, isopyrazam, penflufen, penthiopyrad, pyraclostrobin, pyrametostrobin, pyraoxystrobin, rabenzazole, sedaxane). The arsenal of pesticides based on pyridazine includes mainly herbicides (credazine, pyridafol, pyridate, brompyrazon, chloridazon, dimidazon, flufenpyr, metflurazon, norflurazon, oxapyrazon, pydanon). Because of great interest to these heterocyclic derivatives, in the last two decades the studies in the series of pyrazole and pyridazine derivatives are continued to find new compounds with fungicidal[2-9], herbicidal[10-17] and insecticidal[5,15] activities.

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Pyrazolyl-pyridazines obtained by cyclization of 3-hydrazino-pyridazines have hypotensive, anti- inflammatory, antibacterial and antioxidant activities[18-21]. At the same time in the literature there are practically no data on pesticidal or growth regulatory properties of nonfused pyrazolyl-pyridazines and fused pyrazolo-pyridazines.

The conventional methods of synthesis of these heterocyclic systems in many cases requires prolonged heating, which is associated with the loss of time and energy. In recent years, MW-irradiation method for the synthesis of bioactive heterocyclic compounds has evolved as an effective ecofriendly method[22-26]. MW-assisted synthesis offers several advantages, such as facile work up, shorter reaction time, cleaner products, products selectivity and hence this procedure is consistent with the principles of "Green chemistry".

The purpose of this study was the targeted synthesis of new previously undescribed derivatives based on pyrazolyl-pyridazines using microwave-assisted and conventional procedure, the comparison of these two methods, and biological screening of synthesized compounds.

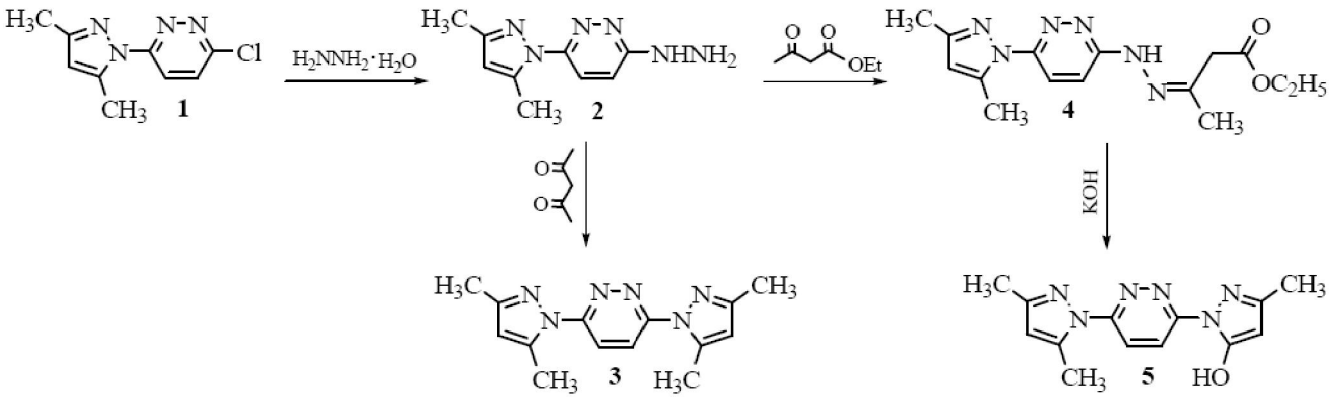
RESULTS AND DISCUSSION

Chemistry

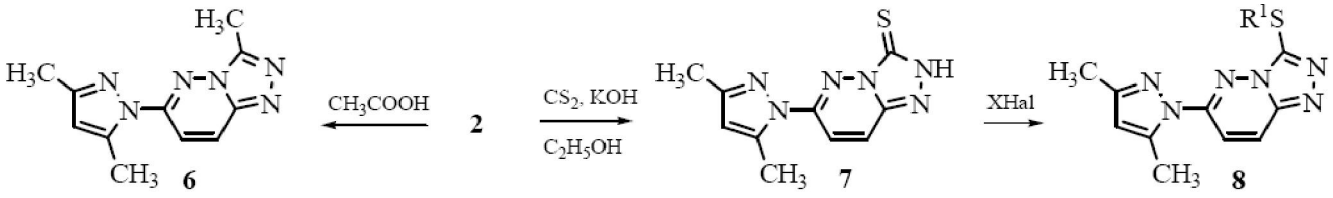
As the initial reactant 3-ñhloro-6-(3,5-dimethyl-pyrazol-1-yl)pyridazine (1) was used. The reaction of compound 1 with hydrazine hydrate afforded (6-(3,5-dimethyl-pyrazol-1-yl)-pyridazin-3-yl)-hydrazine (2).

The interactions of this hydrazine with pentane-2,4-dione, 3-oxo-butyric acid ethyl ester, acetic acid and carbon bisulfide were studied. In the case of reaction with pentane-2,4-dione at room temperature in acetic acid medium in the presence of 1-2 drops of DMF the heterocyclization was occured that led to 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (3) formation. In contrast, when hydrazide 2 reacted with 3-oxo-butyric acid ethyl ester in ethanol the acyclic product 3-((6-(3,5-dimethyl-pyrazol-1-yl)-pyridazin-3-yl)-hydrazono)-butyric acid ethyl ester (4) was obtained, which at further boiling in an alkaline medium was cyclized into 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-(5-methyl-3-hydroxy-2*H*-pyrazol-2-yl)pyridazine (5).

In accordance with the literature data in recent years some researchers attracted attention to the synthesis of fused [1,2,4]triazolo[4,3-b]pyridazines[27-37], among which the compounds with antibacterial and antifungal[31], antihypertensive[32], anticonvul-



Scheme 1 : Transformations of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-hydrazinylpyridazine



$R^1 = CH_3, CH_2CONH_2, CH_2COOMe, CH_2CH_2OC_6H_5, CH(COCH_3)_2$

Scheme 2 : Synthesis of [1,2,4]triazolo[4,3-*b*]pyridazine derivatives

sant[33] and anxiolytic[34] activities, PDE4 inhibitors[35], ligands for GABA receptors and selective agonists for α2- and α3-containing $GABA_A$ receptors[36,37] were discovered.

In order to search for new crop protection chemicals the hydrazide 2 was reacted with acetic acid, which afforded fused 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-methyl-[1,2,4]-triazolo[4,3-b]pyridazine (6). The interaction of the hydrazide (2) with carbon disulfide and potassium hydroxide in absolute ethanol leads to 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3(2*H*)-thione (7) formation. The potassium salt of latter was easily alkylated with halocarboxylic acids derivatives, 3-chloro-pentane-2,4-dione, alkyl halides in DMF and formed the corresponding alkylthio derivatives (8).

In our earlier investigations a number of thiopyridazine derivatives with high growth-regulatory activity have been found[38-40]. From this viewpoint, it was advisable to search a biologically active substances in the series of nonfused pyrazolylthiopyridazine derivatives.

For this purpose, according our developed method[41] from compound 1 the intermediate thiouronium salt was obtained, which was converted into the appropriate 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine-3(2H)-thione. The potassium salt of latter easily reacted with alkyl halides, halogen acetic acide derivatives and formed the corresponding 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-(alkylthio)pyridazines (11).

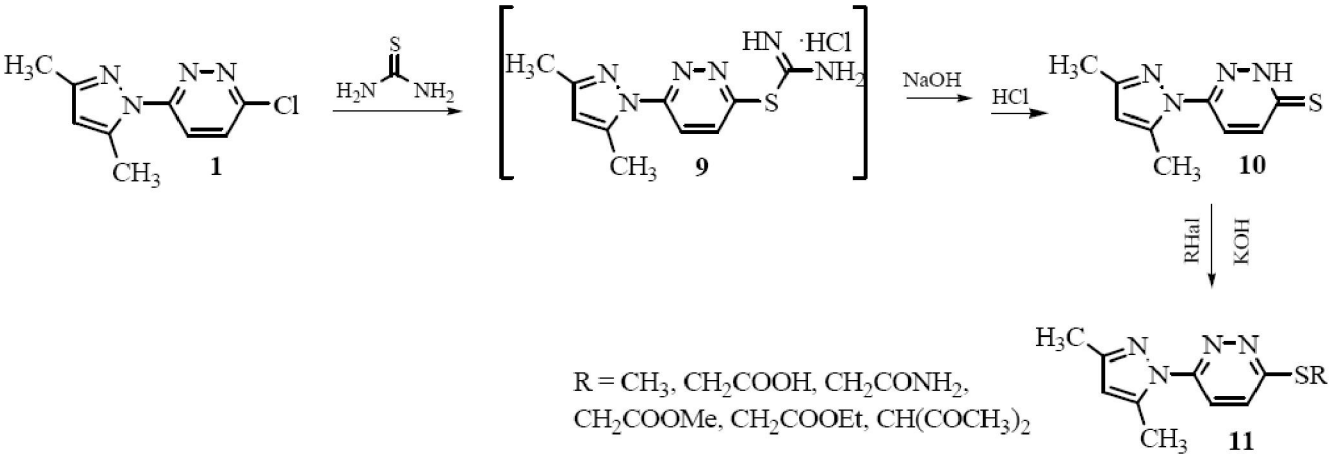
Ñompounds 7 and 10 can exist in two tautomeric forms (thiol or thione). In ^{13}C NMR spectra the signals of C=S double bonds at 161.81 ppm (7) and 177.78 ppm (10), and also absorptions of NH proton in ^1H NMR at 14.6 ppm and 14.41 ppm are observed that agree with thione structure. Their further alkylation leads to S-substituted derivatives, since these signals are disappeared and in NMR spectra the new absorptions due to S-alkyl groups are observed.

The syntesis of the same compounds 3-11 were carried out using MW-irradiation procedure to determine its usefulness and the range of application. In TABLE 1 the comparison of these two methods is described.

From TABLE 1 it follows that when the conventional method is conducted at room temperature then at MW-irradiation the reaction yields are not practically changed, or occurs the resinification of reaction products (compounds 3, 4, 10,11a and 11f), but the synthesis times are shortened to a few minutes. When the MW-irradiation procedure was used for the others, then the yields are increased and the synthesis times are also shortened, compared with conventional method. It can be concluded that the best effect of MW-irradiation is achieved when a conventional method was conducted by prolonged high temperature heating.

Biological properties

At preliminary screening the herbicidal, fungicidal and growth regulatory activities of novel synthesized compounds were studied. All preparations did not posses noticeable herbicidal or antifungal properties, but they showed the growth stimulate



Scheme 3 : Synthesis of 6-S-substituted 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazines

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TABLE 1 : Comparison of conventional and MWI procedures for the synthesis of compounds 1-11

№	Conventional procedure		MWI procedure	
	Temperature, (time)	Yield (%), (solvent)	Yield (%) (solvent)	Time (min)
1	78-80 ^{0}C, (5 h)	84, (C_2H_5OH)	92, (C_2H_5OH)	10
2	110-115 ^{0}C, (10h)	82, (dioxane)	88, (dioxane)	30
3	Rt, (1day)	85, (CH_3COOH)	85, (CH_3COOH)	10
4	Rt, (1day)	96, (CH_3COOH)	*	*
5	90-95, (3h)	60, (H_2O)	60, (CH_3COOH)	30
6	115-118 ^{0}C, (8h)	59, (CH_3COOH)	90, (CH_3COOH)	30
7	75-80 ^{0}C, (10h)	81, (CS_2, C_2H_5OH)	*	*
8a	50-55 ^{0}C, (4-5h)	77, (DMF)	84, (DMF)	15
8b	55-60 ^{0}C, (6-8h)	63, (DMF)	67, (DMF)	10
8c	55-60 ^{0}C, (6-8h)	50, (DMF)	67, (DMF)	15
8d	40-45 ^{0}C, (3-5h)	58, (DMF)	81, (DMF)	15
8e	40-45 ^{0}C, (3-5h)	62, (DMF)	*	*
9	55-60 ^{0}C, (3-5h)	92, (acetone)	*	*
10	Rt, (1h)	80, (H_2O)	76, (H_2O)	10
11a	Rt, (1 day)	87, (H_2O)	95, (H_2O)	15
11b	78-80 ^{0}C, (2 h)	77, (C_2H_5OH)	77, (C_2H_5OH)	30
11c	50-55 ^{0}C, (3 h)	70, (DMF)	88, (DMF)	10
11d	50-55 ^{0}C, (3 h)	70, (DMF)	74, (DMF)	10
11e	50-55 ^{0}C, (3 h)	86, (DMF)	35, (DMF)	10
11f	Rt, (2 days)	80, (DMF)	*	*

***Resinification of the reaction product**

TABLE 2 : Growth stimulant activity of compounds 3-11

№	Growth stimulant activity (%)		№	Growth stimulant activity (%)	
	25 mg L^{-1}	50 mg L^{-1}		25 mg L^{-1}	50 mg L^{-1}
IAA	100	100	8d	-	83.9
3	73.4	75.7	8e	76.1	45.9
4	-	53.2	10	63.3	79.1
5	65.1	76.1	11a	52.5	66.8
6	64.7	62	11b	71.4	57.7
7	51.9	45.7	11c	62.5	69.9
8a	-	-	11d	60.4	60.5
8b	70.2	54.8	11e	63.9	48.5
8c	77.2	58.7	11f	68.1	80.2

activity.

The object of study were the seeds and seedlings of common bean (*Phaseolus vulgaris* L.). Experiments were performed on two schemes.

By the first scheme the effect of aqueous suspension of compounds 3-11 and heteroauxin (IAA) in concen-trations 25 and 50 mg L^{-1} on the viability of seeds, germination and seedlings were studied. The seeds were incubated for 24 hours in an appropriate mediums in the dark at 25°C. Then the seeds were transplanted into soil and watered daily. The experiment was repeated twice.

By the second experimental setup the bean seeds were sown in the soil in small vessels. When the length of the stems reached 15-20 cm, plants were dug out, the root parts were washed with water and cut off. Series of 8-10 cut plants were immersed in the prepared aqueous solutions of IAA and investi-

gated preparations in concentrations 25 mg L^{-1} and 50 mg L^{-1}. After 24 hours, they were washed and dipped into the vessels with water. Water in the vessels was changed every day. The formation of root system has already been observed on 8-9 day. The calculations were produced in 20-25 days. The experiment was repeated twice. The number of the plants roots of each series, their length and weight in the moist and dry forms, their average values were calculated.

The obtained results of both experiments for synthesized compounds solutions were compared with similar data of plants placed in IAA solutions, on the basis of which the activities of preparations were determined in comparison with IAA (in %) (TABLE 2). Eight obtained compounds, which have shown activity higher than 70%, are preparing for further field trials.

CONCLUSIONS

The simple and convenient high yield methods for the synthesis of new nonfused and fused bi- and triheterocyclic systems derivatives with a combination of pyrazole, pyridazine, and triazole rings in the same molecules based on pyrazolyl-pyridazine were elaborated. The same products were obtained using MW-irradiation procedure. It is found that the application of this method has the greatest advantage when conventional methods of synthesis carried out for a long time and at high temperatures.

The synthesized compounds have shown the pronounced plant growth stimulate properties. Eight compounds having high activity (higher than 70% compared with heteroauxin) were selected for deeper study and further field trials. These results indicate that the new synthesized heterocyclic systems can be of interest for the search of new plants growth stimulators.

EXPERIMENTAL

General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at 30 ^{0}C on Varian Mercury-300 spectrometer with standard pulse sequences operating in the mixture of solvents DMSO-d_6 and CCl_4 (1:3) using tetramethylsilane (0.0 ppm) as internal standard. The NMR multiplicities br s, s, d, t, q, and m stand for broad singlet, singlet, doublet, triplet, quartet and multiplet, respectively. The reaction progress and purity of the obtained substances were checked by using the tlc method on "Silufol UV-254" plates and acetone/hexane mixture (2:1) as eluent. All melting points were determined in open capillaries and are uncorrected.

MWI procedure

For MW-experiments the domestic microwave oven Gorenje Model No. MO 17 L (2450 MHz, power output 800 W) was used. It was subjected to microwave irradiation at 160 W power with interruption after each 30 seconds.

Conventional syntheses

3-Chloro-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (1)

The synthesis was done according the method discribed by G. Szilagyi[18]. ^{1}H NMR: δ= 2.25 (s, 3H, 3-CH_3), 2.72 (s, 3H, 5-CH_3), 5.92 (s, 1H, CH-pyraz.), 7.78 and 8.17 (d,d, 2H, *J*=9.3 Hz, CH=CH). ^{13}C NMR: δ= 13.06, 14.44, 109.88, 122.13, 129.99, 141.43, 150.31, 152.75, 155.51. Anal. Calcd for $C_9H_9ClN_4$: C 51.81; H 4.35; Cl 16.99; N 26.85. Found: C 51.65; H 4.28; Cl 16.72; N 26.63.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-hydrazinylpyridazine (2)

To a mixture of compound 1 (10 mmol) and 3 mL of dioxane, 4 mL of hydrazine hydrate (70 %) was added. The mixture was stirred on oil bath for 10 h at 110-115 ^{o}C. After cooling, 20 mL of cold water was added, the precipitate was filtered off and dried. Brown solid; m.p. 142-145 ^{o}C; yield 1.67 g (82%); ^{1}H NMR: δ= 2.21 (s, 3H, 3-CH_3), 2.56 (s, 3H, 5-CH_3), 4.10 (brs, 2H, NH_2), 5.92 (s, 1H, CH-pyraz.), 7.15 and 7.67 (d,d, *J*=9.4 Hz, 2H, CH=CH), 7.80 (brs, 1H, NH). ^{13}C NMR: δ= 13.07, 13.49, 107.71, 115.83, 122.00, 139.73, 148.03, 150.07, 159.74. Anal. Calcd for $C_9H_{12}N_6$: C 52.93; H 5.92; N 41.15. Found: C 53.01; H 6.02; N 41.38.

Synthesis of compounds 3,4

To a mixture of compound 2 (10 mmol) and 10 mL of acetic acid, 3 drops of DMF, and then 10 mmol of pentane-2,4-dione (or 3-oxo-butyric acid ethyl es-

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ter) were added. The mixture was allowed to stand overnight at room temperature. On the next day 20-30 mL of cold water was added, the precipitate was filtered off and dried.

3,6-Bis(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (3)

Brown solid; m.p. 170-172 °C, yield 2.3 g (85%); ^{1}H NMR: δ= 2.25 (s, 6H, 2x3-CH_3), 2.77 (s, 6H, 2x5-CH_3), 6.05 (s, 2H, CH-pyraz.), 8.22 (s, 2H, CH=CH). Anal. Calcd for $C_{14}H_{16}N_6$: C 62.67; H 6.01; N 31.32. Found: C 62.77; H 6.0; N 31.55.

Ethyl 3-(2-(6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)hydrazono)butanoate (4)

Brown solid; m.p. 118-120 °C, yield 2.3 g (96%); ^{1}H NMR: δ= 1.29 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.06 (s, 3H, N=CCH_3), 2.23 (s, 3H, 3-CH_3), 2.60 (s, 3H, 5-CH_3), 3.30 (s, 2H, N=CCH_2), 4.14 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 5.95 (s, 1H, CH-pyraz.), 7.55 and 7.83 (d,d, *J*=9.6 Hz, 2H, CH=CH), 10.06 (brs, 1H, NH). Anal. Calcd for $C_{15}H_{20}N_6O_2$: C 56.95; H 6.37; N 26.56. Found: C 57.06; H 6.45; N 26.38.

1-(6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)-3-methyl-1*H*-pyrazol-5-ol (5)

To a solution of compound 4 (10 mmol) in 20 mL of water, 0.01 mol of potassium hydroxide was added. The mixture was heated at continuous stirring for 3 h. After cooling, 10 mL of cold water was added and the solution was acidified with hydrochloric acid (pH~4). The precipitate was filtered off and purified by recrystallization from DMF. White solid; m.p. 248-250°C, yield 1.6 g (60%); ^{1}H NMR: δ= 2.24 (s, 6H, 3-CH_3 and 32 -CH_3), 2.68 (s, 3H, 5-CH_3), 5.00 (s, 1H, CH-pyraz.), 6.02 (s, 1H, CH-pyraz.), 8.12 and 8.92 (d,d, *J*=9.4 Hz, 2H, CH=CH), 12.36 (brs, 1H, OH). Anal. Calcd for $C_{13}H_{14}N_6O$: C 57.77; H 5.22; N 31.09. Found: C 57.56; H 5.13; N 31.48.

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine (6)

To compound 2 (10 mmol), 15 mL of acetic acid was added, and the mixture was boiled at continuous stirring for 8 h. After cooling, 15-20 mL of cold water was added and the solution was alkalify with ammonia solution. The precipitate was filtered off, dried and purified by recrystallization from hexane. White solid; m.p. 165-167 °C, yield 1.3 g (59%); ^{1}H NMR: δ= 2.27 (s, 3H, 3-CH_3), 2.71 and 2.72 (s,s, 6H, 5-CH_3 and 3-CH_3), 6.10 (s, 1H, CH-pyraz.), 7.96 and 8.25 (d,d, *J*=9.9 Hz, 2H, CH=CH). Anal. Calcd for $C_{11}H_{12}N_6$: C 57.88; H 5.30; N 36.82. Found: C 58.02; H 5.40; N 36.69.

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-3(2H)-thione (7)

To compound 2 (10 mmol), 10 mL of ethanol and 0.015 mol of carbon bisulfide were added. The mixture was heated up to 50 ^{0}C, and the solution of potassium hydroxide (0.02 mol) in 20 mL of ethanol was added dropwise. The reaction mixture was stirred at 75-80 ^{0}C for 10 h. The solvent was evaporated, the residue was dissolved in 25-30 mL of water and acidified with hydrochloric acid (pH 4). Yellow solid; m.p. 265-267°C, yield 2.0 g (81%); ^{1}H NMR: δ= 2.23 (s, 3H, 3-CH_3), 2.80 (s, 3H, 5-CH_3), 6.10 (s, 1H, CH-pyraz.), 8.03 and 8.08 (d,d, *J*=9.9 Hz, 2H, CH=CH), 14.60 (s, 1H, NH). ^{13}C NMR: δ= 13.08, 14.61, 110.31, 118.91, 126.00, 140.14, 142.14,149.54, 150.35, 161.81. Anal. Calcd for $C_{10}H_{10}N_6S$: C 48.77; H 4.09; N 34.12; S 13.02. Found: C 49.01; H 4.18; N 33.84; S 13.24.

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-(methylthio)-[1,2,4]triazolo[4,3-*b*]pyridazine (8a)

The potassium salt of compound 7 (10 mmol) in 15 mL of DMF and 11 mmol of DMS was stirred at room temperature for 6 h and allowed to stand overnight. The reaction mixture was heated at 50-55 ^{0}C for 4-5 h till pH 7, the solvent was evaporated and the residue was processed with water, filtered off and dried. Yellow solid; m.p. 173-175 °C, yield 2.0 g (77%); ^{1}H NMR: δ= 2.26 (s, 3H, 3-CH_3), 2.72 (d, *J*=0.9 Hz, 3H, 5-CH_3), 2.81 (s, 3H, S-CH_3), 6.11 (s, 1H, CH-pyraz.), 7.98 and 8.27 (d,d, *J*=9.9 Hz, 2H, CH=CH). ^{13}C NMR: δ= 13.03, 13.18, 14.22, 110.45, 115.59, 118.87, 125.82, 141.45, 145.76, 149.59, 150.46. Anal. Calcd for $C_{11}H_{12}N_6S$: C 50.75; H 4.65; N 32.28; S 12.32. Found: C 50.82; H 4.68; N 32.41; S 12.51.

Synthesis of compounds 8b,c

To potassium salt of compound 7 (10 mmol) in 15 mL of DMF, 10 mmol of NaI, 11 mmol of 2-chloroacetamid or 11 mmol of halogenocarboxylic acid ester were added. The mixture was heated at 55-60 ^{0}C with continuous stirring for 6-8 h. The solvent was evaporated, the residue was processed with water, filtered off and dried. To remove the residual amounts of NaI, $Na_2S_2O_3$ was added and processed with a dilute solution of KOH.

2-((6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)thio)acetamide (8b)

Brown solid; m.p. 212-214 ^{0}C, yield 1.9 g (63%); ^{1}H NMR: δ= 2.26 (s, 3H, 3-CH_3), 2.75 (s, 3H, 5-CH_3), 4.00 (s, 2H, S-CH_3), 6.12 (s, 1H, CH-pyraz.), 7.00 and 7.52 (brs, 2H, NH_2), 7.98 and 8.28 (d,d, *J*=9.9 Hz, 2H, CH=CH). Anal. Calcd for $C_{12}H_{13}N_7HS$: C 47.51; H 4.31; N 32.22; S 10.57. Found: C 47.38; H 4.28; N 32.41; S 10.38.

Methyl 2-((6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)thio)acetate (8c)

Yellow solid; m.p. 192-195 ^{0}C, yield 1.6 g (50%); ^{1}H NMR: δ= 2.26 (s, 3H, 3-CH_3), 2.73 (s, 3H, 5-CH_3), 3.73 (s, 3H, OCH_3), 4.18 (s, 2H, S-CH_3), 6.13 (s, 1H, CH-pyraz.), 8.01 and 8.32 (d,d, *J*=9.9 Hz, 2H, CH=CH). MS: (M+H) 319. Anal. Calcd for $C_{13}H_{14}N_6H_2S$: C 49.05; H 4.43; N 26.40; S 10.07. Found: C 49.21; H 4.55; N 26.25; S 10.24.

Synthesis of compounds 8d,e

To a caustic potash (10 mmol) in 15 mL of DMF, compound 7 (10 mmol) was added at 0 ^{0}C. The mixture was stirred at room temperature for 1 h until the complete formation of salt, and at 0 ^{0}C 11 mmol of (2-bromo-ethoxy)-benzene or 3-chloro-pentane-2,4-dione was added. The precipitate was allowed to stand overnight at room temperature, then heated at 40-45 ^{0}C for 3-5 h. The solvent was partially evaporated and the residue was processed with water, filtered off and dried.

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-((2-phenoxyethyl)thio)-[1,2,4]triazolo[4,3-*b*]-pyridazine (8d)

Yellow solid; m.p. 124-126 ^{0}C, yield 2.1 g (58%); ^{1}H NMR: δ= 2.24 (s, 3H, 3-CH_3), 2.73 (s, 3H, 5-CH_3), 3.52 (t, *J*=6.5 Hz, 2H, SCH_2), 4.37 (t, *J*=6.5 Hz, 2H, OCH_2), 6.12 (s, 1H, CH-pyraz.), 6.83-7.24 (m, 5H, C_6H_5), 8.00 and 8.31 (d,d, *J*=9.9 Hz, 2H, CH=CH). Anal. Calcd for $C_{18}H_{18}N_6OS$: C 59.00; H 4.95; N 22.93; S 8.75. Found: C 59.18; H 4.99; N 23.14; S 8.89.

3-((6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-3-yl)thio)-pentane-2,4-dione (8e)

Yellow solid; m.p. 156-158 ^{0}C, yield 2.1 g (62%); ^{1}H NMR: δ= 2.26 (s, 3H, 3-CH_3), 2.45 (s, 6H, 2xCH_3), 2.75 (s, 3H, 5-CH_3), 6.14 (s, 1H, CH-pyraz.), 8.01 and 8.34 (d,d, 2H, *J*=9.9 Hz, CH=CH). Anal. Calcd for $C_{15}H_{16}N_6O_2S$: C 52.31; H 4.68; N 24.40; S 9.31. Found: C 52.48; H 4.75; N 24.61; S 9.14.

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazine-3(2*H*)-thione (10)

The compound 9 (10 mmol) was dissolved in 30 mL of water, 20 mmol of potassium hydroxide was added and the solution was carefully acidified with hydrochloric acid (pH 4). In 1 h the precipitate was filtered off, washed with water and dried. Yellow solid; m.p. 208-210 ^{0}C, yield 1.6 g (80%); ^{1}H NMR: δ= 2.21 (s, 3H, 3-CH_3), 2.54 (s, 3H, 5-CH_3), 5.98 (s, 1H, CH-pyraz.), 7.61 and 7.78 (d,d, *J*=9.5 Hz, 2H, CH=CH), 14.41 (s, 1H, NH). ^{13}C NMR: δ= 13.02, 13.70, 109.31, 120.59, 140.47, 142.34, 147.43, 149.49, 177.78. Anal. Calcd for $C_9H_{10}N_4S$: C 52.41; H 4.89; N 27.16; S 15.55 Found: C 52.53; H 4.99; N 27.03; S 15.67.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-(methylthio)pyridazine (11a)

To a mixture of potassium hydroxide (10 mmol) and 10 mmol of compound 10 in 25-30 mL of water, at room temperature 11 mmol of dimethylsulfate was added dropwise with continuous stirring. The reaction mixture was allowed to stand overnight, then 10-15 mL of cold water was added. The precipitate was filtered off and dried. Yellow solid; m.p. 96-98 ^{0}C, yield 1.9 g (87%); ^{1}H NMR: δ= 2.24 (s, 3H, 3-CH_3), 2.70 and 2.71 (s,s, 6H, S-CH_3 and 5-CH_3), 6.00 (s, 1H, CH-pyraz.), 7.52 and 7.93 (d,d, *J*=9.3 Hz, 2H, CH=CH). Anal. Calcd for $C_{10}H_{12}N_4S$: C

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54.52; H 5.49; N 25.43; S 14.55. Found: C 54.66; H 5.54; N 25.27; S 14.38.

2-((6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)thio)acetic acid (11b)

To potassium salt of compound 10 (10mmol) in 10-15 mL of ethanol, 10 mmol of chloro-acetic acid was added. The mixture was boiled on water bath with continuous stirring for 2 h. Ethanol was evaporated and the precipitate was washed with 15-20 mL of water, filtered off and dried. Yellow solid; m.p. 128-130 ^{0}C, yield 2.03 g (77%); ^{1}H NMR: δ= 2.23 (s, 3H, 3-CH_3), 2.69 (s, 3H, 5-CH_3), 4.06 (s, 2H, SCH_2), 6.01 (s, 1H, CH-pyraz.), 7.63 and 7.96 (d,d, *J*=9.3 Hz, 2H, CH=CH), 12.10 (brs, 1H, OH). Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C 49.99; H 4.58; N 21.20; S 12.13. Found: C 50.03; H 4.61; N 21.34; S 12.21.

Synthesis of compounds 11c-e

To compound 10 (10 mmol), 10 mmol of potassium hydroxide and 30 mL of DMF, 10 mmol of NaI and 11 mmol of 2-chloro-acetamide or 11 mmol of halogeno-carboxylic acid were added. The mixture was heated with continuous stirring at 50-55 ^{0}C for 3 h. The solvent was evaporated, the residue processed with water, filtered off and dried. To remove the residual amounts of NaI, $Na_2S_2O_3$ was added and processed with a dilute solution of KOH.

2-((6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)thio)acetamide (11c)

Yellow solid; m.p. 128-130 ^{0}C, yield 1.8 g (70%); ^{1}H NMR: δ= 2.23 (s, 3H, 3-CH_3), 2.68 (s, 3H, 5-CH_3), 3.96 (s, 2H, SCH_2), 6.01 (s, 1H, CH-pyraz.), 6.94 and 7.37 (brs, 2H, NH_2), 7.66 and 7.96 (d,d, *J*=9.3 Hz, 2H, CH=CH). ^{13}C NMR: δ= 13.07, 14.25, 109.19, 119.47, 127.57, 140.73, 149.53, 154.10, 158.40, 168.44.Anal. Calcd for $C_{11}H_{13}N_5OS$: C 50.17; H 4.98; N 26.60; S 12.18. Found: C 50.02; H 5.07; N 26.78; S 12.01.

Methyl 2-((6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)thio)acetate (11d)

Yellow solid; m.p. 139-140 ^{0}C, yield 1.9 g (70%); ^{1}H NMR: δ= 2.22 (s, 3H, 3-CH_3), 2.70 (s, 3H, 5-CH_3), 3.74 (s, 3H, OCH_3), 4.15 (s, 2H, SCH_2), 6.01 (s, 1H, CH-pyraz.), 7.63 and 7.98 (d,d, *J*=9.3 Hz, 2H, CH=CH). Anal. Calcd for $C_{12}H_{14}N_4O_2S$: C 51.78; H 5.07; N 20.13; S 11.52. Found: C 51.59; H 4.95; N 20.36; S 11.31.

Ethyl 2-((6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)thio)acetate (11e)

Yellow solid; m.p. 115-117 ^{0}C, yield 2.5 g (86%); ^{1}H NMR: δ= 1.28 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.23 (s, 3H, 3-CH_3), 2.69 (d, *J*=0.8 Hz, 3H, 5-CH_3), 4.11 (s, 2H, SCH_2), 4.17 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 6.01 (q, *J*=0.8 Hz, 1H, CH-pyraz.), 7.64 and 7.98 (d,d, *J*=9.2 Hz, 2H, CH=CH). ^{13}C NMR: δ= 13.07, 13.70, 14.29, 60.57, 109.26, 119.44, 127.37, 140.84, 149.58, 154.20, 156.87, 167.38. Anal. Calcd for $C_{13}H_{16}N_4O_2S$: C 53.41; H 5.52; N 19.16; S 10.97. Found: C 53.48; H 5.60; N 19.28; S 11.12.

3-((6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-yl)thio)pentane-2,4-dione (11f)

To potassium salt of compound 10 in 10-15 mL of DMF at 0 ^{0}C 11 mmol of 3-chloro-pentane-2,4-dione was added. The mixture was stirred at room temperature for 1 day, then the solvent was evaporated and the residue was processed with water, filtered off and dried. Brown solid; m.p. 119-120 ^{0}C, yield 2.4 g (80%); ^{1}H NMR: δ= 2.24 (s, 3H, 3-CH_3), 2.33 (s, 6H, 2xCH_3) 2.72 (s, 3H, 5-CH_3), 6.02 (q, *J*=0.8 Hz, 1H, CH-pyraz.), 7.58 and 7.98 (d,d, *J*=9.2 Hz, 2H, CH=CH), 17.4 (s, 0.8H, OH-enol). Anal. Calcd for $C_{14}H_{16}N_4O_2S$: C 55.25; H 5.30; N 18.41; S 10.53. Found: C 55.32; H 5.21; N 18.34; S 10.47.

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