Synthesis of novel 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one derivatives and their preliminary biological evaluation

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Simple and accessible pathways for the synthesis of a series of novel 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one derivatives including compounds with a combination of a pyrazolyl-pyridazine moiety with pyrimidine, 1,3,5-triazine and 1,3,4-oxadiazole rings in the same molecules were established. The tautomeric structures of 3-oxopyridazine and 5-thioxo-1,3,4-oxadiazole rings and also the position of their alkylation were shown. At preliminary screening the synthesised compounds showed pronounced plant growth stimulant activity. The most active compounds were selected for deeper studies and further field trials.

Keywords: 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one, *N*- and *O*-azinyl substituted pyridazines, heterocyclisation, [(5-alkylthio-1,3,4-oxadiazol-2-yl)methyl]pyridazines, plant growth stimulant activity

On the basis of pyrazole and pyridazine heterocycles a large number of compounds have been synthesised, which are widely used not only in medical practice, but also in agriculture for plant 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 the great interest in these heterocyclic derivatives, in the last two decades studies on the series of pyrazole and pyridazine derivatives have continued to find new compounds with fungicidal,[2–9] herbicidal[10–17] and insecticidal[5,15] activities.

Pyrazolyl-pyridazines obtained by cyclisation 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 non-fused heterocyclic system derivatives with a combination of pyrazolyl-pyridazines with azines or azoles, in particular pyrimidine, 1,3,5-triazine or 1,3,4-oxadiazole, despite the fact that on the basis of each of these heterocycles a number of pesticides and plant growth regulators have been synthesised.[1]

Pyrimidine derivatives exhibit a wide spectrum of biological activities. Some of the nucleic acids, vitamins, antibiotics (amitsetin, bleomycin), certain drugs (barbiturates, pyrimidine sulfonamides, ftorafur, orotic acid), a strong poison (tetrodotoxin) and coenzymes (uridine diphosphate glucose) contain the pyrimidine ring. As a result of continuing research on the series of substituted pyrimidines, compounds possessing antitumour,[22,23] anti-tuberculosis,[24] cardiotonic,[25] anti-HIV,[26] antibacterial[27] and antiviral (hepatitis C)[28] activities have been discovered. Some derivatives are proposed as potential antagonists of adenosine receptors[29] and protein kinase inhibitors.[30]

Pyrimidine derivatives are also used in agriculture as fungicides, insecticides and acaricides.[1]

1,3,5-Triazine-containing pesticides are widely used, mainly to control weeds and include chloro-, fluoroalkyl-, methoxy- and methylthio-substituted triazines and triazinone derivatives.[1] In the last two to three decades, a series of very active sulfonylurea herbicides, based on pyrimidine and 1,3,5-triazine, has been discovered.[1] They have high efficiency, very low application rates and low toxicity.

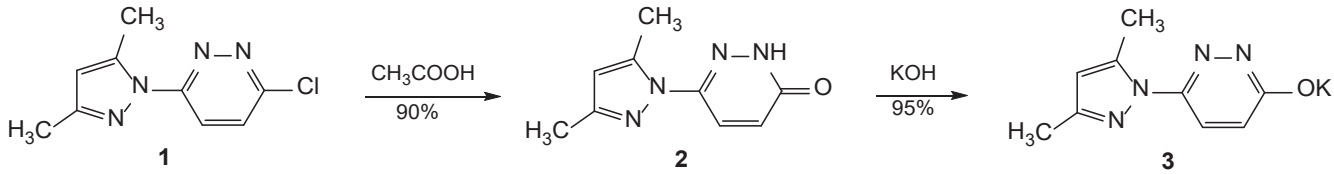
The spectrum of the pesticidal activity of 1,3,4-oxadiazole derivatives is more limited. However, in recent years, derivatives of this heterocycle have been the subject of many studies in terms of searching for new biologically active compounds.

The increase in environmental requirements, as well as the fact that harmful organisms can acquire resistance to the chemical means of plant protection, make it necessary to replenish systematically the arsenal of pesticides with new more environmentally friendly preparations having different mechanisms of action. In this regard, the targeted synthesis of new compounds with a combination of listed pharmacophore heterocycles in the same molecule could lead to new biologically active derivatives, with respect to which the above-mentioned resistance has not yet emerged.

The purpose of this work was to develop accessible and effective methods for the synthesis of novel pyrazolyl-pyridazine derivatives, as well as compounds in which the pyrazolyl-pyridazine moiety is linked with pyrimidine, 1,3,5-triazine or 1,3,4-oxadiazole rings and to study their biological activities in terms of searching for new environmentally friendly pesticides or plant growth regulators.

Results and discussion

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazin-3-ol (**2**) was synthesised by the reaction of previously obtained 3-chloro-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazine (**1**)[31] with acetic acid (Scheme 1). Compound **2** can exist in two tautomeric forms, depending on the position of the mobile hydrogen atom, and the



Scheme 1 Synthesis of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one (**2**) and its potassium salt (**3**).

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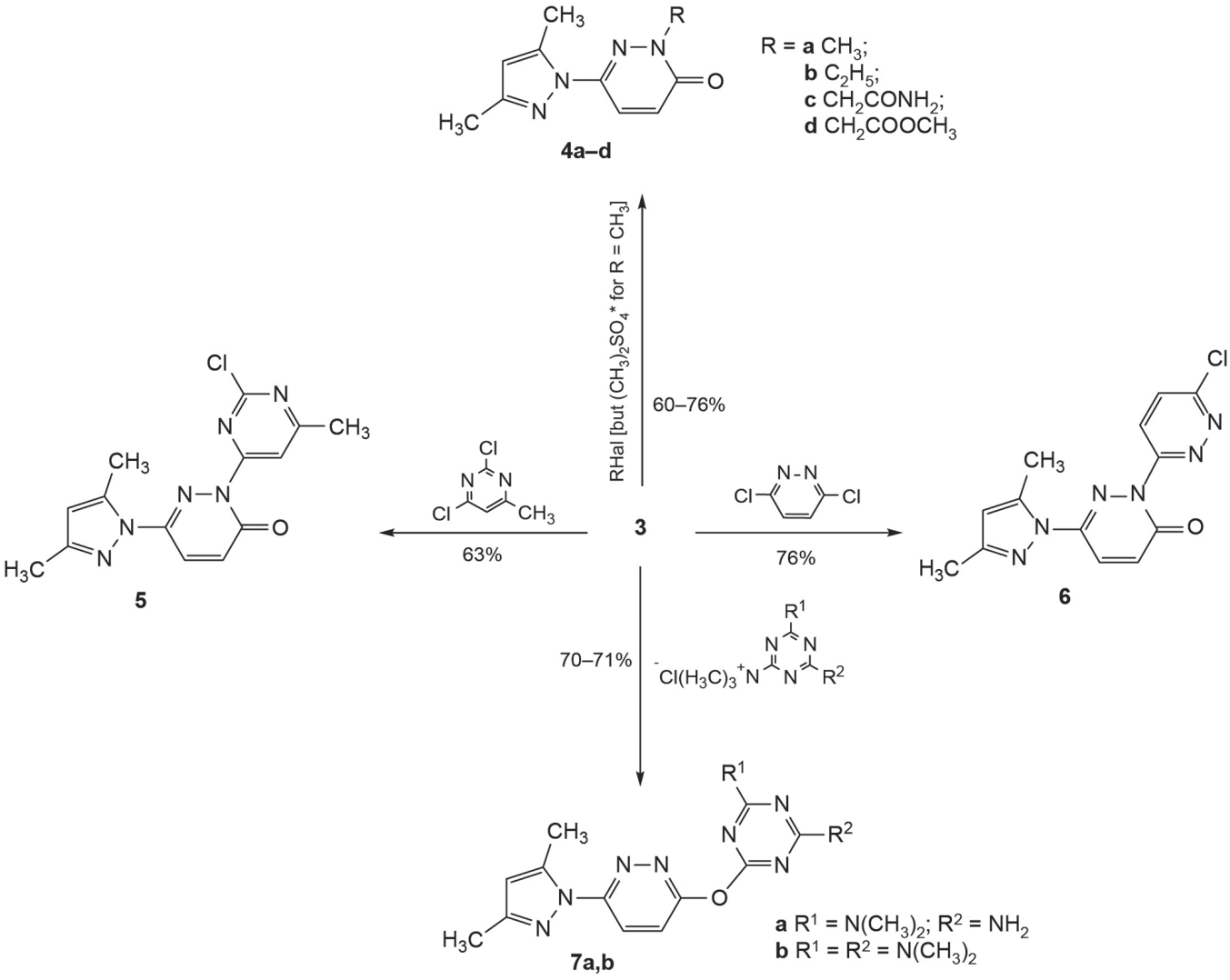
substitution reactions can occur both at the cyclic nitrogen atom, adjacent to the carbonyl group, and the oxygen atom of the OH group in the other tautomer. In the IR spectrum of tautomer **2**, an absorption at 1672 cm^{-1}, corresponding to the double C=O bond is observed, which agrees with the oxo-structure (**2**). Compound **2** was converted into the corresponding potassium salt (**3**), which was subjected to alkylation reactions (Scheme 2). In this case, an interesting regularity was discovered. It was found that the reaction with alkyl halides proceeds through the endocyclic nitrogen atom of the pyridazine ring, which leads to N-substituted products (**4a–d**). This structure is supported by the fact that in the IR spectra of compounds 4a,b the absorptions of the double C=O bond at 1668 (**4a**) and 1671 cm^{-1} (**4b**) remained and in the IR spectra of compounds **4c**,**d** the signals of two carbonyl groups at 1709–1744 and 1664–1672 cm^{-1} were observed. The reaction of the potassium salt (**3**) with 2,4-dichloro-6-methylpyrimidine and 3,6-dichloropyridazine also afforded products of N-substitution (**5**,**6**); the C=O bond absorptions (1679 and 1678 cm^{-1}) remained in their IR spectra. It should be noted that the reaction with 2,4-dichloro-6-methylpyrimidine is carried out at the chlorine atom of the fourth position of the pyrimidine ring. This was proved in our earlier work on the basis of ^{13}C NMR spectra of compounds with similar structures.[32]

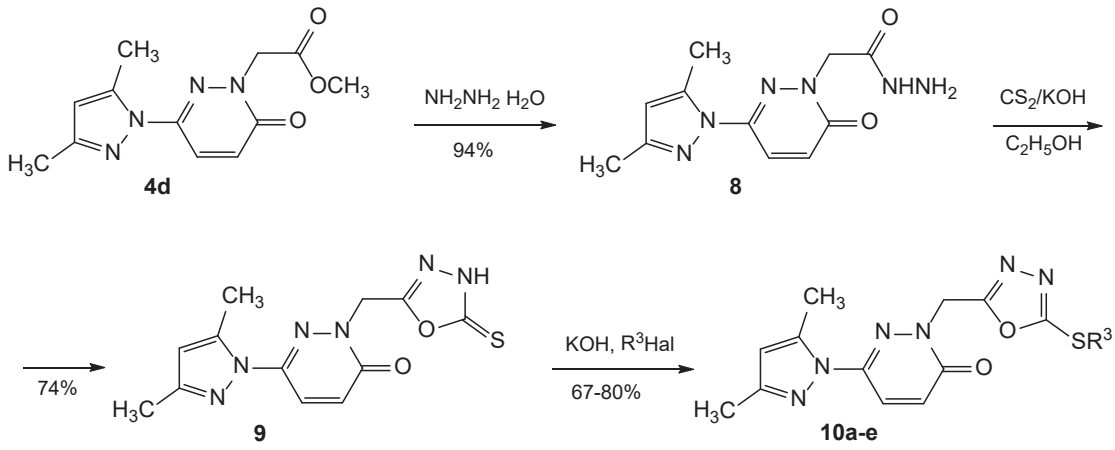
In contrast to chloro-azines, the reaction of the salt (**3**) with the quaternary ammonium salts of substituted 1,3,5-triazines occurs at the oxygen atom of the pyridazine ring to form the O-substituted products (**7a**,**b**), since in the corresponding IR spectra the absorption of the C=O bond disappears. Hindered internal rotation around the N-heterocycle bond occurs in these compounds and in ^{1}H and ^{13}C NMR spectra two signals are observed due to protons of *N*-methyl groups. This process was discussed in detail in a previous paper.[33]

To introduce the 1,3,4-oxadiazole ring into the structure, the ester (**4d**) was at first converted into the corresponding hydrazide (**8**) by reaction with hydrazine hydrate (see Safety caution on hydrazine hydrate and hydrazines in the Experimental section). The heterocyclisation of **8** with carbon disulfide and KOH in an alcohol medium led to a target product with a combination of three pharmacophore heterocyclic rings (**9**) (Scheme 3).

The 5-thioxo-1,3,4-oxadiazole ring can exist in thione and thiol tautomeric forms. In the ^{13}C NMR spectrum of compound **9** a signal corresponding to the carbon atom of the C=S double bond is observed at 178 ppm, which agrees with the thionic structure of the tautomer (**9**). At the same time, when it is alkylated with alkylating agents, the substitution proceeds through the exocyclic sulfur atom of the 1,3,4-oxadiazole ring. In the ^{13}C NMR spectra of substituted products (**10a–e**), the signal of the C=S bond carbon atom disappears and the signals corresponding to S-alkyl substituents appear in the ^{1}H and ^{13}C NMR spectra.



Scheme 2 Substitution reactions of potassium salt (**3**). *See Safety caution on dimethyl sulfate in the Experimental section



R^3 = **a** CH_3; **b** CH_2COOCH_3; **c** CH_2COOH; **d** CH_2CONH_2; **e** $CH_2CH_2OC_6H_5$

Scheme 3 Synthesis of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]pyridazin-3(2*H*)-one (**9**) and its S-substituted derivatives.

Biological properties

Preliminary screening of the synthesised compounds showed pronounced plant growth stimulant activity. The objects of study were the seeds of the common bean (*Phaseolus vulgaris* L.). The effect of aqueous suspension of compounds **2–10** and heteroauxin [(indol-3-yl)acetic acid, IAA] in concentrations of 25 and 50 mg L^{-1} on the viability of seeds, germination and seedlings was studied. The experimental data for suspensions of the synthesised compounds were compared with similar data from plants placed in IAA solutions and the activities of preparations were determined in comparison with IAA (in %). Eleven obtained compounds (**2**, **4a**, **4d**, **5**, **6**, **7a**, **7b**, **10a**, **10c**, **10d**, **10e**), which have shown activity higher than 70%, are being prepared for deeper studies and further field trials.

Experimental

IR spectra were obtained on an Avatar 330 FTIR (Thermo Nicolet) spectrometer, using the attenuated total reflectance method. ^{1}H and ^{13}C NMR spectra were recorded at 30 °C on a Varian Mercury-300 (300 and 75 MHz appropriately) spectrometer with standard pulse sequences operating in a mixture of solvents [DMSO-d_6 and CCl_4 (1:3)], using tetramethylsilane (0.0 ppm) as internal standard. The NMR multiplicities brs, 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 using TLC on "Silufol UV-254" plates and an acetone/hexane mixture (2:1) as eluent. Elemental analysis was carried out on a Eurovector EA3000 elemental CHNS-O analyser. All melting points were determined in open capillaries and are uncorrected.

*Synthesis of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(*2H*)-one (***2***)*

A mixture of 3-chloro-6-methylpyridazine (**1**) (10 mmol) and acetic acid (15 mL) was stirred at 120 °C for 4 h and the residual acetic acid was evaporated. Water (20 mL) was added to the mixture and after 0.5 h the precipitate was filtered off and dried to give: Yellow crystals; yield 1.7 g (90%); m.p. 250–252 °C; IR ν (cm^{-1}): 1672 (C=O); ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.50 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 5.93 (1H, brs, =CH), 6.91 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.89 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 12.72 (1H, brs, OH); ^{13}C NMR: δ 13.0, 13.2, 108.4, 128.7, 131.6, 139.8, 141.9, 148.6, 159.2. Anal. calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46; found: C, 56.69; H, 5.19; N, 29.22%.

*Synthesis of potassium salt of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl) pyridazin-3(*2H*)-one (***3***)*

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one (**2**) (10 mmol) was added to a solution of KOH (10 mmol) in water (40 mL). The mixture was evaporated on a hot water bath for 3–5 h until the salt formed to give: Yellow crystals; yield 2.2 g (95%); m.p. >300 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.50 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 5.93 (1H, brs, =CH), 6.90 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.88 (1H, d, *J* = 10.0 Hz, =CH pyrid.).

Synthesis of compounds **4a–d***; general procedure*

CAUTION: Appropriate precautions must be taken when using dimethyl sulfate which is carcinogenic, mutagenic and highly toxic.

Dimethyl sulfate, ethyl iodide or a chloroacetic acid derivative (11 mmol) was added to a mixture of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one potassium salt (**3**) (10 mmol) in DMF (5 mL), at 0 °C with continuous stirring; then the mixture was stirred at 60–65 °C until it reached pH 7. The precipitate was washed, filtered off and dried.

*6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-methylpyridazin-3(*2H*)-one* (**4a**): Yellow crystals; yield 1.2 g (60%); m.p. 85–87 °C; IR ν (cm^{-1}): 1668 (C=O); ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.51 3H, (d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 3.68 (3H, s, NCH_3), 5.95 (1H, brs, =CH), 6.98 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.93 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 12.9, 13.3, 39.0, 108.6, 127.7, 130.7, 139.7, 141.2, 148.6, 157.6. Anal. calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43; found: C, 58.69; H, 5.81; N, 27.60%.

*6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-ethylpyridazin-3(*2H*)-one* (**4b**): Yellow crystals; yield 1.5 g (70%); m.p. 58–60 °C; IR ν (cm^{-1}): 1671 (C=O); ^{1}H NMR: δ 1.37 (H, t, *J* = 7.2 Hz, 3$CH_3$$CH_2$N), 2.20 (3H, s, 3-$CH_3$-pyraz.), 2.51 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 4.10 (3H, q, *J* = 7.2 Hz, CH_3CH_2N), 5.96 (1H, brs, =CH), 6.97 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.92 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 12.9, 13.0, 13.4, 45.4, 108.6, 127.4, 131.0, 139.6, 141.4, 148.6, 157.2. Anal. calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67; found: C, 60.69; H, 6.57; N, 25.88%.

*2-[3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-oxopyridazin-1(*6H*)-yl] acetamide* (**4c**): Yellow crystals; yield 1.5 g (62%); m.p. 208–210 °C; IR ν (cm^{-1}): 1709, 1664 (C=O); ^{1}H NMR: δ 2.21 (3H, s, 3-CH_3-pyraz.), 2.49 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 4.59 (2H, s, NCH_2), 5.95 (1H, brs, =CH), 6.97 (1H, brs, NH), 7.01 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.40 (1H, brs, NH), 7.93 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.2, 53.2, 108.4, 128.1, 130.9, 140.2, 141.2, 148.6, 157.8, 167.3. Anal. calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32; found: C, 53.28; H, 5.14; N, 28.08%.

*Methyl 2-[3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-oxopyridazin-1(*6H*)-yl]acetate* (**4d**): Yellow crystals; yield 2.0 g (76%); m.p. 115–117 °C; IR ν (cm^{-1}): 1744, 1672 (C=O); ^{1}H NMR: δ 2.21 (3H, s, 3-CH_3-pyraz.), 2.50 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 3.75 (3H, s, OCH_3), 4.78 (2H, s, NCH_2), 5.95 (1H, brs, =CH), 7.04 (1H, d, *J* = 10.0 Hz, =CH pyrid.),

8.02 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.3, 51.9, 108.8, 128.7, 131.0, 140.1, 141.6, 148.9, 157.57, 166.8. Anal. calcd for $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36; found: C, 54.77; H, 5.30; N, 21.17%.

*Synthesis of 2-(2-chloro-6-methylpyrimidin-4-yl)-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one (***5***)*

A mixture of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one potassium salt (**3**) (10 mmol) in water (10 mL) was stirred until the salt dissolved. Then at 0 °C acetone (15 mL) and 2,4-dichloro-6-methylpyrimidine (10 mmol) were added. The mixture was stirred at 0–5 °C for 0.5 h, then at room temperature for 1 h. Later the mixture was heated at 55–60 °C for 4 h, then at 65–70 °C for 6 h. The mixture was treated with a dilute solution of potassium hydroxide to give a solid which was filtered off, washed with water and dried: White crystals; yield 2.0 g (63%); m.p. 188–190 °C; IR ν (cm^{-1}): 1679 (C=O); ^{1}H NMR: δ 2.23 (3H, s, 3-CH_3-pyraz.), 2.62 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 2.63 (3H, s, CH_3-pyrim.), 6.02 (1H, brs, =CH-pyraz.), 7.17 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.93 (1H, s, CH-pyrim.), 8.16 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.7, 23.5, 109.4, 113.3, 128.8, 132.6, 141.0, 142.5, 149.4, 157.4, 159.4, 159.5, 171.5. Anal. calcd for $C_{14}H_{13}ClN_6O$: C, 53.09; H, 4.14; Cl, 11.19; N, 26.53; found: C, 52.88; H, 4.02; Cl, 11.00; N, 26.27%.

*Preparation of 6′-chloro-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6*H*-(1,3′-bipyridazin)-6-one (***6***)*

3,6-Dichloropyridazine (10 mmol) was added to a mixture of potassium salt (**3**) (10 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 1 h then heated at 90–100 °C for 8–10 h. The solvent was evaporated off at normal pressure and the residue was washed with water, filtered off and dried to give: Yellow crystals; yield 2.3 g (76%); m.p. 233–235 °C; IR ν (cm^{-1}): 1678 (C=O); ^{1}H NMR: δ 2.24 (3H, s, 3-CH_3-pyraz.), 2.54 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 6.01 (1H, brs, =CH-pyraz.), 7.21 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.93 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.13 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.19 (1H, d, *J* = 10.0 Hz, =CH pyrid.). Anal. calcd for $C_{13}H_{11}ClN_6O$: C, 51.58; H, 3.66; Cl, 11.71; N, 27.76; found: C, 51.39; H, 3.51; Cl, 11.55; N, 27.50%.

Synthesis of compounds **7a,b***; general procedure*

The substituted 1,3,5-triazinyl-trimethyl ammonium chloride (10 mmol) was added in portions to a suspension of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyridazin-3(2*H*)-one potassium salt (**3**) (10 mmol) in anhydrous acetone (10 mL), at 0–4 °C. The mixture was stirred at room temperature for 5–6 h, then at 45–50 °C until the completion of product formation which was monitored with hydrochloric acid. The solvent was evaporated off at normal pressure and then the residue was treated with ice-cold water, filtered off and dried.

*6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-[(2-amino-4-dimethylamino-1,3,5-triazine-6-yl)oxy]-pyridazine* (**7a**): White crystals; yield 2.3 g (70%); m.p. 204–206 °C; IR ν (cm^{-1}): 1655 (NH_2); ^{1}H NMR: δ 2.25 (3H, s, 3-CH_3-pyraz.), 2.72 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 3.00 (3H, s, NCH_3), 3.11 (3H, s, NCH_3), 6.04 (1H, brs, =CH), 6.49 (1H, brs, NH), 6.67 (1H, brs, NH), 7.60 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.18 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 14.3, 35.5, 35.7, 109.3, 122.5, 124.4, 141.0, 149.6, 154.7, 160.6, 166.2, 167.7, 169.5. Anal. calcd for $C_{14}H_{17}N_9O$: C, 51.37; H, 5.23; N, 38.51; found: C, 51.58; H, 5.37; N, 38.78%.

*6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-[(2,4-bis-dimethylamino-1,3,5-triazine-6-yl)oxy]-pyridazine* (**7b**): White crystals; yield 2.5 g (71%); m.p. 166–168 °C; IR ν (cm^{-1}): no C=O; ^{1}H NMR: δ 2.25 (3H, s, 3-CH_3-pyraz.), 2.74 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 3.02 (6H, s, $N(CH_3)_2$), 3.13 (6H, s, $N(CH_3)_2$), 6.03 (1H, brs, =CH), 7.56 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.19 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 14.4, 35.2, 35.4, 35.5, 35.6, 109.3, 122.0, 124.1, 141.1, 149.5, 154.7, 160.4, 165.7, 169.1. Anal. calcd for $C_{16}H_{21}N_9O$: C, 54.07; H, 5.96; N, 35.47; found: C, 54.20; H, 5.88; N, 35.61%.

*Preparation of 2-[3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-oxopyridazin-1(6*H*)-yl]acetohydrazide (8)*

CAUTION: Appropriate precautions must be taken when using hydrazine hydrate or hydrazines due to their toxicity and possible explosive nature.

Hydrazine hydrate (10 mmol) was added slowly with continuous stirring to a mixture of compound **4d** (10 mmol) and isopropanol (5 mL), at 0 °C. The reaction mixture was stirred at room temperature for 4 h and allowed to stand overnight. The mixture was treated with water (8–10 mL) and then the precipitate was filtered off and dried to give: White crystals; yield 2.5 g (94%); m.p. 183–185 °C; IR ν (cm^{-1}): 1691, 1679 (C=O); ^{1}H NMR: δ 2.21 (3H, s, 3-CH_3-pyraz.), 2.48 (3H, d, *J* = 0.8 Hz, 5-CH_3-pyraz.), 4.05 (2H, brs, NH_2), 4.60 (2H, s, NCH_2), 5.95 (1H, brs, =CH-pyraz.), 7.00 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 7.94 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 9.25 (1H, brs, NH); ^{13}C NMR: δ 13.0, 13.3, 52.2, 108.5, 128.2, 130.9, 140.3, 141.3, 148.7, 157.8, 165.4. Anal. calcd for $C_{11}H_{14}N_6O_2$: C, 50.38; H, 5.38; N, 32.04; found: C, 50.22; H, 5.27; N, 31.80%.

*Preparation of 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]pyridazin-3(2*H*)-one (***9***)*

A mixture of compound **8** (11 mmol), KOH (11 mmol), CS_2 (20 mmol) and absolute ethanol (10 mL) was stirred at 75–80 °C for 10 h. The solvent was evaporated off at normal pressure and the residue was treated with water and filtered off. The filtrate was acidified with a concentrated solution of hydrochloric acid to pH 4. Then the precipitate was filtered off, washed with water and dried to give: White crystals; yield 2.3 g (74%); m.p. 198–200 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.43 (3H, d, *J* = 0.8 Hz, 5-CH_3-pyraz.), 5.31 (2H, s, NCH_2), 5.97 (1H, brs, =CH-pyraz.), 7.09 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.03 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 14.32 (1H, brs, NH); ^{13}C NMR: δ 13.0, 13.4, 44.6, 109.1, 128.6, 131.3, 140.4, 141.9, 149.1, 157.1, 157.7, 178.0. Anal. calcd for $C_{12}H_{12}N_6O_2S$: C, 47.36; H, 3.97; N, 27.62; found: C, 47.24; H, 3.86; N, 27.39%.

Synthesis of compounds **10a–e***; general procedure*

KOH (10 mmol) and alkyl halide or haloacetic acid derivative (11 mmol) were added to a mixture of compound **9** (10 mmol) and DMF (10 mL) while stirring. The mixture was stirred at room temperature for 1 h then at 60–65 °C for 4–6 h. The solvent was evaporated off at normal pressure and then the residue was treated with water, filtered off and dried.

*6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-[(5-methylthio-1,3,4-oxadiazol-2-yl)methyl]pyridazin-3(2H)-one* (**10a**): Yellow crystals; yield 2.4 g (77%); m.p. 118–120 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.39 (3H, d, *J* = 0.8 Hz, 5-CH_3-pyraz.), 2.72 (3H, s, SCH_3), 5.44 (2H, s, NCH_2), 5.96 (1H, brs, =CH-pyraz.); 7.10 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.04 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.3, 13.9, 44.3, 109.0, 128.5, 131.3, 140.3, 141.9, 149.1, 157.1, 161.9, 164.9. Anal. calcd for $C_{13}H_{14}N_6O_2S$: C, 49.05; H, 4.43; N, 26.40; found: C, 49.18; H, 4.51; N, 26.27%.

*Methyl 2-[(5-{[3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-oxopyridazin-1(6*H*)-yl]methyl}-1,3,4-oxadiazol-2-yl)thio]acetate* (**10b**): Yellow crystals; yield 2.8 g (75%); m.p. 90–92 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.37 (3H, d, *J* = 0.8 Hz, 5-CH_3-pyraz.), 3.73 (3H, s, OCH_3), 4.12 (2H, s, SCH_2), 5.45 (2H, s, NCH_2), 5.97 (1H, brs, =CH-pyraz.), 7.10 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.03 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.3, 33.3, 44.3, 52.1, 109.0, 128.5, 131.3, 140.4, 141.9, 149.1, 157.1, 162.2, 163.4, 166.9. Anal. calcd for $C_{15}H_{16}N_6O_4S$: C, 47.87; H, 4.28; N, 22.33; found: C, 47.71; H, 4.18; N, 22.08%.

*2-[(5-{[3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-oxopyridazin-1(6*H*)-yl]methyl}-1,3,4-oxadiazol-2-yl)thio]acetic acid* (**10c**): Yellow crystals; yield 2.5 g (68%); m.p. 110–112 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.37 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 4.03 (2H, s, SCH_2), 5.45 (2H, s, NCH_2), 5.97 (1H, brs, =CH-pyraz.), 7.10 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.03 (1H, d, *J* = 10.0 Hz, =CH pyrid.),

10.56 (1H, brs, COOH); ^{13}C NMR: δ 13.0, 13.3, 34.0, 44.4, 109.1, 128.6, 131.3, 140.4, 142.0, 149.1, 157.2, 162.1, 163.8, 167.8. Anal. calcd for $C_{14}H_{14}N_6O_4S$: C, 46.40; H, 3.89; N, 23.19; found: C, 46.21; H, 3.77; N, 23.36%.

*2-[(5-{[3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-6-oxopyridazin-1(6*H*)-yl]methyl}-1,3,4-oxadiazol-2-yl)thio]acetamide* (**10d**): White crystals; yield 2.4 g (67%); m.p. 206–208 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.38 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 3.98 (2H, s, SCH_2), 5.44 (2H, s, NCH_2), 5.97 (1H, brs, =CH-pyraz.), 7.08 and 7.55 (2H, brs, NH_2), 7.10 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.03 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.3, 35.9, 44.4, 109.0, 128.5, 131.3, 140.4, 141.9, 149.1, 157.2, 161.9, 164.4, 167.0. Anal. calcd for $C_{14}H_{15}N_7O_3S$: C, 46.53; H, 4.18; N, 27.13; found: C, 46.39; H, 4.03; N, 27.39%.

*6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-{[5-(2-phenoxyethylthio)-1,3,4-oxadiazol-2-yl]methyl}pyridazin-3(*2H*)-one* (**10e**): Brown crystals; yield 3.4 g (80%); m.p. 100–102 °C; ^{1}H NMR: δ 2.20 (3H, s, 3-CH_3-pyraz.), 2.36 (3H, d, *J* = 0.7 Hz, 5-CH_3-pyraz.), 3.63 (t, *J* = 6.1 Hz, SCH_2), 4.33 (t, *J* = 6.1 Hz, OCH_2), 5.45 (2H, s, NCH_2), 5.94 (1H, brs, =CH-pyraz.), 6.85–7.26 (5H, m, C_6H_5), 7.09 (1H, d, *J* = 10.0 Hz, =CH pyrid.), 8.03 (1H, d, *J* = 10.0 Hz, =CH pyrid.); ^{13}C NMR: δ 13.0, 13.3, 31.1, 44.3, 65.1, 109.0, 114.0, 120.4, 128.5, 128.8, 131.3, 140.3, 141.9, 149.0, 157.1, 157.6, 162.1, 154.1. Anal. calcd for $C_{20}H_{20}N_6O_3S$: C, 56.59; H, 4.75; N, 19.80; found: C, 56.39; H, 4.61; N, 19.69%.

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Electronic Supplementary Information

The ESI (^{1}H and ^{13}C NMR spectra of compounds **2–10**) is available through
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