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Synthesis and biological evaluation of 3-*O*-substituted 1-benzyl-6-oxo-1,6-dihydropyridazine derivatives

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Abstract

On the basis of 2-benzyl-6-hydroxypyridazin-3(2*H*)-one, a series of its novel *O*-substituted (including 6-(1,3,5-triazin-2-yl)oxy) derivatives is prepared. It is proven that the substitution reactions in the initial compound occur mainly at the oxygen atom of the hydroxy group. On the basis of the obtained oxy-aceto(propane)hydrazides, the corresponding azides and anilides are synthesized. A series of 2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-*N′*-(substituted benzylidene)aceto(propane)hydrazides is obtained via the reaction of various aromatic aldehydes with the same hydrazides. Heterocyclization of the latter affords compounds with a combination of pyridazine and 1,3,4-oxadiazole rings in the molecule. The reaction of oxy-acetohydrazide with potassium thiocyanate and a mixture of CS_2/KOH leads to potassium salts of 2-{[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]methyl}hydrazine-1-carbothioamide and 2-{2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetyl}hydrazine-1-carbodithioic acid, respectively. Acid hydrolysis of the latter affords 2-benzyl-6-[(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)methoxy]pyridazin-3(2*H*)-one.

Keywords

2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-*N*'-(substituted benzylidene)aceto(propane)hydrazides, 2-benzyl-6-[(1,3,5-triazin-2-yl)oxy]pyridazin-3(2*H*)-one, 2-benzyl-6-[(5-thioxo-4,5-dihydro-1,3,4-oxa(thia)diazol-2-yl)methoxy] pyridazin-3(2*H*)-ones, 2-benzyl-6-hydroxypyridazin-3(2*H*)-one, heterocyclization, oxo-oxy-tautomerism, plant growth stimulant activity

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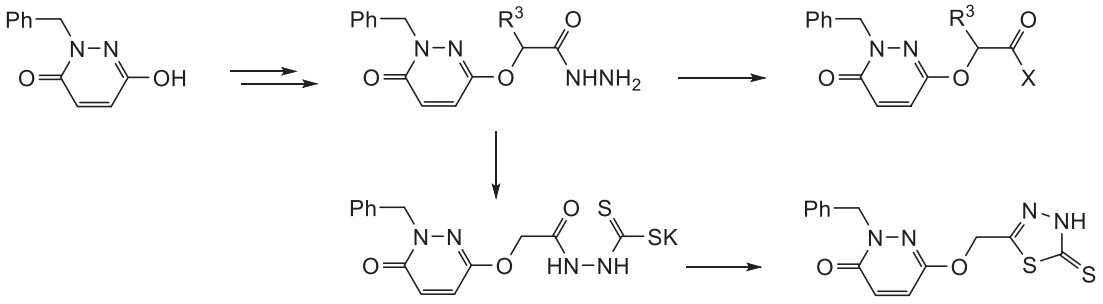

Introduction

In medical and agricultural practice, a range of medicines and plant protection chemicals created on the basis of azines and azoles are used. Pyridazine derivatives represent one of the most active classes of organic compounds possessing a broad spectrum of biological activity. Pyridazin-3-ones, a form of pyridazine with a carbonyl group, also exhibit a diverse range of pharmaceutical properties. A variety of drugs (e.g. chloridazon,

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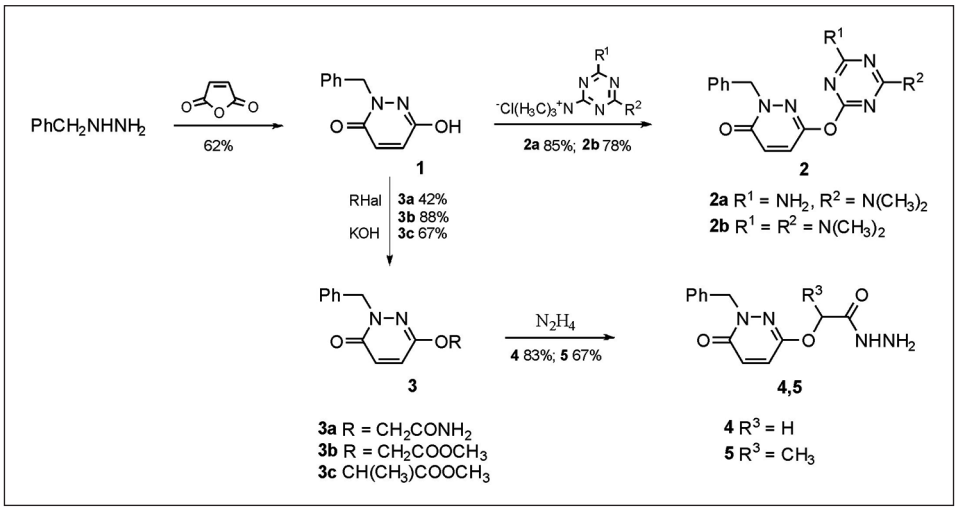


Scheme 1. Synthesis and substitution reactions of 2-benzyl-6-hydroxypyridazin-3(2*H*)-one (**1**).

emorfazone, zardaverine, pyridaphenthion, minaprine, gabazine, hydralazine, levosimendan, amipizone, indolidan, imazodan, pimobedan) are widely used in medical therapy.[1] The arsenal of pesticides based on pyridazine and pyridazinone includes mainly herbicides (credazine, pyridafol, pyridate, brompyrazon, chloridazon, dimidazon, flufenpyr, metflurazon, norflurazon, oxapyrazon, pydanon).[2] Because of the significant interest in these heterocyclic derivatives, over the last decades, studies on pyridazine derivatives have continued to lead to new compounds with fungicidal,[3–6] herbicidal,[7,8] and insecticidal[9] activities.

Among the five-membered heterocycles with three heteroatoms, one of the most applicable is 1,2,4-triazole derivatives, which are widely used in medicine, agriculture, and industry. A number of compounds synthesized on the basis of this heterocyclic ring are used in agriculture as plant protection chemicals: herbicides (amitrole, cafenstrole, epronaz, flupoxam, amicarbazone, bencarbazone, carfentrazone, flucarbazone, ipfencarbazone, propoxycarbazone, sulfentrazone, thiencarbazone, and a series of triazolopyrimidines), fungicides (amisulbrom, bitertanol, fluotrimazole, triazbutil, and a large number of conazole fungicides), and organothiophosphate insecticides (isazofos, triazophos).[2]

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

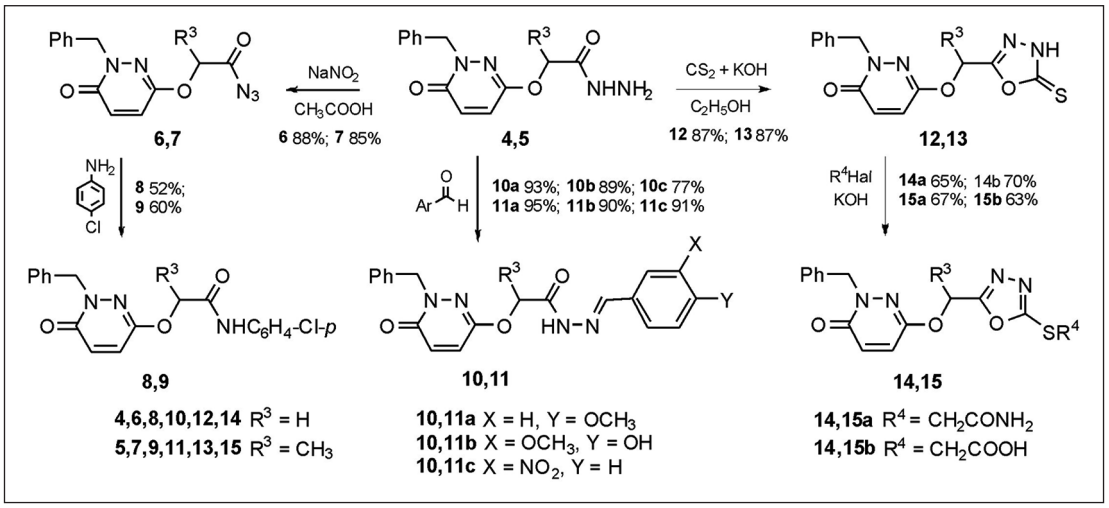
The increase of environmental requirements and the fact that harmful organisms can acquire resistance against the chemical means of plant protection make it necessary to systematically replenish the arsenal of pesticides with new and more environmentally friendly preparations having different mechanisms of action. In this regard, the targeted synthesis of new compounds with a combination of the above mentioned pharmacophore heterocycles in the same molecule could lead to new biologically active derivatives, with respect to which resistance has not yet emerged. The purpose of this study was to develop accessible and effective methods for the synthesis of novel pyridazine derivatives, as well as compounds in which the pyridazine moiety is linked with azines or azoles, and to study their biological activity in terms of searching for new environmentally friendly pesticides or plant growth regulators.

Results and discussion

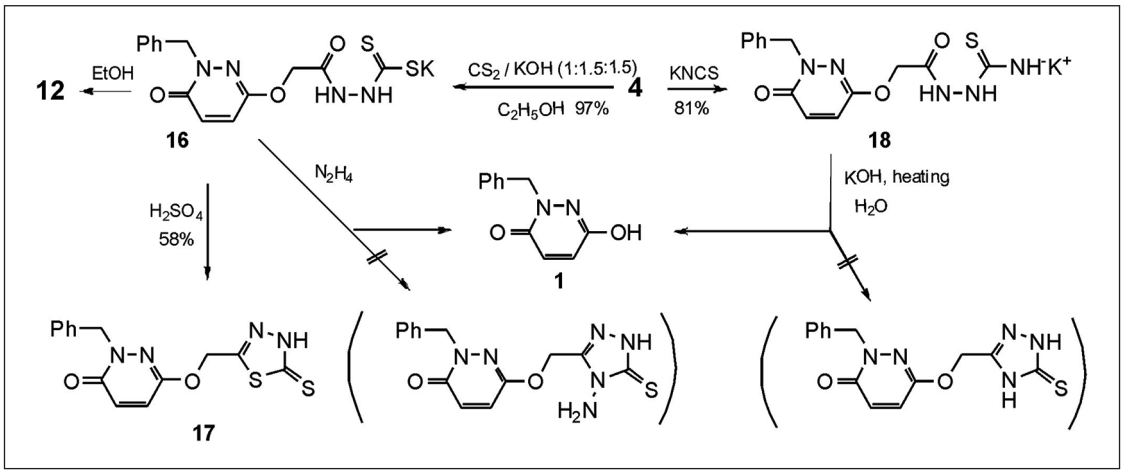
The initial 2-benzyl-6-hydroxypyridazin-3(2*H*)-one (**1**) was obtained from benzylhydrazine and maleic anhydride (Scheme 1). Compound **1** can exist in oxo and oxy tautomeric forms, and the subsequent alkylation can proceed at the oxygen atom or the nitrogen atom of the pyridazine ring. Reaction of 2-benzyl-6-hydroxypyridazin-3(2*H*)-one (**1**) with azinyl-2-yl-trimethylammonium chloride and alkyl halides formed compounds **2** and **3**, respectively. In the IR spectra of compounds **2** and **3**, just as in the case of compound **1**, only one absorption due to the carbonyl group C=O is observed, which indicates that the substitution occurs at the oxygen atom of the hydroxy form. Otherwise, absorptions from two different carbonyl groups should have been observed.

Further syntheses were carried out on the basis of hydrazides **4** and **5** which were obtained by the reaction of esters **3** with hydrazine hydrate (see "Safety warning" in the "Experimental" section).

The reactions of hydrazides **4** and **5** with sodium nitrite in acetic acid afforded 2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetyl azides **6** and **7**, which with 4-chloroaniline formed the corresponding amides **8** and **9** (Scheme 2). Reaction of the initial hydrazides with various aldehydes formed substituted benzylidene acetohydrazides **10** and **11**. The heterocyclization of the same hydrazides (**4** and **5**) under the action of carbon disulfide and an alcoholic solution of potassium hydroxide led to 2-benzyl-6-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) alkyloxy]-3(2*H*)-ones **12** and **13**. The corresponding *S*-substituted products **14** and **15** were obtained by alkylation of the latter with alkyl halides. In this case, it was proved that derivatives **12** and **13** have the thione tautomeric structure, but their alkylation proceeds at the sulfur atom. In the ^{13}C NMR spectra of compounds **12** and **13**, a



Scheme 2. Transformations based on hydrazides (**4,5**).



Scheme 3. Synthesis and transformations of potassium salts of hydrazine-1-carbodithioic acid **16** and hydrazine-1-carbothioamide **18**.

signal for the carbon atom of the exocyclic C=S double bond was observed at 177.7–177.9 ppm, and in the ^{13}C NMR spectra of compounds **14** and **15** this signal disappeared and resonances corresponding to *S*-alkyl groups were observed (Scheme 2).

In order to synthesize compounds with a combination of pyridazine ring and other azoles (1,3,4-thiadiazole or 1,2,4-triazole) in the molecule, potassium 2-{2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetyl}hydrazine-1-carbodithioate (**16**) and potassium (2-{[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]methyl}hydrazine-1-carbonothioyl)amide (**18**) were first obtained (Scheme 3).

The acid hydrolysis of compound **16** afforded the expected 2-benzyl-6-[(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)methoxy]pyridazin-3(2*H*)-one (**17**), and boiling of the same salt in ethanol led to compound **12**. At the same time, the reaction of compound **16** with hydrazine or alkaline hydrolysis of compound **18** failed to yield the target 6-[(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl) methoxy]-2-benzylpyridazin-3(2*H*)-one and 2-benzyl-6-[(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methoxy] pyridazin-3(2*H*)-one. In both reactions, the O–C bond was broken to form the initial 2-benzyl-6-hydroxypyridazin-3(2*H*)-one (**1**) (Scheme 3).

Biological properties

Preliminary screening of the pesticidal and growth regulatory activities of the novel synthesized compounds was studied. None of the preparations demonstrated any noticeable herbicidal or fungicidal properties, but they showed pronounced growth stimulation activity.

For the evaluation of growth regulatory properties, the action of aqueous emulsions (25 and 50 mg L^{-1}) of the compounds synthesized on the germination, growth, and survivability of seeds and seedlings of dicotyledonous bean (*Phaseolus vulgaris* L.) were studied and compared with that of heteroauxin (IAA). Two series of bean seeds were incubated for 24 h in appropriate mediums in the dark at 25 °C. Then, the seeds were transplanted into soil and watered daily. The experimental data calculations were produced in 20–25 days. The number of plant roots of each series, their length and weight in moist and dry forms, and their average values were calculated. The results were compared with similar data

of plants placed in IAA solutions, and the activities of preparations in comparison with IAA (in %) were determined.

Twelve of the obtained compounds **(2b**, **5**, **7**, **10a–c**, **11a–c**, **12**, **13**, **18)**, which have shown activity higher than 70%, are being prepared for more detailed studies and further field trials.

Experimental

IR spectra were obtained on an Avatar 330FT-IR (Thermo Nicolet) spectrometer, using the attenuated total reflectance (ATP) 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 *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 was checked by thin-layer chromatography (TLC) on "Silufol UV-254" plates with acetone/hexane mixture (2:1) as the eluent. Elemental analysis was carried out on a Eurovector EA3000 elemental CHNS-O analyzer. All melting points were determined in open capillaries and are uncorrected.

Synthesis of 2-Benzyl-6-hydroxypyridazin-3(2H)-one (**1**): To a mixture of benzylhydrazine (10 mmol), water (100 mL), and hydrochloric acid (10 mmol), maleic anhydride was added (10 mmol). The mixture was stirred at 110–120 °C for 6 h, cooled, and the precipitate was filtered off and dried to give product **1**. Brown crystals; yield 1.2 g (62%); m.p. 204–206 °C; IR ν (cm^{-1}): 1660 (C=O); ^{1}H NMR: δ 5.06 (2H, s, NCH_2), 6.82 (1H, d, J = 9.7 Hz, = CH pyrid.), 6.94 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.19–7.35 (5H, m, C_6H_5), 10.76 (1H, s, OH); ^{13}C NMR: δ 52.9, 126.6, 126.8, 127.6, 127.8, 132.4, 136.9, 152.2, 157.5. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.18; H, 4.79; N, 13.66.

Synthesis of compounds **2a,b***; general procedure*

To a mixture of potassium salt of compound **1** (10 mmol) in anhydrous acetone (10 mL) at 0–5 °C, substituted 1,3,5-triazinyl-trimethyl ammonium chloride (10 mmol) was added in portions. The mixture was stirred at room temperature for 5–6 h and then at 45–50 °C until the amine had been evaporated. The solvent was evaporated off at normal pressure and the residue was treated with ice-cold water and filtered off.

6-{[4-Amino-6-(dimethylamino)-1,3,5-triazin-2-yl]oxy}-2-benzylpyridazin-3(2H)-one (**2a**): White crystals; yield 2.9 g (85%); m.p. 184–186 °C; IR ν (cm^{-1}): 1663 (C=O); ^{1}H NMR: δ 2.99 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 5.14 (2H, s, NCH_2), 6.43 and 6.71 (2H, br s, NH_2), 6.92 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.20–7.38 (6H, m, = CH pyrid. and C_6H_5); ^{13}C NMR: δ 35.5, 35.7, 53.8, 127.1, 127.9, 128.0, 130.1, 130.7, 136.0, 147.6, 158.3, 166.0, 167.6, 169.3. Anal. Calcd for $C_{16}H_{17}N_7O_2$: C, 56.63; H, 5.05; N, 28.89. Found: C, 56.50; H, 5.14; N, 28.61.

2-Benzyl-6-{[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]oxy}pyridazin-3(2H)-one (**2b**): White crystals; yield 2.8 g (78%); m.p. 142–144 °C; IR ν (cm^{-1}): 1664 (C=O); ^{1}H NMR: δ 3.00 and 3.11 (12H, s, 4×NCH_3), 5.15 (2H, s, NCH_2), 6.91 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.19–7.37 (m, 6H, = CH pyrid. and C_6H_5); ^{13}C NMR: δ 35.4, 35.6, 53.8, 127.0, 127.8, 127.9, 129.8, 130.6, 136.0, 147.6, 158.1, 165.6, 169.0. Anal. Calcd for $C_{18}H_{21}N_7O_2$: C, 58.84; H, 5.76; N, 26.69. Found: C, 58.72; H, 5.67; N, 26.41.

Synthesis of compounds **3a–c***; general procedure*

To a mixture of the potassium salt of compound **1** (10 mmol) in dimethylformamide (DMF; 10 mL), NaI (10 mmol) and an appropriate alkyl halide (10 mmol) were added. The mixture was stirred at room temperature for 5 h and then allowed to stand overnight. After stirring at 65–70 °C for 5–6 h, the solvent was evaporated at normal pressure, the residue was washed with aqueous $Na_2S_2O_3$ solution, and the precipitate was filtered off and dried.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetamide (**3a**): White crystals; yield 1.1 g (42%); m.p. 157–158 °C; ^{1}H NMR: δ 4.46 (2H, s, OCH_2), 5.06 (2H, s, NCH_2), 6.87 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.13 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.13–7.37 (7H, m, NH_2 and C_6H_5); ^{13}C NMR: δ 53.4, 64.5, 126.4, 127.0, 127.8, 128.1, 132.4, 136.2, 150.7, 157.5, 168.3. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.38; H, 5.18; N, 16.50.

Methyl 2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetate (**3b**): White crystals; yield 2.4 g (88%); m.p. 90–92 °C; IR ν (cm^{-1}): 1757, 1663 (C=O). ^{1}H NMR: δ 3.62 (3H, s, OCH_3), 4.68 (2H, s, OCH_2), 5.04 (2H, s, NCH_2), 6.93 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.12 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.20–7.32 (5H, m, C_6H_5); ^{13}C NMR: δ 51.1, 53.1, 62.5, 125.6, 127.0, 127.8, 127.9, 133.0, 136.1, 150.2, 157.3, 167.1. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.22; H, 5.10; N, 10.02.

Methyl 2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]propanoate (**3c**): White crystals; yield 1.9 g (67%); m.p. 86–88 °C; ^{1}H NMR: δ 1.52 (3H, d, J = 7.0 Hz, CH_3), 3.55 (3H, s, OCH_3), 4.93 (1H, q, J = 7.0 Hz, OCH), 4.89 and 5.14 (2H, d, d, J = 13.8 Hz, NCH_2), 6.92 (1H, d, J = 9.7 Hz, = CH pyrid), 7.07 (1H, d, J = 9.7 Hz, = CH pyrid), 7.20–7.32 (5H, m, C_6H_5); ^{13}C NMR: δ 16.9, 51.2, 51.2, 53.0, 70.1, 125.6, 126.9, 127.8, 127.9, 132.9, 136.1, 150.2, 157.2, 170.2. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.31; H, 5.45; N, 9.55.

Synthesis of compounds **4**, **5***; general procedure*

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

To compound **3b** or **3c** (10 mmol) in isopropanol (10 mL), 63% hydrazine hydrate (15 mmol) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 4–5 h and allowed to stand overnight. Water

(20–25 mL) was added and the precipitate was filtered off, washed with water, and dried.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetohydrazide (**4**): White crystals; yield 2.3 g (83%); m.p. 138–140 °C; ^{1}H NMR: δ 3.94 (2H, brs, NH_2), 4.53 (2H, s, OCH_2), 5.05 (2H, s, NCH_2), 6.86 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.13 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.20–7.36 (5H, m, C_6H_5), 9.21 (1H, brs, NH); ^{13}C NMR: δ 53.3, 64.0, 126.5, 127.0, 127.8, 128.1, 132.3, 136.2, 150.6, 157.5, 165.7. Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.79; H, 5.07; N, 20.28.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]propanehydrazide (**5**): White crystals; yield 1.9 g (67%); m.p. 160–162 °C; ^{1}H NMR: δ 1.45 (3H, d, J = 6.7 Hz, CH_3), 3.88 (2H, br s, NH_2), 4.97 (1H, q, J = 6.7 Hz, OCH), 4.99 and 5.07 (2H, d, d, J = 13.8 Hz, NCH_2), 6.84 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.08 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.20–7.37 (5H, m, C_6H_5), 9.17 (1H, br s, NH); ^{13}C NMR: δ 17.6, 53.2, 71.1, 126.6, 126.9, 127.8, 128.2, 132.1, 136.3, 150.3, 157.3, 169.3. Anal. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.19; H, 5.44; N, 19.27.

Synthesis of compounds **6, 7***; general procedure*

To a mixture of compound **4** or **5** (20 mmol) in water (10 mL), $NaNO_2$ (56 mmol) was added. Then, at 0 °C, acetic acid (56 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3–4 h, washed with water, the precipitate filtered off, washed with water, and dried.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetyl azide (**6**): White crystals; yield 2.5 g (88%); m.p. 96–98 °C; ^{1}H NMR: δ 4.73 (2H, s, OCH_2), 5.05 (2H, s, NCH_2), 6.94 (1H, d, J = 9.8 Hz,= CH pyrid.), 7.13 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.22–7.31 (5H, m, C_6H_5); ^{13}C NMR: δ 53.0, 64.5, 125.4, 127.1, 127.8, 128.0, 133.2, 136.0, 149.9, 157.3, 174.2. Anal. Calcd for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.88; H, 3.96; N, 24.72.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]propanoyl azide (**7**): White crystals; yield 2.5 g (85%); m.p. 92–94 °C; ^{1}H NMR: δ 1.54 (3H, d, J = 6.9 Hz, CH_3), 4.89 (1H, q, J = 6.9 Hz, OCH), 4.85 and 5.21 (2H, d,d, J = 13.9 Hz, NCH_2), 6.96 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.07 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.20 and 7.38 (5H, m, C_6H_5); ^{13}C NMR: δ 16.7, 52.9, 71.7, 125.3, 127.1, 127.8, 128.0, 133.2, 136.0, 149.9, 157.2, 177.4. Anal. Calcd for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.02; H, 4.23; N, 23.21.

Synthesis of compounds **8, 9***; general procedure*

To compound **6** or **7** (10 mmol) in dry toluene medium, 4-chloroaniline (11 mmol) and two drops of pyridine were added. The mixture was stirred at 120 °C for 4 h, the toluene was evaporated at normal pressure, the residue was washed with hexane, and the precipitate was filtered off and dried.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N-(4-chlorophenyl)acetamide (**8**): Brown crystals; yield 1.9 g (52%); m.p. 146–148 °C; ^{1}H NMR: δ 4.70 (2H, s, OCH_2), 5.03 (2H, s, NCH_2), 6.90 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.18 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.10–7.62 (9H, C_6H_5, C_6H_4), 9.96 (1H, s, NH). Anal. Calcd for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.63; H, 4.27; N, 11.18.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N-(4-chlorophenyl)propanamide (**9**): Brown crystals; yield 2.3 g (60%); m.p. 170–172 °C; ^{1}H NMR: δ 1.56 (3H, d, J = 6.7 Hz, CH_3), 5.03 (1H, q, J = 6.7 Hz, OCH), 4.90 and 5.04 (2H, d,d, J = 13.7 Hz, NCH_2), 6.82 (1H, d, J = 9.7 Hz, = CH pyrid.), 6.93 (1H, d, J = 9.8 Hz, = CH pyrid.), 6.87–7.63 (9H, C_6H_5, C_6H_4), 9.94 (1H, s, NH). Anal. Calcd for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95. Found: C, 62.62; H, 4.62; N, 10.71.

Synthesis of compounds **10a–c, 11a–c***; general procedure*

To compounds **4** or **5** (10 mmol), water (10 mL) and HCl (36%, 1.5 mL) were added. The appropriate aldehyde (10 mmol) was added to the reaction mixture, which was stirred at 20 °C for 24 h. After the addition of water (10–15 mL), the precipitate was filtered off and dried.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N′-(4-methoxybenzylidene)acetohydrazide (**10a**): White crystals; yield 3.6 g (93%); m.p. 78–80 °C; ^{1}H NMR: δ (E/Z = 80:20%) 3.83 (3H, s, OCH_3), 4.65 (Z) and 5.13 (E) (2H, s, OCH_2), 5.02 (E) and 5.05 (Z) (2H, s, NCH_2), 6.86–7.67 (11H, m, CH=CH, C_6H_5 and C_6H_4), 7.91 (E) and 8.22 (Z) (1H, s, CH=N), 11.15 (Z) and 11.37 (E) (s, 1H, NH); ^{13}C NMR: δ 53.4, 54.7, 63.1, 113.6, 126.1, 126.5, 126.9, 127.8, 128.2, 132.5, 136.1, 143.4, 150.9, 157.5, 160.4, 162.4, 167.2. Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.40; H, 5.29; N, 14.44.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N′-(4-hydroxy-3-methoxybenzylidene)acetohydrazide (**10b**): White crystals; yield 3.6 g (89%); m.p. 135–137 °C; ^{1}H NMR: δ 3.82 (E) and 3.84 (Z) (^{3}H, s, OCH_3), 4.65 (Z) and 5.14 (E) (2H, s, OCH_2), 5.01 (E) and 5.03 (Z) (2H, s, NCH_2), 6.89 (E) (0.8H, d, J = 9.8 Hz, = CH pyrid.), 7.13 (E) (0.8H, d, J = 9.8 Hz, = CH pyrid.), 6.74–7.35 (8H, m, C_6H_5 and C_6H_3); 7.86 (E) and 8.15 (Z) (1H, s, CH=N), 8.98 (E) and 9.01 (Z) (1H, s, OH), 11.11 (Z) and 11.30 (E) (1H, s, NH); ^{13}C NMR: δ 53.4 (E), 53.5 (Z), 55.27 (E), 55.33 (Z), 63.1 (E), 64.4 (Z) 108.8 (Z), 109.2 (E), 115.0 (Z), 115.1 (E), 121.2 (E), 121.8 (Z), 125.2 (E), 125.3 (Z), 126.1 (E), 126.3 (Z), 126.97 (E), 127.02 (Z), 127.8 (E), 127.9 (Z), 128.1, 132.5, 136.1, 144.1, 147.6 (E), 147.7, 148.2, 148.8 (E), 149.0 (Z), 150.9, 157.5, 162.4 (Z), 167.1. Anal. Calcd for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.90; H, 4.99; N, 13.97.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N′-(3-nitrobenzylidene)acetohydrazide (**10c**): White crystals; yield 3.1 g (77%); m.p. 245–247 °C; ^{1}H NMR: δ (E/Z = 80:20%) 4.69 (*Z*) and 5.18 (*E*) (2H, s, OCH_2), 5.02 (*E*) and 5.05 (*Z*) (2H, s, NCH_2), 6.90 (E) (0.8H, d, J = 9.8 Hz, = CH pyrid.), 7.14 (E) (0.8H, d, J = 9.8 Hz, = CH pyrid.), 7.10–8.75 (9H, m, C_6H_5 and C_6H_4), 8.09 (1H, s, CH=N), 11.55 (Z) and 11.78 (E) (1H, s, NH). Anal. Calcd for $C_{20}H_{17}N_5O_5$: C, 58.97; H, 4.21; N, 17.19. Found: C, 58.81; H, 4.12; N, 16.91.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N′-(4-methoxybenzylidene)propanehydrazide (**11a**): White crystals; yield 3.8 g (95%); m.p. 194–196 °C; ^{1}H NMR: δ (E/Z = 75:25%) 1.54 (Z) and 1.55 (E) (3H, t, J = 6.8 Hz, CH_3), 3.84 (3H, s, OCH_3), 4.79 (E) and 5.07 (E) (1.5H, d, J = 13.5 Hz, NCH_2), 5.00 (Z) and 5.81 (E) (1H, q, J = 6.8 Hz, OCH), 6.85 (E) and 7.05 (E) (1.5H, d, J = 9.7 Hz, = CH pyrid.), 6.87 (Z) (0.25H, d, J = 9.7 Hz, = CH pyrid.), 6.87–7.66 (9H, m, C_6H_5, C_6H_4 and 0.25H, = CH pyrid.), 7.96 (E) and 8.25 (Z) (1H, s, CH=N), 11.10 (Z) and 11.26 (E) (1H, s, NH); ^{13}C NMR: δ 16.4 (E), 17.6 (Z), 53.2 (Z), 54.6 (E), 68.9 (E), 72.0 (Z), 104.5 (Z), 113.6 (E), 125.8 (E), 126.3 (Z), 126.6 (Z), 126.9 (E), 127.7, 127.8, 128.21 (Z), 128.23 (Z), 128.5 (E), 132.4, 136.0, 142.9, 147.2 (Z), 150.4 (E), 157.2 (Z), 160.3 (E), 170.7 (E). Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 65.18; H, 5.55; N, 13.91.

2-((1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)-N′-(4-hydroxy-3-methoxybenzylidene)propanehydrazide (**11b**): White crystals; yield 3.8 g (90%); m.p. 202–204 °C; ^{1}H NMR: δ (E/Z = 70:30%) 1.54 (Z) and 1.55 (E) (3H, t, J = 6.8 Hz, CH_3), 3.84 (E) and 3.88 (Z) (3H, s, OCH_3), 4.76 (E) and 5.10 (E) (1.4H, d, J = 13.5 Hz, NCH_2), 4.99 (Z) and 5.04 (Z) (0.6H, d, J = 13.5 Hz, NCH_2), 5.00 (Z) and 5.80 (E) (1H, q, J = 6.8 Hz, OCH), 6.77–7.34 (10H, m, C_6H_5, C_6H_3 and CH=CH), 7.90 (E) and 8.18 (Z) (1H, s, CH=N), 8.94 (1H, s, OH), 11.06 (*Z*) and 11.20 (*E*) (s, 1H, NH); ^{13}C NMR: δ 16.5 (E), 17.7 (Z), 53.3 (Z), 55.3 (E), 69.0 (E), 71.5 (Z), 108.8 (Z), 109.4 (E), 115.0 (Z), 115.2 (E), 121.1 (E), 122.0 (Z), 125.4 (E), 125.5 (Z), 125.9 (E), 126.4 (Z), 127.0, 127.7 (E), 127.9 (Z), 128.3 (Z), 128.6 (E), 132.5 136.1, 143.7, 147.6 (E), 147.7 (Z), 148.2, 148.8 (E), 149.0 (Z), 150.5 (Z), 150.6 (E), 157.3 (E), 157.4 (Z), 166.0 (Z), 170.7 (E). Anal. Calcd for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.41; H, 5.12; N, 13.05.

2-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]-N′-(3-nitrobenzylidene)propanehydrazide (**11c**): White crystals; yield 3.8 g (91%); m.p. 174–176 °C; ^{1}H NMR: δ (E/Z = 70:30%) 1.56 (Z) and 1.57 (E) (3H, t, J = 6.8 Hz, CH_3), 4.80 (E) and 5.07 (E) (1.4H, d, J = 13.6 Hz, NCH_2), 4.98 (Z) and 5.06 (Z) (0.6H, d, J = 13.6 Hz, NCH_2), 5.03 (Z) and 5.82 (E) (1H, q, J = 6.8 Hz, OCH), 6.87 (E) and 6.89 (*Z*) (1H, d,d, J = 9.7 Hz, = CH pyrid.), 7.06–8.50 (10H, m, C_6H_5, C_6H_4 and = CH pyrid.), 8.13 (*E*) and 8.47 (*Z*) (1H, s, CH=N), 11.55 (*Z*) and 11.67 (*E*) (1H, s, NH); ^{13}C NMR: δ 16.5 (E), 17.5 (Z), 53.2 (E), 53.8 (Z), 68.8 (E), 71.7 (Z), 120.8 (E), 121.2 (Z), 123.4 (E), 123.5 (Z), 125.8 (E), 126.2 (Z), 126.88 (Z), 126.91 (E), 127.7 (E), 127.8 (Z), 128.16 (Z), 128.24 (E), 129.4 (Z), 129.5 (E), 131.8 (E), 132.3 (Z), 132.6 (E), 135.9, 136.0, 136.3(Z), 140.7, 144.8, 148.0 (Z), 148.1 (E), 150.3 (Z), 150.4 (E), 157.26 (E), 157.31 (Z), 166.6 (Z), 171.2 (E). Anal. Calcd for $C_{21}H_{19}N_5O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 59.69; H, 4.48; N, 16.44.

Synthesis of compounds **12, 13***; general procedure*

A mixture of compound **4** or **5** (10 mmol), KOH (10 mmol), CS_2 (10 mmol), and absolute ethanol (15 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 hydrochloric acid (pH = 4), and the precipitate was filtered off, washed with water, and dried.

2-Benzyl-6-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]pyridazin-3(2H)-one (**12**): Yellow crystals; yield 2.7 g (87%); m.p. 190–192 °C; ^{1}H NMR: δ 5.04 (2H, s, NCH_2), 5.20 (2H, s, OCH_2), 6.92 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.13 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.20–7.37 (5H, m, C_6H_5), 14.18 (1H, br s, NH); ^{13}C NMR: δ 53.4, 57.5, 125.6, 127.1, 127.9, 128.1, 133.2, 135.9, 149.9, 157.3, 157.9, 177.9 (C=S). Anal. Calcd for $C_{14}H_{12}N_4O_3S$: C, 53.16; H, 3.82; N, 17.71. Found: C, 53.29; H, 3.94; N, 17.96.

2-Benzyl-6-[1-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethoxy]pyridazin-3(2H)-one (**13**): Yellow crystals; yield 2.9 g (87%); m.p. 168–170 °C; ^{1}H NMR: δ 1.68 (3H, d, J = 6.5 Hz, CH_3), 4.99 and 5.07 (2H, d,d, J = 13.8 Hz, NCH_2), 5.78 (1H, q, J = 6.5 Hz, OCH), 6.91 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.08 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.19–7.33 (5H, m, C_6H_5), 14.32 (1H, br s, NH); ^{13}C NMR: δ 17.4, 53.4, 64.8, 125.8, 127.2, 128.0, 128.2, 133.2, 135.9, 149.6, 157.3, 161.0, 177.7(C=S). Anal. Calcd for $C_{15}H_{14}N_4O_3S$: C, 54.54; H, 4.27; N, 16.96. Found: C, 54.42; H, 4.19; N, 16.71.

Synthesis of compounds **14a,b, 15a,b***; general procedure*

To a mixture of compound **12** or **13** (10 mmol) and DMF (10 mL), the halogenated carboxylic acid or its derivative (11 mmol) was added. The mixture was stirred at room temperature for 1 h and then heated at 65–70 °C for 10–12 h. The solvent was evaporated at low pressure, and the residue was washed with water, filtered off, washed with water, and dried.

2-[(5-{[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)thio]acetamide (**14a**): Yellow crystals; yield 2.4 g (65%); m.p. 122–124 °C; IR ν (cm^{-1}): 1697, 1664 (C=O). ^{1}H NMR: δ 4.00 (2H, s, SCH_2), 5.06 (2H, s, NCH_2), 5.36 (2H, s, OCH_2), 6.92 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.14 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.11 and 7.57 (2H, brs, NH_2), 7.20–7.38 (5H, m, C_6H_5); ^{13}C NMR: δ 35.9, 53.4, 57.4, 125.6, 127.1, 127.9, 128.0, 133.1, 136.0, 150.1, 157.4, 162.2, 164.5, 167.0. Anal. Calcd for $C_{16}H_{15}N_5O_4S$: C, 51.47; H, 4.05; N, 18.76. Found: C, 51.28; H, 4.12; N, 18.51.

2-[(5-{[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)thio]acetic acid (**14b**): Yellow crystals; yield 2.5 g (70%), m.p. 180–182 °C; ^{1}H NMR: δ 4.04 (2H, s, SCH_2), 5.06 (2H, s, NCH_2), 5.34 (2H, s, OCH_2), 6.92 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.13 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.21–7.34 (5H, m, C_6H_5), 12.7 (1H, br s, OH); ^{13}C NMR: δ 34.0, 53.4, 57.4, 125.6, 127.1, 127.9, 128.1, 133.2, 136.0, 150.1, 157.4, 162.3, 163.9, 167.8. Anal. Calcd for $C_{16}H_{14}N_4O_5S$: C, 51.33; H, 3.77; N, 14.97. Found: C, 51.24; H, 3.67; N, 14.73.

2-[(5-{1-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]ethyl}-1,3,4-oxadiazol-2-yl)thio]acetamide (**15a**): White crystals; yield 2.6 g (67%), m.p. 144–146 °C; ^{1}H NMR: δ 1.71 (3H, d, J = 6.5 Hz, CH_3), 3.98 (2H, s, SCH_2), 5.02 (2H, s, NCH_2), 5.94 (1H, q, J = 6.5 Hz, OCH), 6.91

(1H, d, J = 9.7 Hz, = CH pyrid.), 7.09 (d, J = 9.7 Hz, 1H, CH), 7.20–7.37 (5H, m, C_6H_5), 7.13 and 7.57 (2H, br s, NH_2); ^{13}C NMR: δ 17.8, 53.3, 64.9, 125.8, 127.1, 127.9, 128.0, 133.1, 136.0, 149.7, 157.3, 164.0, 165.3, 167.0. Anal. Calcd for $C_{17}H_{17}N_5O_4S$: C, 52.71; H, 4.42; N, 18.08. Found: C, 52.59; H, 4.31; N, 18.29.

2-[(5-{1-[(1-Benzyl-6-oxo-1,6-dihydropyridazin-3-yl) oxy]ethyl}-1,3,4-oxadiazol-2-yl)thio]acetic acid (**15b**): Oil; yield 2.4 g (63%), ^{1}H NMR: δ 1.70 (3H, d, J = 6.5 Hz, CH_3), 4.02 (2H, s, SCH_2), 5.02 (2H, s, NCH_2), 5.97 (1H, q, J = 6.5 Hz, OCH), 6.90 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.10 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.20–7.38 (5H, m, C_6H_5), 10.0 (1H, brs, OH). Anal. Calcd for $C_{17}H_{16}N_4O_5S$: C, 52.57; H, 4.15; N, 14.43. Found: C, 52.44; H, 4.09; N, 14.29.

Synthesis of potassium 2-{2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetyl}hydrazine-1-carbodithioate (**16**): To compound **4** (10 mmol) at 0–5 °C, alcoholic solution of KOH (15 mmol) was added followed by CS_2 (15 mmol). The reaction mixture was stirred at 20 °C for 24 h. The obtained precipitate (salt) was washed with 5–7 mL of ethanol and filtered off. White crystals; yield 3.8 g (97%), m.p. 218–220 °C; ^{1}H NMR: δ (D_2O) 4.82 (2H, s, NCH_2), 5.31 (2H, s, OCH_2), 7.15 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.28 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.32–7.54 (5H, m, C_6H_5); ^{13}C NMR: δ 54.3, 65.4, 127.3, 127.5, 128.3, 131.7, 135.2, 152.9, 154.6, 160.1, 163.0, 165.4. Anal. Calcd for $C_{14}H_{13}KN_4O_3S_2$: C, 43.28; H, 3.37; N, 14.42, Found: C, 43.32; H, 3.44; N, 14.60.

Synthesis of 2-benzyl-6-[(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)methoxy]pyridazin-3(2H)-one (**17**): To compound **16** (10 mmol), concentrated sulfuric acid (3 mL) was added. The mixture was stirred at 20 °C for 6 h and then carefully ice water was added. The mixture was neutralized with a 10% solution of NaOH (until pH = 7), filtered, and the precipitate was washed with water and dried. Yellow crystals; yield 1.9 g (58%), m.p. 203–205 °C, ^{1}H NMR: δ 5.10 (2H, s, NCH_2), 5.24 (2H, s, OCH_2), 6.94 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.08 (1H, d, J = 9.8 Hz, = CH pyrid.), 7.22–7.35 (5H, m, C_6H_5), 14.37 (1H, s, NH); ^{13}C NMR: δ 53.2, 62.1, 125.6, 127.2, 127.9, 128.1, 133.3, 135.9, 150.1, 156.5, 157.3, 188.8 (C=S). Anal. Calcd for $C_{14}H_{12}N_4O_2S_2$: C, 50.59; H, 3.64; N, 16.86. Found: C, 50.47; H, 3.52; N, 16.70.

Synthesis of potassium (2-{2-[(1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]acetyl}hydrazine-1-carbonothioyl) amide (**18**): To compound **4** (10 mmol), ethanol (7–8 mL), KNCS (25 mmol), and two to three drops of HCl were added. The reaction mixture was heated at 80 °C for 6 h and the obtained precipitate was filtered off and washed with ethanol. Yellow crystals; yield 2.8 g (81%), m.p. >300 °C. ^{1}H NMR: δ 4.62 (2H, s, OCH_2), 5.05 (2H, s, NCH_2), 6.90 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.18 (1H, d, J = 9.7 Hz, = CH pyrid.), 7.20–7.40 (5H, m, C_6H_5), 7.68 (1H, brs, NH), 9.10 (1H, brs, NH), 9.98 (1H, brs, NH). Anal. Calcd for $C_{14}H_{14}KN_5O_3S$: C, 45.27; H, 3.80; N, 18.85. Found: C, 45.35; H, 4.03; N, 19.42.

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Supplemental material

The ESI (^{1}H and ^{13}C NMR spectra of compounds **1-18**) is available.

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