



# Rapid synthetic approaches to libraries of diversified 1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones and 3-(2-hydroxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones

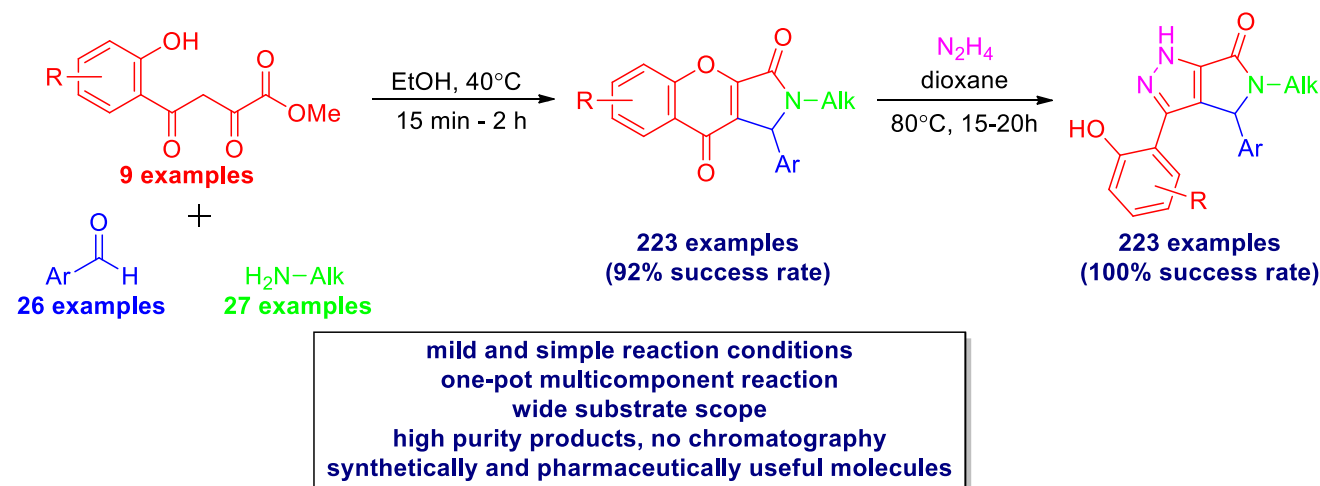
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Received: 22 March 2021 / Accepted: 12 May 2021 / Published online: 4 June 2021  
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## Abstract

An efficient and practical synthetic procedure for libraries of diversified 1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones using a multicomponent process is presented. A convenient synthetic procedure for obtaining functionalized 3-(2-hydroxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones via ring-opening strategy has also been developed. This protocol was found to be compatible with a wide range of substituents and paves the way for the practical synthesis of title compounds with a broad range of substituents under mild condition. The products can be easily isolated by crystallization without the use of chromatography.

## Graphic abstract



**Keywords** Multicomponent cyclization · Combinatorial library · Dihydrochromeno[2,3-*c*]pyrrole-3,9-diones · Dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones · Chromeno[2,3-*c*]pyrroles

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## Introduction

Synthesis of privileged classes of heterocyclic compounds has become one of the prime areas of research in the field of synthetic and medicinal chemistry, as most of the biologically active compounds are derived from heterocyclic structures [1, 2]. The diversification of heterocyclic compounds using diversity-oriented synthesis (DOS) has been proved to be an essential tool for rapid discovery of small biologically active molecules [3, 4]. Therefore, the development of a concise and efficient strategy leading to skeletal and stereochemical diversity has gained much attention in scientific communities involved in drug discovery and biomedical research [5, 6].

In turn, benzopyrans (chromones) are important privileged structural motifs and serve as useful templates for the design of compound libraries in the search for novel biologically important compounds [7–13]. To date, attention was mostly focused on the synthesis of 2(3)-substituted and 2,3-disubstituted chromones. In contrast, synthetic methodologies to access chromone-fused rings are scarce, especially those involving construction of chromone-fused heterocyclic compounds. Existing reviews summarize synthetic approaches to fused pyrazoles [14–16], chromone-pyrazole-fused compounds [17], azachromones, azachromanones [18]. A unique pyrano[2,3-*c*]pyrrole bicyclic skeleton,

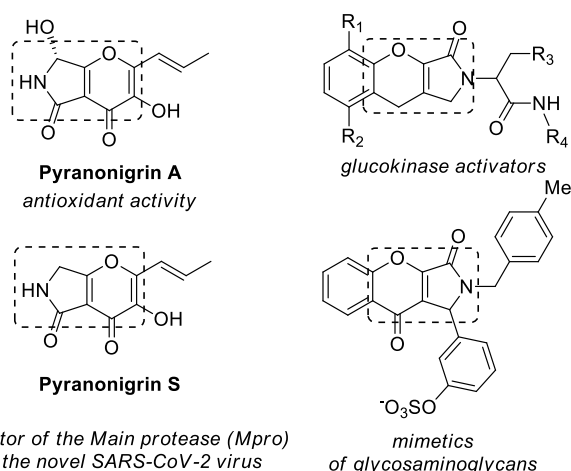
exhibiting antioxidant activity [19–23] and rarely detected in nature, was found in Pyranonigrins—secondary metabolites produced by *Aspergillus niger*. Pyranonigrin A is also a potent inhibitor of the Main protease (Mpro) of the novel SARS-CoV-2 virus [24]. Compounds such as chromeno[2,3-*c*]pyrroles were reported to behave as glucokinase activators [25] and as mimetics of glycosaminoglycans [26] (Fig. 1).

To our knowledge, the chromeno[2,3-*c*]pyrrole scaffold has been rarely mentioned in the literature. Our previous reports focused on the limited examples of the synthesis of chromeno[2,3-*c*]pyrrole derivatives via multistep condensation of methyl 4-(*o*-hydroxyphenyl)-2,4-dioxobutanoate [27–29] and methyl (*E*)-6-phenyl-2,4-dioxohex-5-enoate [30] with aromatic aldehydes and aliphatic amines or ethyl 3-bromomethyl-4-oxochromene-2-carboxylate with amines [31]. Additionally, recent papers reported the synthesis of spiro derivatives of chromeno[2,3-*c*]pyrrole-3,9-diones with *N*-substituted isatins used as the carbonyl component [32, 33]. The acid-catalyzed transformation of some furo [3,4-*b*]chromones into pyrrolo[3,4-*b*]chromones has also been reported [34–38]. The multicomponent reaction of 3-formylchromones with isocyanides and azodicarboxylates is an alternative route to the preparation of chromeno[2,3-*c*]pyrroles [39]. It should be noted that one-pot multicomponent reactions (MCRs) are some of the most efficient tools in modern synthetic organic chemistry for the preparation of highly functionalized organic compounds [40], including *N*-heterocycles [41, 42]. Moreover, they have all the features of a perfect synthetic method: high efficiency and step economy, quick and simple implementation, time and energy reductions, environmental friendliness, and suitability for target and diversity-oriented synthesis [43].

Aiming at accessing diverse privileged skeletons of chromeno[2,3-*c*]pyrrole, we performed rapid and efficient construction of target libraries of drug-like compounds—2-alkyl-1-aryl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones—from relatively simple and commercial available reagents via one-pot multicomponent heterocyclization.

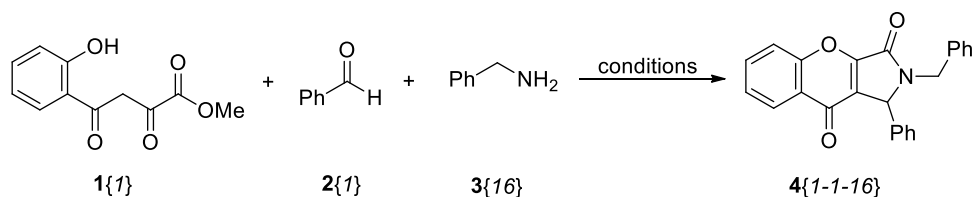
## Results and discussion

As part of our interest in the development of combinatorial chemistry, we aimed to design a previously unreported one-pot multicomponent reaction. Initially, as a model reaction,



**Fig. 1** Examples of the natural and useful pyrano[2,3-*c*]pyrroles

**Scheme 1** Investigation of one-pot three-component reaction of 4-(2-hydroxyphenyl)-2,4-dioxobutanoate **1** [1], benzaldehyde **2** [1] and benzylamine **3** [16] as a model reaction



**Table 1** Optimization of the reaction conditions on the example of compound **4**{*1-1-16*} synthesis<sup>a</sup>

Entry	Solvent	Temperature (°C)	Reaction time (h)	Yield of product (%) <sup>b</sup>
1	MeOH	r.t	1.5	24
2	MeOH	40	1	36
3	EtOH	40	1	26
4	EtOH + MeC(O)OH (1 mL)	40	0.3	74
5	<i>i</i> -PrOH	40	1	42
6	THF	40	2	17
7	acetic acid	40	2	22
8	acetic acid	120	0.5	traces

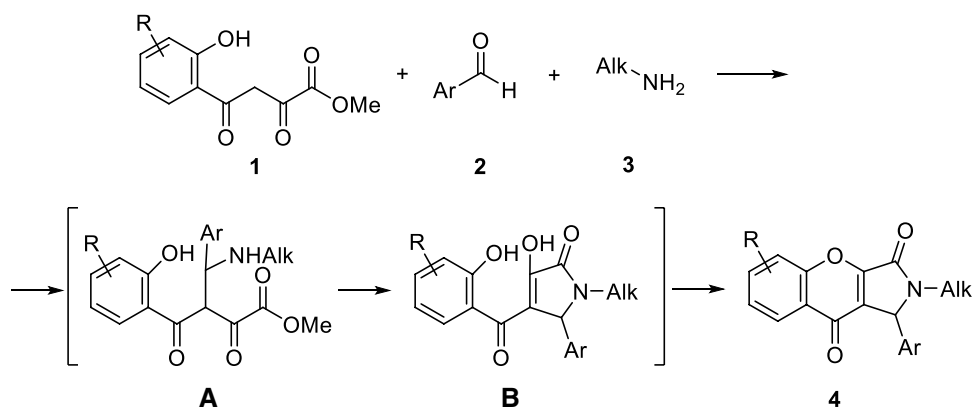
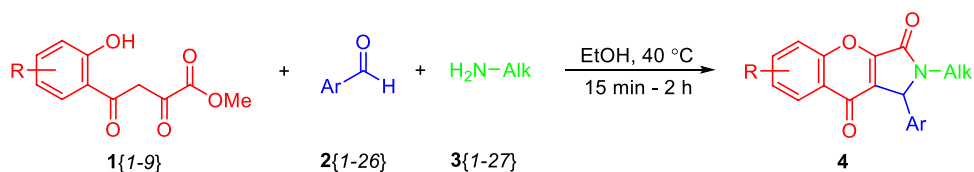
<sup>a</sup>Reaction conditions: 4-(2-hydroxyphenyl)-2,4-dioxobutanoate (1.0 eq.), benzaldehyde (1.0 eq.) and benzylamine (1.0 eq.), appropriate solvent (10 mL), r. t. or heating

<sup>b</sup>Yields of isolated compound **4**{*1-1-16*}

we assessed the three-component reaction of commercially available 4-(2-hydroxyphenyl)-2,4-dioxobutanoate **1**{*1*}, benzaldehyde **2**{*1*} and benzylamine **3**{*16*}, to survey key parameters for one-pot process (Scheme 1). We first tested the reaction of starting reagents (**1**{*1*}, **2**{*1*} and **3**{*16*}) in the presence of different solvents to optimize the reaction conditions (Table 1). Indeed, upon interaction of the starting reagents in a molar ratio of 1:1:1 in 10 mL of absolute MeOH at room temperature for 1.5 h, the reaction gave 2-benzyl-1-phenyl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione (**4**{*1-1-16*}) as the only product with a yield of 24% (Entry 1, Table 1). When the reaction was repeated

at 40 °C, the same product **4**{*1-1-16*} was obtained in the higher yield of 36% (Entry 2, Table 1). The reaction was repeated in EtOH and in EtOH with addition of 1 mL of acetic acid at 40 °C, which resulted in **4**{*1-1-16*} with yields of 26% and 74%, respectively (Entry 3 and 4, Table 1). The product **4**{*1-1-16*} also formed in low yields when using *i*-PrOH (42% yield of the product), THF (17% yield of the product) and acetic acid (22% yield of the product) at 40 °C (Entry 5–7, Table 1). It is noteworthy that in acetic acid under reflux, **4**{*1-1-16*} was obtained in trace amounts in a complex mixture of unidentified products (Entry 8, Table 1). Overall, in almost all cases the yields of the key product were not high. Thus, the best approach (primarily based on the yield of the key reaction product) was to carry out the reaction in absolute EtOH with the addition of acetic acid at 40 °C, which completed in 30 min (Entry 4, Table 1). We also noted that when the reaction was carried out under these conditions with molar ratios of the starting reagents of 1:1.2:1.2 or 1:1.5:1.5, the product **4**{*1-1-16*} formed with moderate yields (up to 36%) together with unidentified mixtures of complex products.

Based on the results of reaction optimization, we propose the following mechanism for this one-pot three-component reaction (Scheme 2). The condensation of starting compounds occurs under basic conditions and gives an adduct **A**, which is then converted into 1-alkyl-5-aryl-4-(2-hydroxybenzoyl)-3-hydroxy-2,5-dihydro-1*H*-pyrrol-2-one **B**. Subsequent dehydration of **B** results in the product **4**. The dehydration is more effective in acidic medium; addition of 1 mL of acetic acid was sufficient to increase the yield, while adding bigger amounts resulted in higher reaction temperature and resulted in noticeably smaller yields.

**Scheme 2** Mechanism of compound **4** synthesis**Scheme 3** 1-aryl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones **4** library generation

With the optimized reaction conditions in hand, we set out to explore the use of substituted methyl 4-(*o*-hydroxyphenyl)-2,4-dioxobutanoates **1**{1–9} (9 examples), aryl aldehydes **2**{1–26} (26 examples) and primary amines **3**{1–27} (27 examples) in the obtainment of a variety of 2-alkyl-1-aryl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones **4** in a one-pot multicomponent reaction (Scheme 3).

The representative substrates—methyl 4-(*o*-hydroxyphenyl)-2,4-dioxobutanoates **1**{1–9}, aryl aldehydes **2**{1–26} and primary amines **3**{1–27}—are listed in Fig. 2. First, the compatibility of different aryl aldehydes and primary amines in these multicomponent heterocyclization was examined. To our delight, a wide range of alkyl groups in the case of aryl aldehydes **2**{1–26}, including methoxy, methyl, ethyl, propyl, butyl, allyl, benzyl and halogen, were well compatible in this transformation. The electronic effects of substituents had little influence on the cyclization. Note that a small excess of amines (1.1 eq.) was used in the interaction of aldehydes with a phenolic hydroxyl group. It should be mentioned that the substituted primary amines were also suitable for the transformation and synthesis of 2-alkyl-1-aryl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones **4**. But longer heating (up to 2 h) was required when using aldehydes with donor groups and shorter heating (15–20 min) when using aldehydes with acceptor groups. Methyl 4-(*o*-hydroxyphenyl)-2,4-dioxobutanoates with methyl, chloro and fluoro substituents were also tolerated in this one-pot multicomponent procedure, demonstrating the generality of the method. As a result, 223 out of 240 experiments allowed us to obtain the target 1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones (92% success rate) with good purity (>95% according to HPLC). In most cases, yields were in the 43–86% range, and for more than 50% of the representative set, the yield was more than 70%.

Chromones are widely used as excellent matrices for performing structural modifications allowing the synthesis of a wide range of compounds with different pharmacological profiles, which is certainly interesting for drug discovery [44–48]. Thus, the incorporation of pyrazole motif into the heterocyclic systems has led to important scaffolds attracted the attention of both industrial and medicinal chemists [44]. To demonstrate further the synthetic utility of the obtained 2-alkyl-1-aryl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones **4**, we developed ring-opening strategy with hydrazine hydrate, provides a wide scope of differently substituted pyrrolopyrazolones.

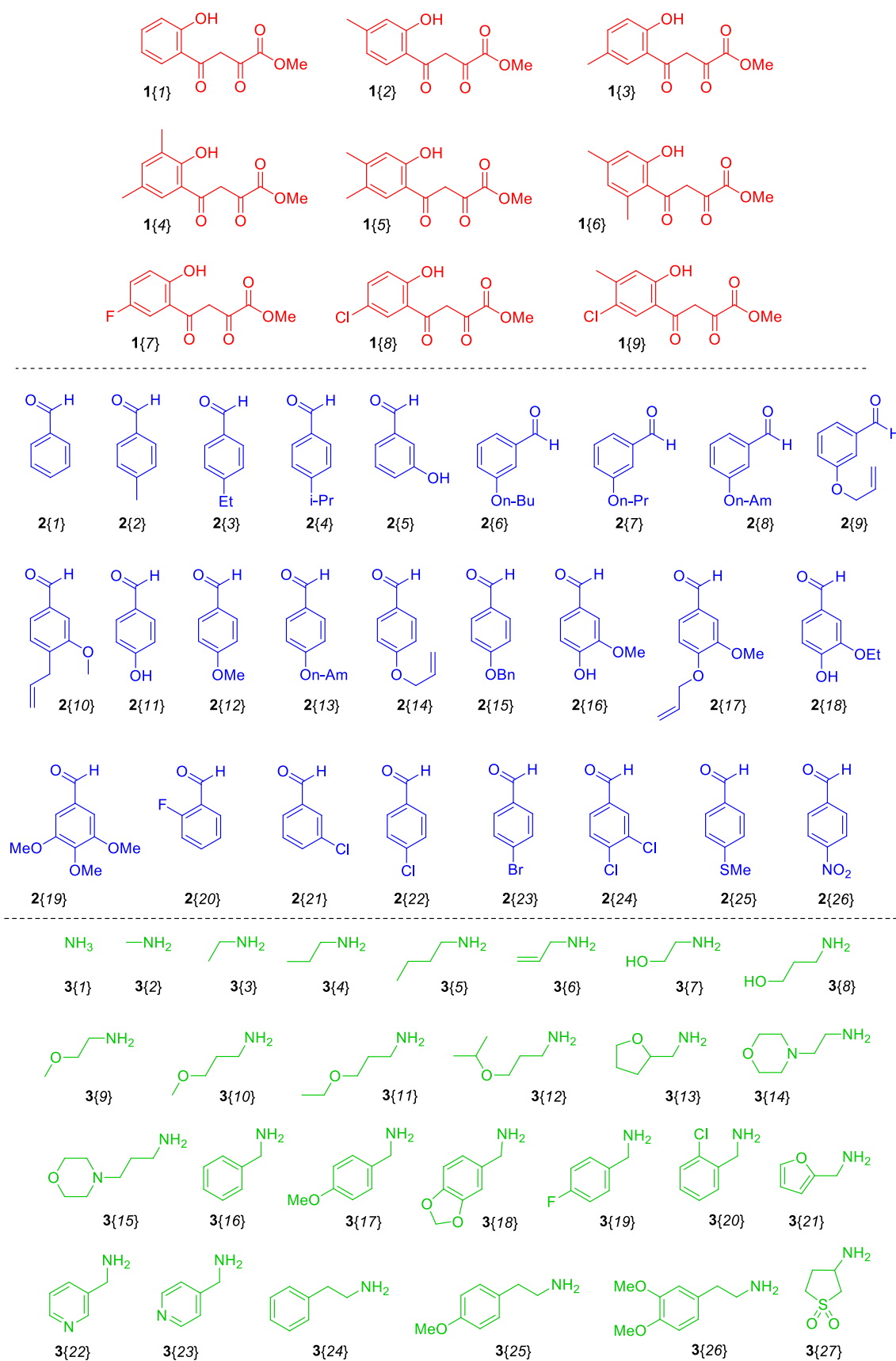
Initially, the recyclization of 2-methyl-1-phenyl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione **4**{3–1–2} with hydrazine hydrate was examined (Scheme 4). We first tested the known literature method used for the recyclization of benzopyran-4-ones with hydrazine hydrate [17]. For compound **4**{3–1–2} as a model compound, it was

found that recyclization under the action of hydrazine hydrate proceeded in EtOH at different molar ratios of the starting reagents (from 1: 1 to 1: 3); however, the yields of the target product were rather low—up to 18% when the reaction was carried out at room temperature and not exceeding 30% at 80 °C. To increase the yield of the final product, an optimization of the reaction conditions was carried out. We varied the solvent, temperature, ratio of the reagents. The results obtained from the optimization are shown in Table 2. It should be noted that the yield of the target product **5**{3–1–2} increased, and the reaction completion time decreased with an increase in the reaction temperature in both EtOH and dioxane, and with an increase in the molar ratio of the starting reagents (Entry 1–3 and 5–7). However, the reaction with the molar ratio of 1: 7 gave the product with a lower yield, and a complex mixture of unidentified products containing pyrazolecarboxylic acid hydrazide (Entry 4 and 8) was observed in the reaction mixture. Fairly efficient reaction conditions were found to be the use of the starting reagents in a molar ratio of 1: 5 in dioxane at 40 °C (Entry 7). An increase in the reaction temperature to 80 °C resulted in the lower yield (56%) of the product **5**{3–1–2} in 4–6 h (Entry 9) due to the formation of a complex mixture of unidentified products. Finally, the product **5**{3–1–2} was obtained with 78% yield when the reaction mixture was kept in dioxane at 80 °C for 20 h (Entry 10); notably, despite a noticeable amount of intermediate products being observed in the <sup>1</sup>H NMR spectra of the reaction mixture after 4 and 12 h, only one key product was detected after 20 h.

Under the optimized conditions, a series of substituted 3-(2-hydroxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (**5**) were synthesized in a 20-mL glass vial using 1:5 molar ratio of chromeno[2,3-*c*]pyrrole-3,9-diones and hydrazine hydrate in dioxane by operationally simple procedure (Scheme 5). The wide availability of 1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones makes the developed synthetic protocol a powerful tool for achieving a great variety of final products—4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones **5**.

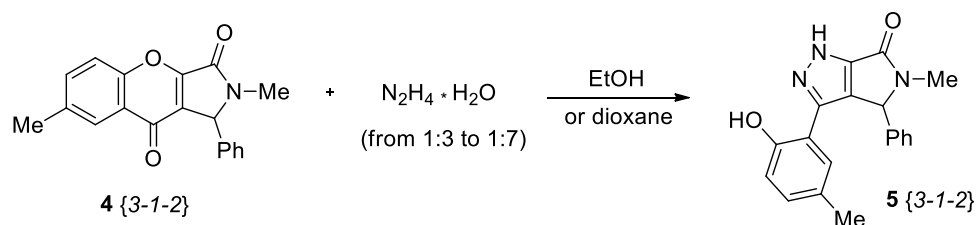
As a result, 223 experiments allowed us to obtain the target 4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones (100% success rate) and with good purity (>95% according HPLC). In most cases, yields were in the 72–94% range, and for 50% of the representative set, the yield was more than 80%.

The correlation of proton signals in <sup>1</sup>H NMR spectra of chromeno[2,3-*c*]pyrrole-3,9-diones can be in most cases performed quite easily based on signal multiplicity, but the appearance of the <sup>13</sup>C NMR spectra was less predictable. The use of two-dimensional NMR spectroscopy methods on substance **4**{3–1–2} made it possible to not only confirm the shown structure, but also to accurately identify the range of characteristic signals of the chromeno[2,3-*c*]



**Fig. 2** Scope of 4-(2-hydroxyphenyl)-2,4-dioxobutanoates **1**{1–9}, aryl aldehydes **2**{1–26} and primary amines **3**{1–27}

**Scheme 4** Investigation of recyclization of model compound (**4**{3-1-2}) with hydrazine hydrate

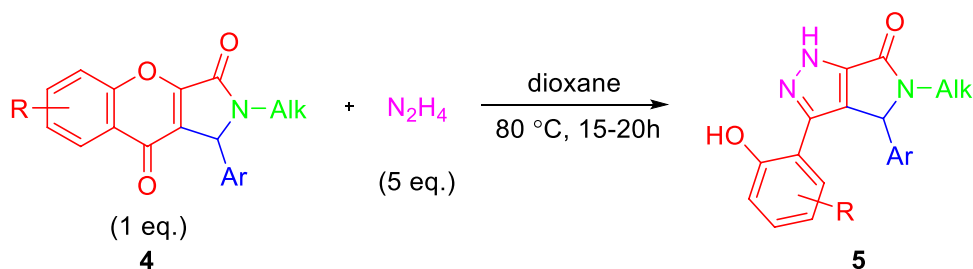


**Table 2** Optimization of the reaction conditions on the example of compound **5**{3-1-2} synthesis<sup>a</sup>

Entry	Molar ratio of reagents <b>4</b> {3-1-2}:hydrazine hydrate	Solvent	Temperature (°C)	Reaction time (h)	Yield of product (%) <sup>b</sup>
1	1:3	EtOH	r. t	6	18
2	1:3	EtOH	80	6	30
3	1:5	EtOH	80	4	42
4	1:7	EtOH	80	3	31
5	1:3	Dioxane	r. t	4	32
6	1:3	Dioxane	40	4	34
7	1:5	Dioxane	40	4	64
8	1:7	Dioxane	40	4–5	38
9	1:5	Dioxane	80	4–6	56
10	1:5	Dioxane	80	20	78

<sup>a</sup>Reaction conditions: 2-methyl-1-phenyl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione (1.0 eq.) with hydrazine hydrate (3.0 eq. or 5 eq., or 7 eq.), appropriate solvent (10 mL), heating

<sup>b</sup>Yields of isolated compound **5**{3-1-2}



**Scheme 5** 3-(2-hydroxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones **5** library generation

pyrrole-3,9-dione system in <sup>13</sup>C NMR spectra. The signal of  $\gamma$ -pyrone carbonyl group's carbon is observed in the weakest field (more than 170 ppm); the carbon signal of the pyrrolone carbonyl group is observed in the field around 160 ppm which is characteristic for amide groups. The carbon signal of the methine fragment of pyrrolone in the studied substance was slightly more than 60 ppm, although the spectra of some other derivatives, especially those with alkoxy groups, show other signals in the same region. For two-dimensional NMR experiments, CF<sub>3</sub>COOD was used because **4**{3-1-2} is significantly higher solvable in it than in DMSO-*d*<sub>6</sub>; however, a comparison with the spectra taken in DMSO-*d*<sub>6</sub> shows insignificant difference in chemical shifts. Figure 3 shows

the assignments and the most important HMBC correlations (black dotted) and NOESY correlations (red) for **4**{3-1-2}.

As expected, <sup>1</sup>H NMR spectra in DMSO-*d*<sub>6</sub> show a significant high-field shift of protons of 2-hydroxyphenyl moiety of 4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-ones (**5**) compared to protons of chromone fragment of chromeno[2,3-*c*]pyrrole-3,9-diones (**4**). With no other substituents present, signals of the corresponding protons are located at 7.5–8.1 ppm for products **4** and at 6.7–7.5 ppm for products **5**. However, <sup>13</sup>C NMR spectra in DMSO-*d*<sub>6</sub> of compounds **5** do not allow to identify carbon atoms of the pyrazole ring because of quick tautomeric transformations of pyrazole, and due to the weak intensity of the most low-field carbon atom of the pyrrolone carbonyl group, located



with chemical ionization (CI). LC–MS data were acquired on an Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diode matrix and mass-selective detector. Melting points were measured on a MPA100 OptiMelt automated melting point system.

Combustion elemental analysis was performed by hand in the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry analytical laboratory. The carbon and hydrogen contents were determined using the Pregl gravimetric method, nitrogen—using the Duma's gasometrical micromethod, sulfur—by the Scheininger titrimetric method, chlorine—by the mercurimetric method.

Experimental Section describes 25 compounds selected in random manner, which corresponds to generally accepted approaches in combinatorial chemistry (according to ACS standards).

### General procedure for the synthesis of 1-aryl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-diones 4

To a solution of 0.01–0.011 mol of aryl aldehyde **2**{*1*–*26*} in 10–15 mL of dry EtOH, 0.01–0.011 mol of primary amine **3**{*1*–*27*} was added at room temperature and mixture was stirred for 0.3 h. Then, 0.01 mol of methyl *o*-hydroxybenzoylpyruvate **1**{*1*–*9*} was added. The mixture was heated at 40 °C for 15–20 min, and 1 mL acetic acid was added. The resulting mixture was refluxed at 80 °C for 20 h; the reaction progress was monitored with TLC. After the completion of the reaction, the mixture was allowed to cool down to rt, and precipitate was filtered off (in most cases) or concentrated under vacuum and the residues were purified by crystallized from ethanol.

*2-(Pyridin-4-ylmethyl)-1-(p-tolyl)-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione (4{1-2-23})* Yield: 70%; mp 220–223 °C; IR (KBr): 2902, 1715 (C=O), 1656 (C=O), 1611, 1462, 1403, 1273, 1208, 1174, 894, 860, 822, 759, 556, 534 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.45 (d, *J*=5.8 Hz, 2H), 8.03 (d, *J*=8.3 Hz, 1H), 7.95–7.85 (m, 2H), 7.55 (ddd, *J*=8.0, 5.6, 2.6 Hz, 1H), 7.23–7.15 (m, 4H), 7.13 (d, *J*=7.9 Hz, 2H), 5.57 (s, 1H), 4.85 (d, *J*=16.4 Hz, 1H), 4.03 (d, *J*=16.4 Hz), 2H, 2.27 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 173.1, 162.2, 156.5, 155.0, 150.1, 145.8, 138.8, 135.5, 130.9, 129.9, 128.6, 128.0, 126.7, 125.7, 125.4, 122.9, 119.7, 60.2, 43.5, 21.2. APSI MS: 383.2 (M<sup>+</sup>+1). Anal. Calcd for C<sub>24</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 75.38; H, 4.74; N, 7.33%. Found: C, 75.35; H, 4.79; N, 7.39%.

*1-(4-(Allyloxy)phenyl)-2-methyl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione (4{1-14-2})* Yield: 66%; mp 202–205 °C; IR (KBr): 2919, 1711 (C=O), 1657 (C=O), 1609, 1514, 1460, 1419, 1391, 1258, 1177, 1098, 896, 831, 758, 690, 565 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.03 (d, *J*=7.9 Hz, 1H), 7.92–7.81 (m, 2H), 7.54 (t, *J*=7.1 Hz, 1H), 7.26 (d, *J*=6.8 Hz, 2H), 6.94 (d,

*J*=6.8 Hz, 2H), 6.10–5.96 (m, 1H), 5.56 (s, 1H), 5.39 (d, *J*=17.3 Hz, 1H), 5.24 (d, *J*=10.4 Hz, 1H), 4.59–4.51 (m, 2H), 2.79 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 161.5, 158.9, 156.4, 155.4, 135.3, 134.1, 129.6, 127.6, 126.6, 126.2, 125.7, 125.4, 119.7, 118.0, 115.4, 68.7, 60.9, 27.7. APSI MS: 348.2 (M<sup>+</sup>+1). Anal. Calcd for C<sub>21</sub>H<sub>17</sub>NO<sub>4</sub>: C, 72.61; H, 4.93; N, 4.03%. Found: C, 72.64; H, 4.90; N, 4.12%.

*1-(2-Fluorophenyl)-2-propyl-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione (4{1-20-4})* Yield: 67%; mp 210–215 °C; IR (KBr): 2934, 1706 (C=O), 1655 (C=O), 1610, 1489, 1408, 1288, 1225, 1173, 1106, 757, 689 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.05 (d, *J*=7.9 Hz, 1H), 7.94–7.82 (m, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 7.47–7.33 (m, 2H), 7.30–7.14 (m, 2H), 5.90 (s, 1H), 3.67–3.53 (m, 1H), 2.85 (dt, *J*=13.7, 6.7 Hz, 1H), 1.61–1.34 (m, 2H), 0.80 (t, *J*=7.4 Hz, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 172.9, 161.7, 161.4 (d, *J*=247.2 Hz), 156.4, 155.4, 135.4, 131.4 (d, *J*=8.5 Hz), 126.9, 126.7, 125.7, 125.5 (d, *J*=3.2 Hz), 125.1, 121.2 (d, *J*=11.8 Hz), 119.7, 116.3 (d, *J*=21.4 Hz), 42.6, 21.4, 11.5. APSI MS: 338.0 (M<sup>+</sup>+1). Anal. Calcd for C<sub>20</sub>H<sub>16</sub>FNO<sub>3</sub>: C, 71.21; H, 4.78; N, 4.15%. Found: C, 71.24; H, 4.75; N, 4.26%.

*1-(3,4-Dichlorophenyl)-2-(1,1-dioxidotetrahydrothiophen-3-yl)-1,2-dihydrochromeno[2,3-*c*]pyrrole-3,9-dione (4{1-24-27})* Yield: 71%; mp 200–202 °C; IR (KBr): 3558, 2951, 1717 (C=O), 1668 (C=O), 1608, 1463, 1402, 1365, 1313, 1267, 1203, 1122, 755, 570 cm<sup>-1</sup>. Two diastereomers. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.01 (d, *J*=7.7 Hz, 1H), 7.93–7.84 (m, 3H), 7.63 (dd, *J*=8.3, 5.2 Hz, 1H), 7.59–7.48 (m, 2H), 5.93 (s, 0.5H), 5.86 (s, 0.5H), 4.54–4.41 (m, 0.5H), 4.37–4.23 (m, 0.5H), 3.61 (dd, *J*=12.9, 10.6 Hz, 0.5H), 3.46–3.25 (m, 2H with H<sub>2</sub>O), 3.19–3.04 (m, 1.5H), 2.77–2.63 (m, 0.5H), 2.36–2.18 (m, 1H), 2.13–2.01 (m, 0.5H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 177.7, 177.7, 167.2, 167.1, 161.1, 161.1, 159.8, 159.5, 140.9, 140.6, 140.3, 136.7, 136.7, 136.6, 136.5, 136.1, 136.1, 135.8, 135.7, 133.8, 133.6, 132.0, 131.8, 131.5, 131.4, 130.4, 130.0, 124.4, 64.3, 63.5, 56.3, 56.3, 56.2, 55.3, 55.0, 31.7, 31.5. APSI MS: 463.8 (M<sup>+</sup>+1). Anal. Calcd for C<sub>21</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>3</sub>S: C, 54.32; H, 3.26; Cl, 15.27; N, 3.02; S, 6.90%. Found: C, 54.34; H, 3.29; Cl, 15.36; N, 3.13; S, 6.98%.

*2,7-Dimethyl-1-phenyl-1H-chromeno[2,3-*c*]pyrrole-3,9-dione (4{3-1-2})* Yield: 76%; mp 242–244 °C; IR (KBr): 2921, 1710 (C=O), 1651 (C=O), 1614, 1477, 1422, 1386, 1276, 1255, 1212, 1137, 1096, 835, 703 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CF<sub>3</sub>COOD) δ 8.13 (s, 1H), 7.84 (br. d, *J*=8.3 Hz, 1H), 7.73 (d, *J*=8.6 Hz, 1H), 7.53–7.41 (m, 3H), 7.33 (d, *J*=5.9 Hz, 2H), 5.73 (s, 1H), 3.15 (s, 3H), 2.56 (s, 3H). <sup>13</sup>C NMR (125 MHz, CF<sub>3</sub>COOD, APT): 175.9 (C), 163.4 (C), 155.3 (C), 155.0 (C), 138.3 (C), 137.4 (CH), 129.7 (CH), 129.5 (C), 128.9 (CH), 126.9 (CH), 126.6 (C), 124.4 (CH), 123.2 (C), 117.9 (CH), 63.8 (CH), 26.8 (CH<sub>3</sub>), 18.8 (CH<sub>3</sub>).



APSI MS: 306 ( $M^+ + 1$ ). Anal. Calcd for  $C_{19}H_{17}NO_3$ : C, 74.74; H, 4.95; N, 4.59%. Found: C, 74.84; H, 5.03; N, 4.53%.

*2-Allyl-1-(4-ethylphenyl)-7-methyl-1,2-dihydrochromeno[2,3-c]pyrrole-3,9-dione (4{3-3-6})* Yield: 43%; mp 235–237 °C; IR (KBr): 2965, 1709 (C=O), 1652 (C=O), 1615, 1477, 1408, 1279, 1211, 1138, 836  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.81 (s, 1H), 7.74–7.63 (m, 2H), 7.20 (s, 4H), 5.80–5.66 (m, 1H), 5.57 (s, 1H), 5.16–5.03 (m, 1H), 4.30 (dd,  $J = 15.7, 3.3$  Hz, 1H), 3.41 (dd,  $J = 15.4, 6.0$  Hz, 1H), 2.61 (q,  $J = 7.5$  Hz, 2H), 2.42 (s, 3H), 1.18 (t,  $J = 7.5$  Hz, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  173.0, 161.4, 154.9, 154.6, 144.7, 136.3, 132.9, 131.4, 128.6, 128.4, 127.6, 125.0, 124.9, 119.3, 118.2, 59.5, 43.0, 28.3, 20.8, 15.8. APSI MS: 360.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{23}H_{21}NO_3$ : C, 76.86; H, 5.89; N, 3.90%. Found: C, 76.89; H, 5.86; N, 3.96%.

*2-(2-Hydroxyethyl)-5,7-dimethyl-1-(3,4,5-trimethoxyphenyl)-1,2-dihydrochromeno[2,3-c]pyrrole-3,9-dione (4{4-19-7})* Yield: 52%; mp 195–197 °C; IR (KBr): 3371, 2936, 1711, 1593, 1505, 1462, 1422, 1355, 1256, 1231, 1122, 1073, 1000, 823, 766, 705, 569  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.63 (s, 1H), 7.55 (s, 1H), 6.67 (s, 2H), 5.67 (s, 1H), 4.86 (br. s, 1H), 3.81–3.68 (m, 7H), 3.65 (s, 3H), 3.57–3.44 (m, 2H), 2.92–2.81 (m, 1H), 2.49 (s, 3H), 2.37 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  173.2, 161.9, 155.0, 153.5, 153.1, 137.9, 137.0, 135.5, 130.1, 128.3, 126.9, 125.0, 122.7, 105.8, 60.7, 60.4, 58.9, 56.5, 43.2, 20.8, 15.6. APSI MS: 440.1 ( $M^+ + 1$ ). Anal. Calcd for  $C_{24}H_{25}NO_7$ : C, 65.59; H, 5.73; N, 3.19%. Found: C, 65.56; H, 5.76; N, 3.27%.

*1-(4-(Allyloxy)-3-methoxyphenyl)-2-(2-methoxyethyl)-6,7-dimethyl-1,2-dihydrochromeno[2,3-c]pyrrole-3,9-dione (4{5-17-9})* Yield: 55%; mp 166–169 °C; IR (KBr): 2924, 1712 (C=O), 1659 (C=O), 1622, 1517, 1465, 1426, 1262, 1230, 1143, 1013  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.71 (br. s, 1H), 7.59 (br. s, 1H), 6.92 (d,  $J = 7.3$  Hz, 1H), 6.88 (s, 1H), 6.09–5.95 (m, 1H), 5.63 (s, 1H), 5.38 (d,  $J = 16.9$  Hz, 1H), 5.24 (d,  $J = 9.8$  Hz, 1H), 4.54 (s, 2H), 3.84 (d,  $J = 13.5$  Hz, 1H), 3.69 (s, 3H), 3.40 (m, in  $H_2O$ ), 3.21 (s), 2.91 (d,  $J = 14.0$  Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  172.8, 161.7, 154.8, 154.6, 149.6, 148.3, 145.5, 135.6, 134.2, 127.5, 126.7, 125.1, 123.1, 121.1, 119.3, 118.0, 113.7, 111.8, 69.6, 69.3, 60.2, 58.4, 56.1, 20.3, 19.3. APSI MS: 450.2 ( $M^+ + 1$ ). Anal. Calcd for  $C_{26}H_{27}NO_6$ : C, 69.47; H, 6.05; N, 3.12%. Found: C, 69.45; H, 6.07; N, 3.25%.

*7-Fluoro-2-(4-methoxyphenethyl)-1-(3-propoxyphenyl)-1,2-dihydrochromeno[2,3-c]pyrrole-3,9-dione (4{7-7-25})* Yield: 58%; mp 170–172 °C; IR (KBr): 2911, 1713 (C=O), 1656 (C=O), 1620, 1517, 1477, 1401, 1252, 1134  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.96 (dd,  $J = 9.2, 4.2$  Hz, 1H), 7.81–7.73 (m, 1H), 7.70 (dd,  $J = 8.3, 3.0$  Hz, 1H), 7.27

(t,  $J = 7.8$  Hz, 1H), 7.06 (d,  $J = 8.5$  Hz, 2H), 6.94–6.84 (m, 3H), 6.82 (d,  $J = 8.5$  Hz, 2H), 5.54 (s, 1H), 3.94–3.80 (m, 3H), 3.71 (s, 3H), 3.03–2.90 (m, 1H), 2.86–2.75 (m, 1H), 2.68–2.58 (m, 1H), 1.71 (dt,  $J = 13.9, 6.9$  Hz, 2H), 0.96 (t,  $J = 7.4$  Hz, 1H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  172.3, 160.7, 160.27 (d,  $J = 213.6$  Hz), 158.7, 158.3, 155.7, 152.8, 135.7, 130.7, 130.3, 130.01, 126.6 (d,  $J = 7.0$  Hz), 126.5, 123.2 (d,  $J = 23.6$  Hz), 122.4 (d,  $J = 8.2$  Hz), 120.4, 115.1, 114.6, 114.3, 110.5 (d,  $J = 20.9$  Hz), 69.4, 59.8, 55.4, 42.4, 22.5, 10.8. APSI MS: 488.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{29}H_{26}FNO_5$ : C, 71.45; H, 5.38; N, 2.87%. Found: C, 71.47; H, 5.40; N, 2.94%.

*7-Chloro-1-(4-hydroxyphenyl)-2-phenethyl-1,2-dihydrochromeno[2,3-c]pyrrole-3,9-dione (4{8-11-24})* Yield: 72%; mp > 295 °C; IR (KBr): 3386, 1701 (C=O), 1647 (C=O), 1605, 1517, 1451, 1417, 1253, 1225, 1171, 1113, 840, 696  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.53 (s, 1H), 7.95–7.89 (m, 3H), 7.27 (t,  $J = 7.3$  Hz, 2H), 7.20 (t,  $J = 6.8$  Hz, 1H), 7.13 (dd,  $J = 13.5, 7.9$  Hz, 4H), 6.75 (d,  $J = 8.4$  Hz, 2H), 5.46 (s, 1H), 3.90–3.78 (m, 1H), 3.03–2.92 (m, 1H), 2.91–2.80 (m, 1H), 2.72–2.60 (m, 1H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  171.9, 160.9, 158.3, 155.4, 155.0, 138.8, 135.1, 131.0, 129.7, 129.0, 128.9, 127.5, 126.9, 126.5, 124.65, 123.7, 122.2, 116.0, 59.5, 42.0, 34.1. APSI MS: 432.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{25}H_{18}ClNO_4$ : C, 69.53; H, 4.20; Cl, 8.21; N, 3.24%. Found: C, 69.51; H, 4.23; Cl, 8.29; N, 3.28%.

*7-Chloro-2-(furan-2-ylmethyl)-1-(3-hydroxyphenyl)-6-methyl-1,2-dihydrochromeno[2,3-c]pyrrole-3,9-dione (4{9-5-21})* Yield: 62%; mp 276–279 °C; IR (KBr): 3330, 1694, 1659 (C=O), 1615, 1487, 1428, 1268, 1208, 1146, 691  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.51 (br. s, 1H), 7.94 (s, 1H), 7.90 (s, 1H), 7.59 (s, 1H), 7.16 (t,  $J = 7.8$  Hz, 1H), 6.74 (m, 2H), 6.68 (m, 1H), 6.39 (dd,  $J = 3.0, 1.9$  Hz, 1H), 6.25 (d,  $J = 3.0$  Hz, 1H), 5.38 (s, 1H), 4.92 (d,  $J = 15.9$  Hz, 1H), 3.90 (d,  $J = 15.9$  Hz, 1H), 2.48 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  171.8, 161.1, 158.1, 154.8, 154.7, 149.6, 144.0, 143.5, 134.9, 131.9, 130.3, 127.6, 124.8, 124.5, 121.8, 118.9, 116.3, 115.1, 111.0, 109.2, 59.8, 37.1, 20.6. APSI MS: 422.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{23}H_{16}ClNO_5$ : C, 65.49; H, 3.82; Cl, 8.40; N, 3.32%. Found: C, 65.45; H, 3.80; Cl, 8.48; N, 3.40%.

### General procedure for the synthesis of 3-(2-hydroxyphenyl)-4,5-dihydropyrrolo-[3,4-c]pyrazol-6(1H)-ones 5

Solution of 0.01 mol of chromeno[2,3-c]pyrrole-3,9-dione 4 and 0.05 mol of hydrazine hydrate in dry dioxane (10 mL) in a 20-mL glass vial was stirred at 80 °C for 15–20 h. After the completion of the reaction (reaction progress was monitored with TLC), the reaction mixture was allowed to cool down to

rt, diluted with distil H<sub>2</sub>O (5 mL); the precipitate was filtered off and recrystallized from ethanol (5–7 mL).

\*The exact position of the C=O and pyrazole signals cannot be established for certain compounds due to their low intensity.

*3-(2-Hydroxyphenyl)-5-methyl-4-phenyl-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{1-1-2})* Yield: 94%; mp > 290 °C; IR (KBr): 3261–2414 (OH, NH), 1674, 1543, 1454, 1401, 1248, 826, 744, 695, 636 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.33–7.20 (m, 4H), 7.16 (d, *J* = 7.1 Hz, 2H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 5.68 (s, 1H), 2.73 (s, 3H); OH and NH exchanged with H<sub>2</sub>O. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 162.6, 154.7, 150.3, 137.6, 134.5, 130.0, 129.2, 128.8, 128.1, 126.7, 119.5, 116.6, 115.7, 62.2, 27.9. APSI MS: 306.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 70.81; H, 4.95; N, 13.76%. Found: C, 70.80; H, 4.92; N, 13.81%.

*3-(2-Hydroxyphenyl)-5-(3-isopropoxypropyl)-4-(p-tolyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{1-2-12})* Yield: 75%; mp 198–200 °C; IR (KBr): 3468–2535 (OH, NH), 1678, 1543, 1464, 1260, 1129, 1090, 820, 760, 700, 638 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.35 (br. s, 1H), 10.40 (br. s, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.13–7.01 (m, 5H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 5.75 (s, 1H), 3.65 (dt, *J* = 14.4, 7.4 Hz, 1H), 3.50–3.39 (m, 1H), 3.30 (t, *J* = 6.0 Hz, 2H), 2.73–2.66 (m, 1H), 2.21 (s, 3H), 1.77–1.53 (m, 2H), 1.02 (dd, *J* = 5.9, 3.0 Hz, 6H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 137.9, 130.9, 129.8, 128.8, 128.1, 119.5, 116.5, 71.0, 65.3, 60.1, 38.1, 28.8, 22.5, 21.2; \*. APSI MS: 406.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>: C, 71.09; H, 6.71; N, 10.36%. Found: C, 71.05; H, 6.73; N, 10.40%.

*3-(2-Hydroxyphenyl)-4-(3-(pentyloxy)phenyl)-5-propyl-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{1-8-4})* Yield: 83%; mp 242–244 °C; IR (KBr): 3339–2720 (OH, NH), 1689, 1583, 1533, 1462, 1427, 1284, 1231, 1091, 1011, 965, 818, 741, 700, 639 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.40 (br. s, 1H), 10.40 (br. s, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.76–6.67 (m, 3H), 5.74 (s, 1H), 3.91–3.77 (m, 2H), 3.63–3.50 (m, 1H), 2.71–2.59 (m, 1H), 1.69–1.58 (m, 2H), 1.56–1.46 (m, 1H), 1.46–1.37 (m, 1H), 1.37–1.24 (m, 4H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 162.8, 159.2, 154.5, 130.3, 130.0, 128.9, 126.6, 119.8, 119.4, 116.4, 114.4, 114.3, 67.8, 59.9, 42.2, 28.7, 28.1, 22.3, 21.5, 14.3, 11.7. APSI MS: 420.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>: C, 71.57; H, 6.97; N, 10.02%. Found: C, 71.55; H, 6.96; N, 10.13%.

*5-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(2-hydroxyphenyl)-4-(4-hydroxyphenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{1-11-18})* Yield: 90%; mp 280–282 °C; IR

(KBr): 3532–2545 (OH, NH), 1664, 1600, 1515, 1473, 1337, 1246, 1209, 1086, 1039, 1000, 926, 841, 804, 740, 670, 564 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.44 (br. s, 1H), 10.32 (br. s, 1H), 9.47 (br. s, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.10–7.06 (m, 1H), 6.87–6.83 (m, 4H), 6.69–6.62 (m, 5H), 5.99 (d, *J* = 6.0 Hz, 2H), 5.42 (s, 1H), 4.86 (d, *J* = 15.2 Hz, 1H), 3.54 (d, *J* = 15.6 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 157.7, 147.9, 146.8, 131.8, 130.0, 129.4, 128.8, 121.4, 119.5, 116.4, 115.9, 108.7, 108.5, 101.4, 59.5, 43.6. APSI MS: 442.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>25</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>: C, 68.02; H, 4.34; N, 9.52%. Found: C, 68.00; H, 4.36; N, 9.60%.

*4-(4-(Benzyloxy)phenyl)-3-(2-hydroxyphenyl)-5-(3-methoxypropyl)-4,5-dihydro-pyrrolo[3,4-c]pyrazol-6(1H)-one (5{1-15-10})* Yield: 72%; mp 173–175 °C; IR (KBr): 3296–2621 (OH, NH), 1668, 1515, 1462, 1250, 1109, 744, 691, 636 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.40 (br. s, 1H), 10.40 (br. s, 1H), 7.46–7.28 (m, 5H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.16–7.06 (m, 3H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 7.3 Hz, 1H), 5.74 (s, 1H), 5.01 (s, 2H), 3.68–3.55 (m, 1H), 3.31–3.23 (m, 2H), 3.18 (s, 3H), 2.79–2.66 (m, 1H), 1.80–1.67 (m, 1H), 1.67–1.54 (m, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 158.7, 137.3, 130.0, 129.5, 128.9, 128.3, 119.5, 116.5, 115.4, 70.0, 69.7, 59.9, 58.3, 38.0, 28.4. APSI MS: 470.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>28</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>: C, 71.62; H, 5.80; N, 8.95%. Found: C, 71.63; H, 5.83; N, 8.99%.

*4-(4-Hydroxy-3-methoxyphenyl)-3-(2-hydroxyphenyl)-5-propyl-4,5-dihydropyrrolo-[3,4-c]pyrazol-6(1H)-one (5{1-16-4})* Yield: 78%; mp 243–245 °C; IR (KBr): 3496–2797 (OH, NH), 1677, 1600, 1515, 1467, 1391, 1258, 1220, 1128, 1183, 1037, 741, 718 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.17 (d, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.76 (s, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.62 (m, 2H), 5.65 (s, 1H), 3.64 (s, 3H), 3.61–3.49 (m, 1H), 2.76–2.64 (m, 1H), 1.57–1.33 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H); OH and NH exchanged with H<sub>2</sub>O. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 162.3, 156.4, 149.0, 148.1, 146.9, 137.5, 129.4, 128.6, 128.2, 127.0, 120.6, 118.5, 116.8, 116.3, 116.1, 112.2, 59.9, 56.1, 42.1, 21.6, 11.7. APSI MS: 380.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: C, 66.48; H, 5.58; N, 11.08%. Found: C, 66.50; H, 5.55; N, 11.12%.

*3-(2-Hydroxyphenyl)-5-(pyridin-4-ylmethyl)-4-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{1-19-23})* Yield: 81%; mp 280–282 °C; IR (KBr): 3451 (OH), 2940, 1689 (C=O), 1658 (C=O), 1596, 1467, 1425, 1263, 1249, 1201, 1129, 1006, 712 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.45 (d, *J* = 5.9 Hz, 2H), 7.30 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.17–7.08 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 6.38 (s, 2H), 5.62 (s, 1H), 4.85 (d, *J* = 16.4 Hz, 1H), 4.15 (d, *J* = 16.4 Hz, 1H), 3.59 (s, 6H), 3.55 (s, 3H); OH and NH exchanged with H<sub>2</sub>O. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 154.7, 153.4, 150.1,

147.1, 137.5, 130.2, 129.1, 122.9, 119.5, 116.3, 105.2, 61.1, 60.3, 56.2, 43.9. APSI MS: 473.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{26}H_{24}N_4O_5$ : C, 66.09; H, 5.12; N, 11.86%. Found: C, 66.06; H, 5.10; N, 11.92%.

4-(4-Chlorophenyl)-5-(1,1-dioxidotetrahydrothiophen-3-yl)-3-(2-hydroxyphenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{1–22–27}) Yield: 75%; mp 240–242 °C; IR (KBr): 3471–2631 (OH, NH), 1671, 1624, 1587, 1544, 1491, 1462, 1412, 1317, 1239, 1127, 1093, 833, 741, 683, 570, 521  $cm^{-1}$ . Two diastereomers.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.57 (br. s, 1H), 10.38 (br. s, 1H), 7.37–7.31 (m, 2H), 7.31–7.21 (m, 3H), 7.12 (t,  $J=7.5$  Hz, 1H), 6.89 (dd,  $J=7.9$ , 3.4 Hz, 1H), 6.75 (td,  $J=7.5$  Hz, 3.2 Hz, 1H), 5.96 (s, 0.5H), 5.92 (s, 0.5H), 4.37–4.25 (m, 0.5H), 4.25–4.16 (m, 0.5H), 3.63–3.52 (m, 0.5H), 3.41 (dd,  $J=12.7$ , 8.1 Hz, 0.5H), 3.34–3.23 (m, 1.5H), 3.13–3.00 (m, 1H), 2.89 (dd,  $J=12.8$ , 8.1 Hz, 0.5H), 2.69–2.53 (m, 0.5H), 2.35 (td,  $J=10.6$ , 7.8 Hz, 0.5H), 2.29–2.19 (m, 0.5H), 1.97–1.86 (m, 0.5H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )\*:  $\delta$  154.6, 133.3, 133.2, 130.3, 130.1, 129.2, 128.7, 128.5, 119.5, 116.4, 61.0, 60.4, 51.8, 51.7, 51.7, 51.2, 50.7, 50.5, 26.9. APSI MS: 444.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{21}H_{18}ClN_3O_4S$ : C, 56.82; H, 4.09; Cl, 7.99; N, 9.47; S, 7.22%. Found: C, 56.80; H, 4.05; Cl, 7.90; N, 9.57; S, 7.28%.

5-(Furan-2-ylmethyl)-3-(2-hydroxyphenyl)-4-(4-methylthio)phenyl)-4,5-dihydro-pyrrolo[3,4-c]pyrazol-6(1H)-one (5{1–25–21}) Yield: 73%; mp 242–244 °C; IR (KBr): 3339–2720 (OH, NH), 1689, 1619, 1583, 1533, 1494, 1462, 1427, 1372, 1231, 1091, 833, 818, 742, 700  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.50 (br. s, 1H), 10.50 (br. s, 1H), 7.60 (s, 1H), 7.30 (d,  $J=7.7$  Hz, 1H), 7.15 (d,  $J=8.1$  Hz, 2H), 7.10 (t,  $J=7.3$  Hz, 1H), 7.04 (d,  $J=7.9$  Hz, 2H), 6.84 (d,  $J=8.1$  Hz, 1H), 6.73 (t,  $J=7.3$  Hz, 1H), 6.41 (s, 1H), 6.24 (d,  $J=2.5$  Hz, 1H), 5.53 (s, 1H), 4.94 (d,  $J=16.0$  Hz, 1H), 3.67 (d,  $J=16.0$  Hz, 1H), 2.41 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )\*:  $\delta$  154.8, 150.9, 143.3, 138.7, 130.2, 128.8, 128.7, 126.3, 119.6, 116.4, 111.0, 108.7, 60.0, 36.9, 14.7. APSI MS: 418.2 ( $M^+ + 1$ ). Anal. Calcd for  $C_{23}H_{19}N_3O_3S$ : C, 66.17; H, 4.59; N, 10.07; S, 7.68%. Found: C, 66.15; H, 4.56; N, 10.17; S, 7.78%.

3-(2-Hydroxy-5-methylphenyl)-5-methyl-4-phenyl-1,4-dihydropyrrolo[3,4-c]pyrazol-6-one (5{3–1–2}) Yield: 85%; mp 275–278 °C; IR (KBr): 3619–2817 (OH, NH), 1649, 1487, 1458, 1383, 1264, 1085, 805, 710  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.35 (t,  $J=7.4$  Hz, 2H), 7.30 (t,  $J=7.0$  Hz, 2H), 7.22 (d,  $J=7.2$  Hz, 2H), 6.96 (br. s, 1H), 6.92 (br. d,  $J=8.2$  Hz, 1H), 6.80 (d,  $J=8.2$  Hz, 1H), 5.70 (s, 1H), 2.76 (s, 3H), 2.08 (s, 3H), OH and NH exchanged with  $H_2O$ .  $^1H$  NMR (400 MHz,  $CF_3COOD$ )  $\delta$  8.84 (br. s, 1H), 8.67–8.66 (m, 1H), 8.52–8.50 (m, 1H), 8.30–8.24 (m, 2H), 7.21 (s, 1H), 4.43 (s, 3H), 3.37 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ , APT)\*: 162.3 (C), 152.5 (C), 137.7 (C), 130.4 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH),

128.0 (C), 116.3 (CH), 115.3 (C), 62.1 (CH), 27.9 ( $CH_3$ ), 20.3 ( $CH_3$ ).  $^{13}C$  NMR (100 MHz,  $CF_3COOD$ ):  $\delta$  159.4, 153.4, 144.2, 142.9, 136.5, 133.4, 132.1, 131.3, 131.2, 131.1, 129.1, 129.0, 117.6, 110.2, 66.2, 29.2, 19.2. APSI MS: 320.4 ( $M^+ + 1$ ). Anal. Calcd for  $C_{19}H_{17}N_3O_2$ : C, 71.5; H, 5.4; N, 13.2%. Found: C, 71.3; H, 5.6; N, 13.4%.

3-(2-Hydroxy-5-methylphenyl)-4-(3-hydroxyphenyl)-5-(3-isopropoxypropyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{3–5–12}) Yield: 78%; mp 232–235 °C; IR (KBr): 3517–2484 (OH, NH), 1686, 1604, 1499, 1458, 1375, 1257, 1223, 1038, 1093, 826, 758, 686  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.27 (br. s, 1H), 10.21 (br. s, 1H), 9.40 (br. s, 1H), 7.13 (t,  $J=7.5$  Hz, 1H), 6.96 (s, 1H), 6.90 (d,  $J=8.3$  Hz, 1H), 6.83–6.71 (m, 2H), 6.66 (d,  $J=7.6$  Hz, 1H), 6.50 (s, 1H), 5.71 (s, 1H), 3.74–3.60 (m, 1H), 3.50–3.41 (m, 1H), 3.34–3.24 (m, 2H), 2.79–2.67 (m, 1H), 2.07 (s, 3H), 1.79–1.57 (m, 2H), 1.11–0.98 (m, 6H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )\*:  $\delta$  158.1, 130.3, 130.1, 129.3, 128.0, 119.3, 116.2, 115.8, 114.3, 71.0, 65.3, 60.0, 38.2, 28.8, 22.4, 20.2. APSI MS: 422.2 ( $M^+ + 1$ ). Anal. Calcd for  $C_{24}H_{27}N_3O_4$ : C, 68.39; H, 6.46; N, 9.97%. Found: C, 68.36; H, 6.54; N, 9.90%.

4-(3-(Allyloxy)phenyl)-3-(2-hydroxy-5-methylphenyl)-5-(2-hydroxyethyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{3–9–7}) Yield: 72%; mp 229–231 °C; IR (KBr): 3431–2627 (OH, NH), 1663, 1583, 1489, 1460, 1274, 1079, 1041, 806, 766  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.32 (br. s, 1H), 10.19 (br. s, 1H), 7.21 (t,  $J=8.0$  Hz, 1H), 6.99 (s, 1H), 6.91 (d,  $J=8.0$  Hz, 1H), 6.88–6.75 (m, 3H), 6.71 (br. d,  $J=6.0$  Hz, 1H), 5.98 (ddd,  $J=22.3$ , 10.5, 5.3 Hz, 1H), 5.84 (s, 1H), 5.33 (d,  $J=17.3$  Hz, 1H), 5.21 (d,  $J=10.7$  Hz, 1H), 4.82 (br. t,  $J=4.6$  Hz, 1H), 4.54–4.39 (m, 2H), 3.78–3.66 (m, 1H), 3.53 (td,  $J=10.8$ , 5.2 Hz, 1H), 3.44 (td,  $J=10.8$ , 5.6 Hz, 1H), 2.76–2.63 (m, 1H), 2.08 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )\*:  $\delta$  158.7, 152.4, 133.9, 130.4, 130.3, 129.2, 127.9, 120.2, 117.9, 116.2, 115.0, 114.5, 68.6, 60.8, 59.4, 43.2, 20.2. APSI MS: 406.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{23}H_{23}N_3O_4$ : C, 68.13; H, 5.72; N, 10.36%. Found: C, 68.15; H, 5.75; N, 10.31%.

3-(2-Hydroxy-3,5-dimethylphenyl)-5-(2-hydroxyethyl)-4-(4-methoxyphenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{4–12–7}) Yield: 81%; mp 192–194 °C; IR (KBr): 3428–2749 (OH, NH), 1661, 1511, 1483, 1391, 1241, 1174, 1063, 831, 784, 744, 696  $cm^{-1}$ .  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  14.20 (br. s, 1H), 10.65 (br. s, 1H), 7.20 (br. d,  $J=6.4$  Hz, 2H), 6.90 (d,  $J=8.1$  Hz, 2H), 6.80 (s, 1H), 6.74 (s, 1H), 5.89 (s, 1H), 4.83 (br. s, 1H), 3.78–3.60 (m, 4H), 3.60–3.49 (m, 1H), 3.49–3.39 (m, 1H), 2.74–2.62 (m, 1H), 2.13 (s, 3H), 2.02 (s, 3H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )\*:  $\delta$  159.8, 131.6, 129.9, 126.7, 114.7, 60.2, 59.4, 55.6, 43.2, 20.2, 16.5. APSI MS: 394.0 ( $M^+ + 1$ ). Anal. Calcd for  $C_{22}H_{23}N_3O_4$ : C, 67.16; H, 5.89; N, 10.68%. Found: C, 67.14; H, 5.86; N, 10.73%.

5-(2-Chlorobenzyl)-4-(3-ethoxy-4-hydroxyphenyl)-3-(2-hydroxy-3,5-dimethyl-phenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{4-18-20}) Yield: 84%; mp 247–249 °C; IR (KBr): 3571–2597 (OH, NH), 1689, 1610, 1515, 1443, 1276, 1237, 1210, 1120, 1039, 825, 750, 617 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.47–7.39 (m, 1H), 7.35–7.24 (m, 2H), 7.18 (dd, *J* = 5.4, 3.9 Hz, 1H), 6.80 (d, *J* = 3.9 Hz, 2H), 6.74 (s, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 5.58 (s, 1H), 4.91 (d, *J* = 16.3 Hz, 1H), 4.01 (d, *J* = 16.2 Hz, 1H), 3.86 (q, *J* = 6.9 Hz, 2H), 2.12 (s, 3H), 2.00 (s, 3H), 1.24 (t, *J* = 6.9 Hz, 3H), OH and NH exchanged with H<sub>2</sub>O. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)\*: δ 154.5, 151.0, 147.4, 147.1, 134.8, 132.5, 131.7, 129.8, 129.5, 127.8, 126.9, 125.2, 120.8, 116.2, 115.6, 114.0, 64.3, 60.4, 42.1, 20.2, 16.6, 15.0. APSI MS: 504.0 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>28</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>4</sub>: C, 66.73; H, 5.20; Cl, 7.03; N, 8.34%. Found: C, 66.71; H, 5.23; Cl, 7.13; N, 8.41%.

4-(4-Bromophenyl)-3-(2-hydroxy-3,5-dimethylphenyl)-5-(pyridin-3-ylmethyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{4-23-22}) Yield: 81%; mp 241–244 °C; IR (KBr): 3367–2426 (OH, NH), 1699, 1559, 1481, 1435, 1253, 1072, 1011, 835, 751, 712, 636 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.47 (d, *J* = 4.3 Hz, 1H), 8.36 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.33 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.17 (br. s, 2H), 6.83–6.74 (m, 2H), 5.77 (br. s, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 3.91 (d, *J* = 16.0 Hz, 1H), 2.11 (s, 3H), 2.02 (s, 3H), OH and NH exchanged with H<sub>2</sub>O. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)\*: δ 149.5, 149.0, 136.0, 133.3, 132.2, 130.8, 126.4, 124.1, 59.6, 42.2, 20.2. APSI MS: 489.0 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>25</sub>H<sub>21</sub>BrN<sub>4</sub>O<sub>2</sub>: C, 61.36; H, 4.33; N, 11.45%. Found: C, 61.33; H, 4.30; N, 11.49%.

5-(4-Fluorobenzyl)-3-(2-hydroxy-4,5-dimethylphenyl)-4-(4-(methylthio)phenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{5-25-19}) Yield: 81%; mp 210–213 °C; IR (KBr): 3466–2483 (OH, NH), 1678, 1510, 1464, 1227, 1092, 1070, 825 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.25 (br. s, 1H), 9.88 (br. s, 1H), 7.28–6.99 (m, 8H), 6.93 (s, 1H), 6.63 (s, 1H), 5.50 (br. s, 1H), 4.91 (d, *J* = 15.2 Hz, 1H), 3.73 (br. d, *J* = 14.4 Hz, 1H), 2.42 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 162.8, 161.8 (d, *J* = 243.3 Hz), 152.3, 149.7, 138.7, 138.4, 135.0, 134.2, 133.7, 130.1 (d, *J* = 8.2 Hz), 129.5, 128.9, 127.0, 126.3, 117.4, 115.78 (d, *J* = 21.4 Hz), 112.4, 59.6, 43.3, 19.7, 18.5, 14.7. APSI MS: 474.2 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>27</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>2</sub>S: C, 68.48; H, 5.11; N, 8.87; S, 6.77%. Found: C, 68.45; H, 5.13; N, 8.81; S, 6.87%.

3-(5-Chloro-2-hydroxy-4-methylphenyl)-5-(2-chlorobenzyl)-4-(4-hydroxy-3-methoxyphenyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{9-16-20}) Yield: 79%; mp 242–244 °C; IR (KBr): 3371–2622 (OH, NH), 1679, 1515, 1454, 1264, 1228, 1171, 1141, 1031, 764 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.07 (br. s,

1H), 7.47–7.39 (m, 1H), 7.34–7.26 (m, 2H), 7.24 (s, 1H), 7.19–7.12 (m, 1H), 6.80 (s, 1H), 6.71–6.60 (m, 2H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.55 (s, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 4.00 (d, *J* = 16.0 Hz, 1H), 3.64 (s, 3H), 2.18 (s, 3H); another OH and NH exchanged with H<sub>2</sub>O. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)\*: δ 147.9, 146.9, 137.0, 134.9, 132.5, 129.9, 129.8, 129.4, 128.5, 127.8, 123.5, 120.3, 118.6, 116.2, 112.4, 60.4, 55.9, 42.1, 19.9. APSI MS: 510.0 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>26</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>: C, 61.19; H, 4.15; Cl, 13.89; N, 8.23%. Found: C, 61.16; H, 4.19; Cl, 13.97; N, 8.31%.

3-(5-Chloro-2-hydroxy-4-methylphenyl)-4-(3-chlorophenyl)-5-(3-hydroxypropyl)-4,5-dihydropyrrolo[3,4-c]pyrazol-6(1H)-one (5{9-21-8}) Yield: 80%; mp 275–277 °C; IR (KBr): 3479–2513 (OH, NH), 1674, 1466, 1397, 1297, 1096, 1071, 704 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.45 (br. s, 1H), 10.55 (br. s, 1H), 7.37–7.32 (m, 2H), 7.30 (s, 1H), 7.25 (s, 1H), 7.13–7.05 (m, 1H), 6.83 (br. s, 1H), 5.85 (s, 1H), 4.47 (br. s, 1H), 3.67 (dt, *J* = 14.1, 7.2 Hz, 1H), 3.40–3.35 (m, 2H), 2.75 (ddd, *J* = 14.1, 8.2, 5.9 Hz, 1H), 2.19 (s, 3H), 1.72–1.60 (m, 1H), 1.60–1.48 (m, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)\*: δ 153.3, 137.1, 133.7, 131.2, 128.8, 128.2, 126.6, 123.5, 118.7, 59.6, 58.8, 38.2, 31.5, 19.9. APSI MS: 432.0 (M<sup>+</sup> + 1). Anal. Calcd for C<sub>21</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>: C, 58.35; H, 4.43; Cl, 16.40; N, 9.72%. Found: C, 58.32; H, 4.40; Cl, 16.48; N, 9.79%.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11030-021-10234-2>.

**Acknowledgements** Authors are grateful grateful to ENAMINE Ltd., Kyiv for financial support and for providing NMR spectra.

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