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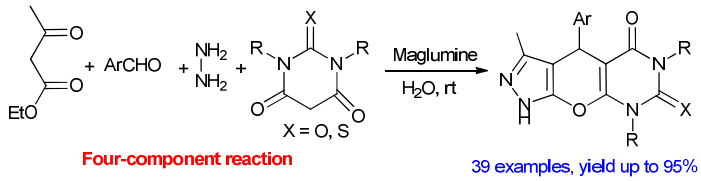
• **Graphical Abstract:**



Four-component reaction

39 examples, yield up to 95%

Meglumine catalyzed expeditious four-component domino protocol for synthesis of pyrazolopyranopyrimidines in aqueous medium

Xiao-Tang Li, Ai-Dong Zhao, Li-Ping Mo and Zhan-Hui Zhang*

Meglumine has been found to be an efficient catalyst for the synthesis of structurally diverse tricyclic fused pyrazolopyranopyrimidines by one-pot, four-component reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and barbituric acid in water.

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Meglumine catalyzed expeditious four-component domino protocol for synthesis of pyrazolopyranopyrimidines in aqueous medium

Xiao-Tang Li[a], Ai-Dong Zhao[b], Li-Ping Mo[a], Zhan-Hui Zhang[a,*]

A facile and highly efficient protocol for the one-pot, four-component reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and barbituric acid has been developed using meglumine as an inexpensive, biodegradable and reusable catalyst. This methodology provides a mild and fast route to structurally diverse tricyclic fused pyrazolopyranopyrimidines in good to excellent yields. Simplicity, room temperature reaction condition, green solvent, easy work-up process, inexpensive price and reusability of the catalyst are the main advantages of this method.

Introduction

The development of simple, efficient, environmentally benign and economically viable processes in organic synthesis is in great demand. In this regard, domino multicomponent reactions (MCRs) have been refined as powerful and useful tools for the construction of novel and structurally complex molecules from simple and readily accessible starting materials. Such reactions reduce the consumption of solvent, catalyst, and energy, thereby allowing a minimization of waste, cost, and lobor compared to the corresponding series of individual reactions.[1-4] Owing to the harmful effects of volatile organic solvents on the environment, many green solvent systems have been recently introduced as alternative reaction media.[5] Water is the most amazing gift of nature. It has gained a noteworthy eminence as a green medium in organic synthesis due to it being safe, cheap, eco-friendly, and non-toxic.[6-7] In addition, because of the advantages of high catalytic efficiency, nontoxic nature, low cost, and easy recycling, biodegradable materials have also been receiving more and more attentions.[8] Therefore, from the point of green chemistry, the development of new MCRs in water using biodegradable material as a catalyst is highly welcomed.

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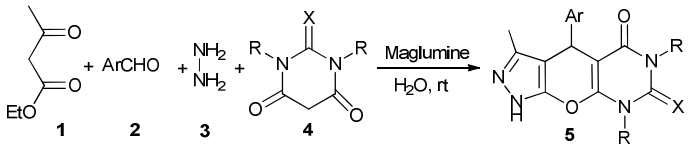
Heterocycles containing pyrimidine, pyran and pyrazole fragment have been found numberous applications in medical and material science. The pyrimidine nucleus is the core structure of many pharmacological agents that exhibits a broad spectrum of biological activitives.[9] Moreover, pyran skeleton is another important stuructural motif in a number of natural products and photochromic materials.[10] The pyrazole is also indispensable heterocycle analogue which plays a vital role in many pharmaceutical and agrochemical industries.[11] The more pronounced effect is generally observed when two or more different heterocyclic moieties exist in a single molecule, because it might possess properties of all moieties and enhance the pharmacological activities. Significant advances have recently been made to design novel polycyclic heterocycles by combining various structurally diverse motifs.[12] In this regard, we sought to explore a single structural framework by combining pyrimidine, pyran, and pyrazole motifs that may show promising medical properties.

Meglumine, an amino sugar derived from sorbitol, contains amino group, primary and secondary hydroxyl groups that can activate the nucleophilic as well as electrophilic components of the reactions by hydrogen bonding and donation of lone pair of electrons, respectively. Owing to its exteraordinary properties, such as low toxicity, biodegradability, physiological intertness, reusability, inexpensive price, and non-corrosion nature, meglumine has stimulated increasing research interest as an important and effective catalyst in organic synthesis.[13] In view of the above consideration, and on the basis of our progressive endeavours in developing multicomponent reactions[14] and environmental benign synthetic methodologies,[15] herein we wish to report meglumine as a biodegradable catalyst for one-pot synthesis of pyrazolopyranopyrimidines via a four-component reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and barbituric acid in water at ambient temperature (Scheme 1).



Scheme 1. Four-component synthesis of pyrazolopyranopyrimidines catalyzed by meglumine in water at room temperature.

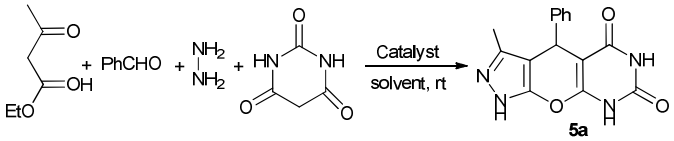
Results and discussion

At the beginning of this study, the four-component reaction of ethyl acetoacetate, hydrazine hydrate, benzaldehyde and barbituric acid was selected as a model to establish optimum reaction conditions. The above four-component reaction was carried out at room temperature in water without any catalyst to

establish the real efficacy of the catalyst. As shown in Table 1, it was observed that only a low yield of product was formed even after the reaction time was prolonged to 2 h (Table 1, entry 1). Then, we tried to optimize the reaction conditions with different catalysts, which might help to reduce the reaction time and improve the yield of the target product. After screening several catalysts, it can be noted that inorganic base such as K_2CO_3 exhibited a slight catalytic activity to give the product in a low yield (26%, Table 1, entry 2). The improventment was observed when several organic bases such as Et_3N, piperidine, DBU, DMAP and DABCO were used, and the desired product was obtained in 38-49% yield (Table 1, entries 3-7). Heravi et al reported that this transformation coulde be completed in the presence of 20 mol% of DABCO in refluxing water.[16] Other catalysts such as chitosan, *L*-proline, Fe_2O_3, ZnO, CuO, MgO were investigated and did not led to any noticeable increase in the yield of the target product (entries 9-14). Further experiments indicated that meglumine was the best catalyst for this transformation and afforded the desired product in 95% within 15 min (Table 1, entry 15).

Some solvents such as H_2O, THF, MeOH, EtOH, PEG 400, and ethanol-water mixture were screened for the model reaction. It was observed that water was the most effective solvent, and the present four-component reaction proceeded smoothly, giving the highest yield. It is noteworthy that when the reaction was performed under solvent-free conditions, low yield of target product was obtained (Table 1, entry 16). Then the effect of catalyst loading was evaluated in the model reaction at room temperature in H_2O. The results showed that 10 mol% of catalyst was the best choice for completing the reaction. Increasing the amount of catalyst had no effect on the product yield (entry 22), conversely, employing a lower percentage of meglumine resulted in a decreased yield of desired product (entry 23).

Table 1 Optimization of the reaction conditions for the synthesis of **5a**[a]



Entry	Catalyst	Solvent	Time (min)	Yield (%)[b]
1	No	H_2O	120	20
2	K_2CO_3	H_2O	60	26
3	Et_3N	H_2O	60	38
4	Piperidine	H_2O	60	53
5	DBU	H_2O	60	40
6	DMAP	H_2O	60	38
7	DABCO	H_2O	60	49
8[c]	DABCO	H_2O	20	99

9	Chitosan	H_2O	60	62
10	*L*-Proline	H_2O	60	42
11	Al_2O_3	H_2O	60	37
12	Fe_2O_3	H_2O	60	30
13	ZnO	H_2O	60	30
14	CuO	H_2O	60	23
15	Meglumine	H_2O	15	95
16	Meglumine	no	60	13
17	Meglumine	THF	60	41
18	Meglumine	MeOH	60	57
19	Meglumine	EtOH	60	60
20	Meglumine	EtOH/H_2O (9:1)	60	65
21	Meglumine	PEG 400	60	52
22[d]	Meglumine	H_2O	15	95
23[e]	Meglumine	H_2O	15	90
24[f]	Meglumine	H_2O	15	96
25[g]	Meglumine	H_2O	15	94, 93, 91

[a] Experimental conditions: ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), barbituric acid (1 mmol), catalyst (0.1 mmol), solvent (4 ml), room temperature. [b] Isolated yield. [c] DABCO (0.2 mmol), reflux. [d] Catalyst (0.2 mmol). [e] Catalyst (0.05 mmol). [f] 50 mmol scale. [g] Catalyst was reused three times.

In addition, to demonstrate the efficiency and practicability of this method in the synthesis of these types of molecules, the model reaction was carried out in a scale of 50 mmol. As expected, the desired product could be obtained with 96% yield in 15 min.

After completion of the reaction, the product was precipitated and was completely isolated by simple filtration from the aqueous phase. The catalyst meglumine still remained in the filtrate that could be reused directly in the next run without any further treatment (Figure 1). The results demonstrated that the yield was still around 90% after the catalyst system was recycled for three times (Table 1, entry 25).

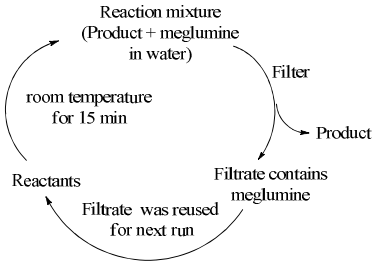


Figure 1. Reusability of meglumine catalyst.

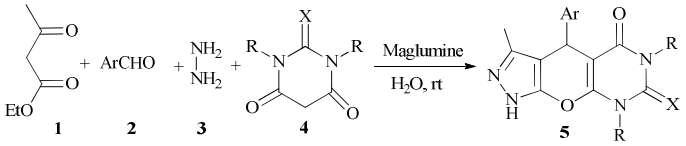
With this optimized procedure in hand, the scope of the four-component reaction was examined by using different aromatic aldehydes, ethyl acetoacetate, hydrazine hydrate, and barbituric acid. The results are summarized in Table 2. As can be seen, the reaction proceeded smoothly with functionality-substituted

aromatic aldehydes to afford the desired products in high to excellent yields. Variation of the electronic properties and the position of functional groups on the aromatic ring of the aldehyde did not show obviously impact on the yield of the reaction. Furthermore, the steric effects of substitutents at the *ortho*-position of aromatic aldehyde had not an obvious impact on the yield of the reaction. In addition, the presence of three methoxy electron donating groups on the aromatic ring of the aldehyde performed well and afforded the desired product in 83% yield (**5e**, entry 5). Remarkably, substrates containing active hydrogen, such as hydroxyl (entries 7, 8, 9, 23, and 27) and carboxylic acid (entry 31) could be tolerated. Notably, the heteroaryl aldehydes such as thiophene-2-carbaldehyde and 2-pyridinecarboxaldehyde and policyclic aldehyde such as 1-naphthaldehyde were also well tolerated to afford their corresponding products **5af-5ah** in high isolated yields. Unfortunately, the reaction was found to be complex with aliphatic aldehydes such as cyclohexanecarbaldehyde and phenylacetaldehyde and failed to give any characterizable product under these reaction conditions.

Additionally, when barbituric acid was switched to 1,3-dimethylbarbituric acid under above conditions, it was observed that 1,3-dimethylbarbituric acid participated in this 4CR as well to afford the respective products in high yields (Table 2, entries 35-37).

To further expand the substrate scope, barbituric acid was replaced by thiobarbituric acid. Pleasingly, the reactions were also successful under the same conditions and resulted in similar yield when compared to those with barbituric acid (Table 2, entries 38 and 39).

Table 2 Synthesis of tricyclic fused pyrazolopyranopyrimidines catalyzed by meglumine in water



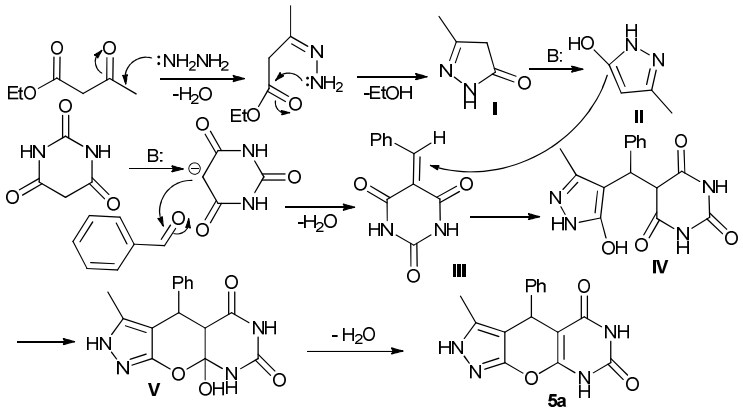
Entry	Aldehydes	R	X	Product	Time (min)	Yield (%)[a]	m.p. (°C)
1	PhCHO	H	O	**5a**	15	95	218-219 (218)[16]
2	2-OMeC$_6$H$_4$CHO	H	O	**5b**	25	89	230-231 (232)[16]
3	3-OMeC$_6$H$_4$CHO	H	O	**5c**	15	89	221-222
4	3,4-(OMe)$_2$C$_6$H$_3$CHO	H	O	**5d**	25	89	275-276
5	2,3,4-(OMe)$_3$C$_6$H$_2$CHO	H	O	**5e**	30	83	193-194

6	3-$PhOC_6H_4CHO$	H	O	**5f**	30	85	230-231
7	2-OH-4-$OMeC_6H_3CHO$	H	O	**5g**	25	87	159-160
8	3-OMe-4-OHC_6H_3CHO	H	O	**5h**	25	89	259-260
9	2-OEt-4-OHC_6H_3CHO	H	O	**5i**	30	87	234-235
10	2-OMe-5-$^{i}PrC_6H_3CHO$	H	O	**5j**	25	87	205-206
11	4-MeC_6H_4CHO	H	O	**5k**	30	90	200-201 (201)[16]
12	4-$CMe_3C_6H_4CHO$	H	O	**5l**	20	89	191-192
13	2-FC_6H_4CHO	H	O	**5m**	20	90	223-224
14	3-FC_6H_4CHO	H	O	**5n**	20	92	242-244
15	4-FC_6H_4CHO	H	O	**5o**	20	94	237-238
16	2-ClC_6H_4CHO	H	O	**5p**	20	89	223-225
17	3-ClC_6H_4CHO	H	O	**5q**	20	90	246-247
18	4-ClC_6H_4CHO	H	O	**5r**	15	92	222-223 (223)[16]
19	2,4-$Cl_2C_6H_3CHO$	H	O	**5s**	20	90	233-234
20	2-BrC_6H_4CHO	H	O	**5t**	20	89	250-251
21	3-BrC_6H_4CHO	H	O	**5u**	20	90	128-129
22	4-BrC_6H_4CHO	H	O	**5v**	15	91	211-212
23	2-OH-5-BrC_6H_3CHO	H	O	**5w**	20	88	220-221
24	2-$NO_2C_6H_4CHO$	H	O	**5x**	20	90	208-209
25	3-$NO_2C_6H_4CHO$	H	O	**5y**	20	90	266-267 (267)[16]
26	4-$NO_2C_6H_4CHO$	H	O	**5z**	20	91	233-234 (231)[16]
27	2-OH-5-$NO_2C_6H_3CHO$	H	O	**5aa**	20	89	261-262
28	3-NO_2-4-OHC_6H_3CHO	H	O	**5ab**	20	91	254-256
29	3-$CF_3C_6H_4CHO$	H	O	**5ac**	20	90	198-199
30	4-$CF_3C_6H_4CHO$	H	O	**5ad**	20	90	222-223
31	4-$COOHC_6H_4CHO$	H	O	**5ae**	20	94	283-284
32	Thiophene-2-carbaldehyde	H	O	**5af**	360	90	176-177
33	Pyridine-2-carbaldehyde	H	O	**5ag**	360	91	247-248
34	1-Naphthaldehyde	H	O	**5ah**	30	90	221-222

35	PhCHO	Me	O	**5ai**	30	95	192-193
36	4-MeC_6H_4CHO	Me	O	**5aj**	60	91	172-173
37	4-ClC_6H_4CHO	Me	O	**5ak**	40	92	199-200
38	PhCHO	H	S	**5al**	15	95	220-221
39	3-$NO_2C_6H_4CHO$	H	S	**5an**	20	92	212-213

[a] Isolated yield.

A proposed mechanism for the synthesis of pyrazolopyranopyrimidine **5a** from ethyl acetoacetate, hydrazine hydrate, benzaldehyde and barbituric acid catalyzed by meglumine is shown in Scheme 2. The 3-methyl-1*H*-pyrazol-5(4*H*)-one (**I**) was formed by condensation of ethyl acetoacetate and hydrazine, which would be converted to its corresponding enolate form **II** in the presence of meglumine. It is worthy noting that, intermediate **II** is relatively stable compared with other enolates since it is aromatic. The amino group in meglumine plays a major role for the formation of intermediate **III** from Knoevenagel condensation of benzaldehyde and barbituric acid. The Knoevenagel products of aromatic aldehydes are stable compared to that of aliphatic aldehydes, which readily participated in this reaction. Aliphatic aldehydes afforded complex mixtures including aldol products and Michael addition products under these conditions. On the one hand, the amino group in meglumine can take away the hydrogen atom of active methylene of barbituric acid to form a corresponding active carbon anion. On the other hand, the bonding interactions between the hydroxyl groups of meglumine and the carbonyl group of the aldehyde increase the electrophilicity of the aldehyde carbon atom. Subsequently, intermediate **II** is reacted with Knoevenagel condensate **III** through Michael addition to produce intermediate **IV**, which underwent intramolecular cyclization by the nucleophilic addition of enolate oxygen to carbonyl group to afford intermediate **V**. Meglumine could assist intermediate **V** to lose a water molecule and provide target product **5a**.



Scheme 2. Plausible mechanism for synthesis of pyrazolopyranopyrimidines.

Conclusion

In summary, we have developed a novel, highly efficient and environmentaly benign procedure for synthesis of tricyclic fused pyrazolopyranopyrimidines via one-pot, four-component reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and barbituric acid in aqueous medium using meglumine as an inexpensive, biodegradable and reusable catalyst. The procedure offers several advantages including the use of biodegradable and inexpensive catalyst, high to excellent yields, green solvents, short reaction time, and simple work-up procedure, which make it a useful and attractive strategy in synthetic organic chemistry.

Experimental section

General information

All chemicals were purchased from commercial sources and used without further purification. Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were taken as KBr discs with a Bruker-TENSOR 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500 MHz and 125 MHz in DMSO-d_6, respectively. Elemental analyses were carried out on a Vario EL III CHNOS instrument.

General procedure for the synthesis of pyrazolopyranopyrimidines

To a mixture of ethyl acetoacetate (1 mmol) and hydrazine hydrate (1 mmol) in water (4 mL) was added aldehydes (1 mmol), barbituric acid (1 mmol), and meglumine (0.1 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, precipitate was formed, filtered and washed with water and ethanol. The resultant product was found to be pure enough for characterization.

Characterization data

3-Methyl-4-phenyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5a). White solid; IR (KBr): 3422, 3028, 1678, 1631, 1545, 1474, 1356 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.23 (s, 3H, CH_3), 5.43 (s, 1H, CH), 7.05 (d, J = 7.5 Hz, 2H, HAr), 7.11 (t, J = 7.5 Hz, 1H, HAr), 7.21 (d, J = 7.5 Hz, 2H, HAr), 10.13 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.1, 80.8, 91.8, 106.3, 125.9, 127.1, 128.3, 142.9, 144.2, 151.2, 160.8; Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N,

18.91. Found: C, 61.00; H, 3.91; N, 19.08.

4-(2-Methoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5b). White solid; IR (KBr): 3458, 1670, 1650, 1489, 1460, 1394 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.26 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 5.65 (s, 1H, CH), 6.80-6.85 (m, 2H, HAr), 7.12 (t, J = 7.5 Hz, 1H, HAr), 6.34 (d, J = 6.5 Hz, 1H, HAr), 10.11 (s, 2H, NH), 13.02 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.7, 19.0, 55.7, 111.0, 112.0, 126.7, 127.4, 128.0, 129.0, 129.9, 133.0, 140.2, 151.0, 151.1, 157.1, 161.3; Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.08; H, 17.00; N, 17.34.

4-(3-Methoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1*H*,4*H*)-dione (5c). White solid; IR (KBr): 3379, 3088, 1701, 1604, 1483, 1431, 1381 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.23 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 5.41 (s, 1H, CH), 6.58 (s, 1H, HAr), 6.64 (d, J = 7.5 Hz, 1H, HAr), 6.70 (dd, J = 8.0, 2.5 Hz, 1H, HAr), 7.13 (t, J = 8.0 Hz, 1H, HAr), 10.23 (s, 2H, NH), 13.19 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.1, 55.2, 91.7, 106.2, 110.3, 113.8, 119.7, 129.4, 144.2, 144.7, 151.3, 159.5, 160.6; Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.08; H, 4.15; N, 17.34.

4-(3,4-Dimethoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5d). White solid; IR (KBr): 3223, 3074, 1742, 1622, 1541, 1464, 1393 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.22 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 5.38 (s, 1H, CH), 6.63 (s, 1H, HAr), 6.78 (d, J = 8.5 Hz, 1H, HAr), 7.12 (d, J = 8.5 Hz, 1H, HAr), 10.10 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 55.9, 56.0, 56.3, 111.6, 115.7, 117.3, 125.8, 132.2, 148.3, 148.7, 150.7, 154.1, 155.9, 161.2, 162.8, 164.5; Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.49; H, 4.36; N, 15.89.

3-Methyl-4-(2,3,4-trimethoxyphenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5e). White solid; IR (KBr): 3526, 2942, 1773, 1616, 1493, 1458, 1394 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.24 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 5.57 (s, 1H, CH), 6.67 (d, J = 9.0 Hz, 1H, HAr), 7.02 (d, J = 8.5 Hz, 1H, HAr), 10.15 (s, 2H, NH), 13.05 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.6, 26.4, 56.2, 60.3, 60.5, 91.4, 107.1, 123.4, 128.7, 130.7, 140.0, 142.2, 143.9, 151.0, 151.4, 152.1, 154.3, 161.5; Anal. Calcd for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 56.15; H, 4.53; N, 14.67.

3-Methyl-4-(3-phenoxyphenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*

)-dione (5f). White solid; IR (KBr): 3161, 3057, 1701,1591, 1483, 1431, 1379 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 1.27 (s, 3H, CH_3), 4.47 (s, 1H, CH), 5.78 (t, *J* = 7 Hz, 2H, HAr), 5.88 (d, *J* = 8 Hz, 1H, HAr), 6.01 (d, *J* = 8.0 Hz, 2H, HAr), 6.15 (t, *J* = 7.5 Hz, 1H, HAr), 6.28 (t, *J* = 8.0 Hz, 1H, HAr), 6.40 (t, *J* = 8.0 Hz, 2H, HAr), 9.18 (s, 2H, NH), 13.23 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.0, 91.6, 115.9, 117.2, 118.6, 119.6, 122.0, 123.6, 124.5, 130.3, 130.7, 131.2, 136.1, 145.6, 151.1, 156.5, 156.6, 157.8, 160.9, 161.6; Anal. Calcd for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43. Found: C, 65.13; H, 3.98; N, 14.60.

4-(2-Hydroxy-4-methoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5g). White solid; IR (KBr): 3188, 3022, 1697, 1620, 1506, 1439, 1370 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.11 (s, 6H, CH_3), 4.98 (s, 1H, CH), 6.50 (s, 1H, OH), 6.52-6.53 (m, 1H, HAr), 6.57-6.59 (m, 2H, HAr), 10.03 (s, 2H, NH), 11.53 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.9, 26.5, 55.3, 88.1, 105.1, 113.4, 116.6, 122.9, 130.9, 141.5, 149.6, 150.8, 161.1, 164.9, 166.4; Anal. Calcd for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.33; H, 3.95; N, 16.54.

4-(4-Hydroxy-3-methoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5h). White solid; IR (KBr): 3421, 3034, 1730, 1622, 1508, 1466, 1398 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.22 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 5.35 (s, 1H, CH), 6.45 (d, *J* = 7.5 Hz, 1H, HAr), 6.61 (d, *J* = 8.0 Hz, 2H, HAr), 8.68 (s, 1H, OH), 10.15 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 30.6, 56.1, 92.1, 106.8, 112.0, 115.4, 119.7, 133.8, 144.0, 144.9, 147.5, 151.2, 161.0, 164.4, 166.2; Anal. Calcd for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.33; H, 3.95; N, 16.55.

4-(3-Ethoxy-4-hydroxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5i). White solid; IR (KBr): 3196, 3034, 1681, 1618, 1514, 1479, 1396 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 1.27 (t, *J* = 6.5 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.87 (q, *J* = 6.5 Hz, 2H, CH_3), 5.34 (s, 1H, CH), 6.45 (d, *J* = 7.5 Hz, 1H, HAr), 6.60 (s, 1H, HAr), 6.62 (d, *J* = 8.5 Hz, 1H, HAr), 8.61(s, 1H, OH), 10.14 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 15.2, 30.4, 64.5, 91.9, 106.8, 113.6, 115.5, 119.8, 133.8, 143.9, 145.2, 146.5, 151.1, 161.1, 166.1; Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.49; H, 4.36; N, 15.89.

4-(5-Isopropyl-2-methoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4H)-dione (5j). White solid; IR (KBr): 3117, 3030, 1697, 1622, 1522,1458, 1362 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 1.23 (d, *J* = 7 Hz, 6H, CH_3), 2.26 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.86 (s, 1H, CH), 5.65 (s, 1H, CH), 6.75 (d, *J* = 8.0 Hz, 1H, HAr), 6.96 (d, *J* = 7.0 Hz, 1H, HAr), 7.30 (s, 1H, HAr),

10.09 (s, 2H, NH), 12.98 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.7, 24.3, 24.5, 24.7, 33.1, 33.2, 118.7, 121.5, 124.5, 130.9, 133.0, 139.5, 150.7, 150.8, 151.1, 155.2, 157.9, 162.1, 164.0; Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.14; H, 5.30; N, 15.38.

3-Methyl-4-(p-tolyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5k). White solid;IR (KBr): 3433, 3043, 1685, 1626, 1508, 1474, 1612, 1364 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 1.31 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 4.48 (s, 1H, CH), 6.01 (d, J = 8.0 Hz, 2H, HAr), 6.15 (d, J = 8.0 Hz, 2H, HAr), 9.22 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 21.0, 21.6, 91.8, 106.5, 127.1, 128.9, 130.0, 134.6, 140.0, 151.1, 161.1, 161.7; Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 62.02; H, 4.38; N, 18.13.

4-(4-(Tert-butyl)phenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*, 4*H*)-dione (5l). White solid; IR (KBr): 3198, 3032, 1695, 1608, 1508, 1452, 1364 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 1.34 (s, 3H, CH_3), 1.62 (s, 9H, CH_3), 4.64 (s, 1H, CH), 6.28 (t, J = 7.5 Hz, 1H, HAr), 6.34 (t, J = 7.5 Hz, 1H, HAr), 6.42 (d, J = 7.5 Hz, 1H, HAr),6.58-6.62 (m, 1H, HAr), 9.25 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.7, 34.4, 125.0, 125.5, 125.8, 126.4, 129.7, 129.9, 134.3, 140.2, 147.9, 151.1, 161.1; Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.95; H, 5.55; N, 16.07.

4-(2-Fluorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1*H*,4*H*)-dione (5m). White solid; IR (KBr): 3165, 3042, 1705, 1627, 1585, 1487, 1381 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.24 (s, 3H, CH_3), 5.66 (s, 1H, CH), 7.00-7.05 (m, 1H, HAr), 7.07 (t, J = 7.5 Hz, 1H, HAr), 7.17-7.21 (m, 1H, HAr), 7.36 (d, J = 8.0 Hz, 1H, HAr), 10.21 (s, 2H, NH), 13.23 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 26.2, 90.6, 115.5 (d, $^2J_{FC}$ =21.9 Hz), 123.9, 128.1 (d, $^3J_{FC}$ =8.0 Hz), 128.3, 129.9, 130.1, 134.2, 151.1, 155.6, 160.7 (d, $^1J_{FC}$ =243.2 Hz), 161.1, 163.0; Anal. Calcd for $C_{15}H_{11}FN_4O_3$: C, 57.33; H, 3.53; N, 17.83. Found: C, 57.52; H, 3.36; N, 18.00.

4-(3-Fluorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5n). White solid; IR (KBr): 3161, 3036, 1701, 1598, 1477, 1438, 1379 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.25 (s, 3H, CH_3), 5.45 (s, 1H, CH), 6.80 (d, J = 10.5 Hz, 1H, HAr), 6.91 (d, J = 7.5 Hz, 1H, HAr), 6.96 (t, J = 7.5 Hz, 1H, HAr), 7.24-7.29 (m, 1H, HAr), 10.23 (s, 2H, NH), 13.31 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.0, 105.9, 112.6,112.7, 114.8 (d, $^2J_{FC}$ =22.3 Hz), 118.7, 118.9, 123.3, 125.3, 130.1 (d, $^3J_{FC}$ =8.4 Hz), 151.1, 160.7, 161.2, 162.7 (d, $^1J_{FC}$ =240.6 Hz); Anal. Calcd for $C_{15}H_{11}FN_4O_3$: C, 57.33; H, 3.53; N, 17.83. Found: C, 57.52; H, 3.36; N, 18.00.

4-(4-Fluorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5o). White solid; IR (KBr): 3161, 3032, 1705, 1624, 1508, 1464, 1375 cm^{-1};^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.24 (s, 3H, CH_3), 5.43 (s, 1H, CH), 7.02-7.10 (m, 4H, HAr), 10.23 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.4, 30.6, 91.8, 106.2, 114.9 (d, $^2J_{FC}$ =20.8 Hz), 128.9 (d, $^3J_{FC}$ =7.5 Hz), 138.8, 138.8, 144.1, 151.4, 159.9, 160.9 (d, $^1J_{FC}$ =234.6 Hz), 160.3; Anal. Calcd for $C_{15}H_{11}FN_4O_3$: C, 57.33; H, 3.53; N, 17.83. Found: C, 57.52; H, 336; N, 18.00.

4-(2-Chlorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5p). White solid; IR (KBr): 3404, 3067, 1701, 1604, 1528, 1468, 1391 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.23 (s, 3H, CH_3), 5.53 (s, 1H, CH), 7.18 (t, J = 7.5 Hz, 1H, HAr), 7.23 (t, J = 7.5 Hz, 1H, HAr), 7.32 (d, J = 7.5 Hz, 1H, HAr), 7.49 (d, J = 6.5 Hz, 1H, HAr), 10.19 (s, 2H, NH), 13.23 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.8, 30.5, 91.1, 126.7, 128.0, 129.9, 130.7, 133.0, 140.2, 143.7, 151.1, 161.3, 165.0; Anal. Calcd for $C_{15}H_{11}ClN_4O_3$: C, 54.47; H, 3.35; N, 16.94. Found: C, 54.66; H, 3.19; N, 17.11.

4-(3-Chlorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5q). White solid; IR (KBr): 3165, 3024, 1701, 1628, 1520, 1474, 1379 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.45 (s, 3H, CH_3), 5.44 (s, 1H, CH), 7.03 (d, J = 6.5 Hz, 2H, HAr), 7.20 (d, J = 7.0 Hz, 1H, HAr), 7.26 (d, J = 8.0 Hz, 1H, HAr), 10.24 (s, 2H, NH), 13.31 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.0, 91.3, 105.7, 126.9, 128.4, 129.3, 130.0, 131.1, 133.2, 136.2, 145.8, 151.1, 161.1, 166.6; Anal. Calcd for $C_{15}H_{11}ClN_4O_3$: C, 54.47; H, 3.35; N, 16.94. Found: C, 54.66; H, 3.19; N, 17.10.

4-(4-Chlorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5r). White solid; IR (KBr): 3134, 3034, 1681, 1589, 1487, 1400, 1368 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.23 (s, 3H, CH_3), 5.40 (s, 1H, CH), 7.06 (d, J = 8.0 Hz, 2H, HAr), 7.26 (d, J = 8.5 Hz, 2H, HAr), 10.21 (s, 2H, NH), 13.23 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 30.7, 128.2, 129.1, 129.2, 130.5, 131.6, 135.1, 142.0, 144.1, 151.1, 160.7, 167.0; Anal. Calcd for $C_{15}H_{11}ClN_4O_3$: C, 54.47; H, 3.35; N, 16.94. Found: C, 54.66; H, 3.19; N, 17.10.

4-(2,4-Dichlorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5s). White solid; IR (KBr): 3433, 3049, 1701, 1589, 1535, 1468, 1379 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.25 (s, 3H, CH_3), 5.52 (s, 1H, CH), 7.35 (d, J = 8.0 Hz, 1H, HAr), 7.47 (s, 1H, HAr), 7.47 (d, J = 8.5 Hz, 1H, HAr), 10.29 (s, 2H, NH); ^{3}C NMR (DMSO-d_6, 125 MHz) δ ppm: 19.0,

30.3, 90.8, 105.0 126.8, 129.2, 131.6, 131.9, 133.9, 139.4, 143.7, 151.2, 160.9, 165.1; Anal. Calcd for $C_{15}H_{10}Cl_2N_4O_3$: C, 49.34; H, 2.76; N, 15.34. Found: C, 49.53; H, 2.59; N, 15.51.

4-(2-Bromophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5t). White solid; IR (KBr):3406, 1701, 1618, 1560, 1437, 1389 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.24 (s, 3H, CH_3), 5.43 (s, 1H, CH), 7.09 (t, *J* = 7.0 Hz, 1H, HAr), 7.27 (t, *J* = 7.0 Hz, 1H, HAr), 7.49 (d, *J* = 7.5 Hz, 2H, HAr), 10.17 (s, 2H, NH), 13.23 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 19.0, 32.8, 91.4, 105.5, 123.7, 127.2, 128.3, 131.0, 133.3, 141.6, 151.2, 161.2, 165.1; Anal. Calcd for $C_{15}H_{11}BrN_4O_3$: C, 48.02; H, 2.96; N, 14.93. Found: C, 48.21; H, 2.79; N, 15.10.

4-(3-Bromophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5u). White solid; IR (KBr): 3000, 1697, 1624, 1591, 1510, 1458, 1381 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.25 (s, 3H, CH_3), 5.45 (s, 1H, CH), 7.09 (d, *J* = 7.5 Hz, 1H, HAr), 7.20 (t, *J* = 7.5 Hz, 2H, HAr), 7.34 (d, *J* = 8.0 Hz, 1H, HAr), 10.24 (s, 2H, NH), 13.35 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 23.2, 121.2, 122.2, 122.7, 128.7, 130.5, 131.4, 132.2, 133.5, 136.1, 151.1, 160.7, 161.0, 166.4; Anal. Calcd for $C_{15}H_{11}BrN_4O_3$: C, 48.02; H, 2.96; N, 14.93. Found: C, 48.21; H, 2.79; N, 15.11.

4-(4-Bromophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5v). White solid; IR (KBr): 3356, 3044, 1693, 1605, 1483, 1467, 1360 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.23 (s, 3H, CH_3), 5.38 (s, 1H, CH), 7.00 (d, *J* = 8.0 Hz, 2H, HAr), 7.40 (d, *J* = 8.5 Hz, 2H, HAr), 10.18 (s, 2H, NH), 13.28 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 30.7, 91.5, 105.9, 118.9, 129.5, 131.1, 142.5, 144.1, 151.1, 160.7; Anal. Calcd for $C_{15}H_{11}BrN_4O_3$: C, 48.02; H, 2.96; N, 14.93. Found: C, 48.20; H, 2.79; N, 15.11.

4-(5-Bromo-2-hydroxyphenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5w). White solid; IR (KBr): 3204, 3041, 1676, 1611, 1528, 1468, 1371 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.23 (s, 3H, CH_3), 5.56 (s, 1H, CH), 6.37 (d, *J* = 8.0 Hz, 1H, HAr), 7.13 (d, *J* = 8.0 Hz, 1H, HAr), 7.39 (s, 1H, HAr), 10.17 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.8, 26.8, 104.3, 110.0, 117.4, 129.7, 131.1, 131.7, 132.1, 134.9, 139.0, 151.2, 154.6, 160.5; Anal. Calcd for $C_{15}H_{11}BrN_4O_4$: C, 46.06; H, 2.83; N, 14.32. Found: C, 46.25; H, 2.66; N, 14.19.

3-Methyl-4-(2-nitrophenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5x). White solid; IR (KBr): 3161, 3057, 1701, 1604, 1523, 1476, 1396 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.21 (s, 3H, CH_3), 5.77 (s, 1H, CH), 7.36 (m, 2H, HAr), 7.52 (t, *J* = 7.5 Hz, 1H, HAr), 7.57

(m, 1H, HAr), 10.15 (s, 2H, NH), 13.26 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 28.5, 90.8, 121.0, 134.2, 135.1, 146.7, 150.4, 150.7, 151.2, 153.0, 160.8, 161.7, 162.9; Anal. Calcd for $C_{15}H_{11}N_5O_5$: C, 52.79; H, 3.25; N, 20.52. Found: C, 52.98; H, 3.08; N, 20.69.

3-Methyl-4-(3-nitrophenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5y). White solid; IR (KBr): 3032, 1709, 1614, 1526, 1479, 1383 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.27 (s, 3H, CH_3), 5.54 (s, 1H, CH), 7.55 (t, J = 7.0 Hz, 2H, HAr), 7.86(s, 1H, HAr), 8.03-8.04 (m, 1H, HAr), 10.27 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.2, 91.4, 105.3, 121.2, 121.6, 129.9, 131.1, 134.3, 135.7, 145.7, 148.2, 151.1, 160.5, 160.9; Anal. Calcd for $C_{15}H_{11}N_5O_5$: C, 52.79; H, 3.25; N, 20.52. Found: C, 52.98; H, 3.08; N, 20.68.

3-Methyl-4-(4-nitrophenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5z). White solid; IR (KBr): 3050, 3138, 1690, 1597, 1518, 1468, 1346 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.26 (s, 3H, CH_3), 5.53 (s, 1H, CH), 7.33 (d, J = 6.0 Hz, 2H, HAr), 8.11 (d, J = 6.5 Hz, 2H, HAr), 10.27 (s, 2H, NH), 13.34 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.6, 91.5, 105.4, 123.6, 128.5, 132.7, 144.2, 146..1, 151.1, 151.7, 160.5; Anal. Calcd for $C_{15}H_{11}N_5O_5$: C, 52.79; H, 3.25; N, 20.52. Found: C, 52.98; H, 3.07; N, 20.67.

4-(2-Hydroxy-5-nitrophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5aa). White solid; IR (KBr): 3400, 3038, 1639, 1709, 1520, 1485, 1383 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.27 (s, 3H, CH_3), 5.62 (s, 1H, CH), 6.87 (d, J = 8.5 Hz, 1H, HAr), 7.97 (d, J = 8.0 Hz, 1H, HAr), 8.24 (s, 1H, HAr), 10.25 (s, 2H, NH), 13.01 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.8, 31.1, 115.5, 119.5, 124.1, 125.5, 128.8, 130.4, 139.5, 140.4, 151.1, 160.5, 160.8, 162.0, 164.2; Anal. Calcd for $C_{15}H_{11}N_5O_6$: C, 50.43; H, 3.10; N, 19.60. Found: C, 50.62; H, 2.93; N, 19.78.

4-(4-Hydroxy-3-nitrophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5ab). White solid; IR (KBr): 3165, 3030, 1707, 1628, 1539, 1489, 1362 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.24 (s, 3H, CH_3), 5.38 (s, 1H, CH), 7.02 (d, J = 8.5 Hz, 1H, HAr), 7.25 (d, J = 8.0 Hz, 1H, HAr), 7.50 (s, 1H, HAr), 10.24 (s, 2H, NH), 10.71 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 30.3, 105.6, 119.5, 120.3, 123.0, 125.7, 134.2, 135.0, 136.1, 137.4, 144.2, 151.0, 151.3, 160.2; Anal. Calcd for $C_{15}H_{11}N_5O_6$: C, 50.43; H, 3.10; N, 19.60. Found: C, 50.61; H, 2.93; N, 19.78.

3-Methyl-4-(3-(trifluoromethyl)phenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5ac). White solid; IR (KBr): 3200, 3049, 1693, 1624, 1585, 1481, 1377 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.28 (s, 3H, CH_3), 5.54 (s, 1H, CH), 7.37 (s, 1H, HAr), 7.40 (d, J = 7.0 Hz,

1H, HAr), 7.47-7.52 (m, 2H, HAr), 10.31 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.4, 31.2, 56.5, 91.5, 105.6, 122.8 (q, $^{3}J_{FC}$ =3.0 Hz), 123.3, 123.4, 124.9 (q, $^{1}J_{FC}$ = 270.5 Hz), 129.1 (q, $^{2}J_{FC}$ = 30.9 Hz), 129.4, 131.5, 135.1, 144.2, 151.3, 160.4; Anal. Calcd for $C_{16}H_{11}F_3N_4O_3$: C, 52.75; H, 3.04; N, 15.38. Found: C, 52.94; H, 2.97; N, 15.55.

3-Methyl-4-(4-(trifluoromethyl)phenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5ad). White solid; IR (KBr): 3304, 3034, 1730, 1604, 1508, 1466, 1398 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.25 (s, 3H, CH_3), 5.50 (s, 1H, CH), 7.27 (d, *J* = 7.5 Hz, 2H, HAr), 7.59 (d, *J* = 8.0 Hz, 2H, HAr), 10.23 (s, 2H, NH), 13.28 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.4, 31.3, 91.6, 105.6, 125.0 (q, $^{1}J_{FC}$ =270.0 Hz), 125.2 (q, $^{3}J_{FC}$ =3.4 Hz), 126.8 (q, $^{2}J_{FC}$ =31.5 Hz), 128.0, 130.0, 144.2, 148.1, 151.3, 160.5; Anal. Calcd for $C_{16}H_{11}F_3N_4O_3$: C, 52.75; H, 3.04; N, 15.38. Found: C, 52.96; H, 2.97; N, 15.56.

4-(3-Methyl-5,7-dioxo-1,4,5,6,7,8-hexahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-4-yl)benzoic acid (5ae). White solid; IR (KBr): 3173, 3049, 1715, 1608, 1521, 1473, 1373 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.24 (s, 3H, CH_3), 5.47 (s, 1H, CH), 7.17 (d, *J* = 8.5 Hz, 2H, HAr), 7.80 (d, *J* = 8.5 Hz, 2H, HAr), 10.23 (s, 2H, NH), 13.13 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.4, 105.9, 127.4, 128.5, 129.0, 129.5, 130.3, 138.0, 144.1, 148.6, 151.1, 160.8, 161.5, 167.3, 167.8; Anal. Calcd for $C_{16}H_{12}N_4O_5$: C, 56.47; H, 3.55; N, 16.46. Found: C, 56.66; H, 3.38; N, 16.63.

3-Methyl-4-(thiophen-2-yl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5af). White solid; IR (KBr): 3431, 3009, 1687, 1589, 1545, 1471, 1361 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.25 (s, 3H, CH_3), 5.57 (s, 1H, CH), 6.56 (s, 1H, HAr), 6.83-6.85 (m, 1H, HAr), 7.22 (d, *J* = 5.0 Hz, 1H, HAr), 10.19 (s, 2H, NH), 13.28 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 9.46, 29.3, 113.6, 113.9, 115.1, 124.8, 129.5, 137.4, 159.4, 160.0, 161.7, 163.5; Anal. Calcd for $C_{13}H_{10}N_4O_3S$: C, 51.65; H, 3.33; N, 18.53. Found: C, 51.84; H, 3.16; N, 18.70.

3-Methyl-4-(pyridin-2-yl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5ag). White solid; IR (KBr): 3345, 3020, 1707, 1610, 1516, 1462, 1365 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.18 (s, 3H, CH_3), 5.01 (s, 1H, CH), 7.37 (s, 2H, HAr), 7.94 (s, 1H, HAr), 8.45 (d, *J* = 3.5 Hz, 1H, HAr), 9.97 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.2, 106.4, 123.7, 126.9, 128.6, 134.1, 138.7, 143.5, 148.8, 151.1, 156.1, 160.3; Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.75; H, 3.56; N, 23.73.

3-Methyl-4-(naphthalen-1-yl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)

-dione (5ah). White solid; IR (KBr): 3034, 1653, 1622, 1508, 1466, 1398cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.20 (s, 3H, CH_3), 5.98 (s, 1H, CH), 7.37 (t, J = 8.0 Hz, 1H, HAr), 7.43-7.46 (m, 3H, HAr), 7.71 (d, J = 8.0 Hz, 1H, HAr), 7.87 (t, J = 6.5 Hz, 1H, HAr),8.19 (d, J = 7.5 Hz, 1H, HAr), 10.00 (s, 1H, NH), 10.19 (s, 1H, NH), 13.33 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 29.5, 81.7, 124.6, 125.3, 125.4, 125.6, 126.1, 126.2, 126.8, 127.5, 129.0, 131.1, 131.8, 134.0, 139.0, 151.0, 161.7; Anal. Calcd for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18. Found: C, 66.08; H, 3.91; N, 16.36.

3,6,8-Trimethyl-4-phenyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5ai). White solid; IR (KBr): 3057, 3026, 1681, 1573, 1493, 1466, 1385 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.28 (s, 3H, CH_3), 3.16 (s, 6H, CH_3), 5.43 (s, 1H, CH), 7.07 (d, J = 7.5 Hz, 2H, HAr), 7.11 (t, J = 7.5 Hz, 1H, HAr), 7.21 (t, J = 7.5 Hz, 2H, HAr); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.4, 28.3, 32.6, 106.4, 125.8, 127.1, 128.3, 133.2, 142.9, 144.3, 152.1, 156.2, 159.6, 161.9, 163.9; Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.76; H, 5.39; N, 17.35.

3,6,8-Trimethyl-4-(*p*-tolyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5aj). White solid; IR (KBr): 3431, 3017, 1685, 1618, 1510, 1454, 1388 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.27 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.12 (s, 6H, CH_3), 5.55 (s, 1H, CH), 6.95-6.98 (m, 4H, HAr), 12.8 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.3, 20.7, 28.1, 106.5, 126.9, 128.6, 128.7, 129.7, 134.4, 139.6, 141.6, 144.0, 152.0, 159.5, 161.5, 163.8; Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 64.08; H, 5.19; N, 16.73.

4-(4-Chlorophenyl)-3,6,8-trimethyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,4*H*)-dione (5ak). White solid; IR (KBr): 3433, 3132, 1685, 1614, 1487, 1452, 1346 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.26 (s, 3H, CH_3), 3.36 (s, 6H, CH_3), 5.54 (s, 1H, CH), 7.05 (d, J = 8.0 Hz, 2H, HAr), 7.25 (d, J = 8.5 Hz, 2H, HAr), 13.60 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.4, 28.2, 115.7, 128.2, 129.0, 129.2, 129.6, 130.4, 130.5, 136.5, 152.1, 159.4, 161.0; Anal. Calcd for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62. Found: C, 57.10; H, 4.04; N, 15.79.

3-Methyl-4-phenyl-7-thioxo-4,6,7,8-tetrahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one (5al). White solid; IR (KBr): 3385, 3032, 1750, 1624, 1533, 1474, 1364 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.25 (s, 3H, CH_3), 5.44 (s, 1H, CH), 7.04 (d, J = 7.5 Hz, 2H, HAr), 7.12 (t, J = 7.5 Hz, 1H, HAr), 7.21 (t, J = 7.5 Hz, 2H, HAr), 11.50 (s, 2H, NH), 13.53 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.4, 31.0, 96.5, 105.9, 126.0, 127.1, 128.4, 142.3, 144.3, 159.7, 163.7, 163.8, 173.5; Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.87; H, 3.70; N, 18.11.

3-Methyl-4-(3-nitrophenyl)-7-thioxo-4,6,7,8-tetrahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one (5am). White solid; IR (KBr): 3103, 3030, 1858, 1500, 1476, 1350 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 2.29 (s, 3H, CH_3), 5.53 (s, 1H, CH), 7.54-7.57 (m, 2H, HAr), 7.84 (s, 1H, HAr), 8.03 (d, J = 7.0 Hz, 1H, HAr), 11.59 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ ppm: 10.5, 31.2, 96.0, 104.9, 121.4, 121.5, 123.1, 130.0, 134.2, 144.5, 144.9, 148.2, 159.2, 163.9, 173.8; Anal. Calcd for $C_{15}H_{11}N_5O_4S$: C, 50.42; H, 3.10; N, 19.60. Found: C, 50.61; H, 2.93; N, 19.77.

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