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MULTICOMPONENT AND REGIOSELECTIVE SYNTHESIS OF DIHYDROPYRAZOLO[1,5-*a*]PYRIMIDINES FROM AROMATIC ALDEHYDES, MELDRUM´S ACID AND AMINOPYRAZOLE CAN508

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Abstract – A regioselective synthesis of dihydropyrazolo[1,5-*a*]pyrimidines is reported. The multicomponent reaction of readily available arylaldehydes, Meldrum´s acid, and aminopyrazole CAN508 afforded fused pyrazolopyrimidines in high yields. The reaction proceeded regioselectively via initial Michael addition of the exocyclic amino group to arylidene Meldrum´s acid intermediate followed by a ring closure at the endocyclic nitrogen of aminopyrazole. The regioselectivity of the reaction was determined by X-ray crystallography.

Pyrazolopyrimidines belong to a class of fused heterocyclic compounds, which have found a broad application in the field of medicinal chemistry. Structures containing pyrazolo[1,5-*a*]pyrimidine core have been reported as antitrichomonal agents,[1] cAMPphosphodiesterase inhibitors,[2] selective COX-2 inhibitors,[3] benzodiazepine receptor antagonists,[4] CRF receptor antagonists,[5] and estrogen receptor antagonists.[6] Structural similarity to purine bases makes them a suitable scaffold for the development of competitive inhibitors of therapeutically useful protein kinases including c-SRC,[7] Jak2,[8] PI3Kβ,[9] and cyclin-dependent kinases.[10] Partially saturated analogues of dihydropyrazolo[1,5-*a*]pyrimidines are also structures of interest from the biological point of view. Recently, they were identified as potent

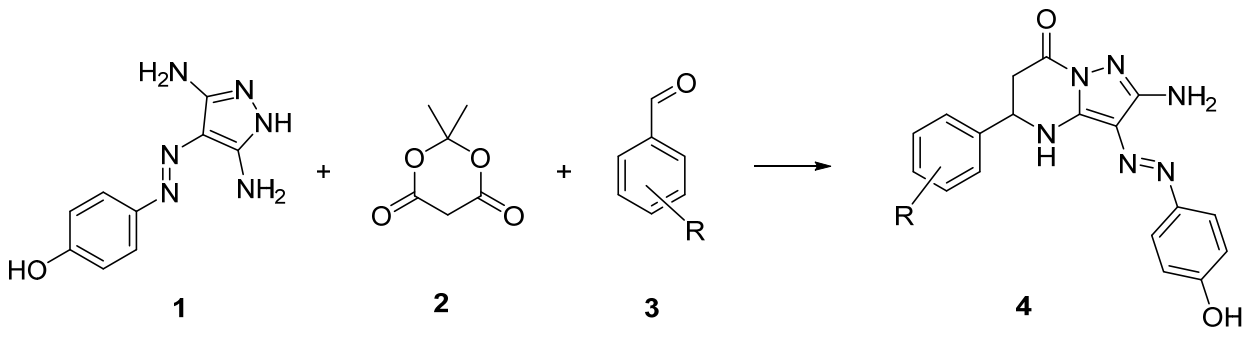
antagonists of potassium channel and the most promising compound entered clinical trials for the treatment of atrial fibrillation.[11]

In general, dihydropyrazolo[1,5-*a*]pyrimidines could be prepared either using sequential protocol starting with the synthesis of the α,β-unsaturated carbonyl compound, followed by cyclocondensation with 3(5)-aminopyrazole,[12] or in one-step via multicomponent Biginelli type reaction of aldehyde, 1,3-dicarbonyl compound and aminopyrazole.[13]

Multicomponent reactions (MCRs) have received appreciable attention from the organic chemists due to several advantages over conventional multistep synthesis, since they provide rapid and effective generation of libraries of heterocyclic compounds with varied substitution patterns. In addition, MCRs are more often atom economic and ecologically benign as they avoid time-consuming and expensive purification processes, as well as protection and deprotection steps.[14] Among numerous MCRs known, a tandem of Knoevenagel condensation and Michael addition transformations utilizing Meldrum´s acid as a C2 synthon represent an outstanding instrument for the synthesis of heterocycles.[15] For instance, the MCRs involving Meldrum´s acid have been reported in the synthesis of pyridine,[16a] pyrimidine,[16b] quinoline,[16c] and spiroindole.[16d]

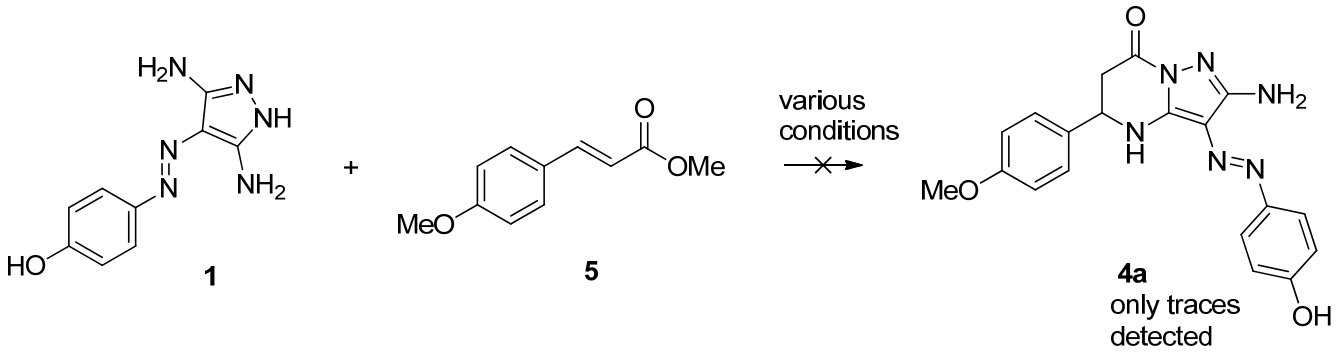
In the course of research program towards the development of synthetic inhibitors of cyclin-dependent kinases (CDKs), aminopyrazole (CAN508,compound **1**) was identified as a potent and selective CDK inhibitor with preference to CDK9.[17] Moreover, compound **(1)** showed antiproliferative activity on several cancer cell lines. In addition, it was found that the introduction of an acyl substituent at the exocyclic amino group increased the potency against CDK2.[17b]

This finding encouraged us to further modify the aminopyrazole core of compound **(1)**. Since some pyrazolopyrimidines are known inhibitors of CDKs and structure **(1)** is appropriate starting material in the synthesis of fused pyrazolopyrimidines, as it contains amidine-like 1,3-bisnucleophilic scaffold, we developed an efficient MCR of aminopyrazole **(1)**, Meldrum´s acid **(2)** and arylaldehydes **(3)**, leading to pyrazolo[1,5-*a*]pyrimidines **(4)** (Scheme 1).



Scheme 1

Initially, we started with the synthesis of pyrazolopyrimidne **(4a)** by the cyclocondensation of commercially available cinnamate **(5)** with aminopyrazole **(1)** (Scheme 2). In general, the reaction of α,β-unsaturated esters with aminoazoles are known to proceed at high temperatures and usually in lower yields.[12a,b] In our case, the cyclocondensation was examined at various conditions using conventional heating or microwave irradiation, acid (HCl, $ZnCl_2$) or base (Et_3N, DBU, NaOH) catalysis, but the desired product was not obtained. Only traces of compound **(4a)** were detected by HPLC-MS in the crude reaction mixture, while the starting materials, ester **(5)** and pyrazole **(1)**, remained almost unreacted. These results indicated, that conjugation of the C=C bond with one ester group is insufficient to allow Michael addition of aminopyrazole **(1)**.



Scheme 2. Conditions: a) 20 mol% $ZnCl_2$ or HCl, MeOH, reflux/MW; b) 10 - 20 mol% DBU or NaOH, MeOH reflux/MW.

In order to increase electrophilicity of the C=C bond it was introduced a second ester group in a form of arylidene Meldrum´s acids. Subsequently, preliminary experiments were focused on the MCR of aminopyrazole **(1)**, Meldrum´s acid **(2)**, and 4-methoxybenzaldehyde **(3a)**, Table 1 (Scheme 1, R = 4-OMe). All three components were stirred in EtOH at room temperature and the desired product **(4a)** was isolated by filtration in 52% yield (Entry 1). The mother liquor contained small amount of **(4a)** together with unreacted pyrazole **(1)** (recovered 23%) and arylidene Meldrum´s acid **(6)**. When the MCR was performed in the presence of a catalytic amount of base, the isolated yield of **(4a)** slightly increased, but the reaction was not complete even after 16 hours (Entries 2, 3, and 4). Attempts to promote the reaction with acid failed, since the addition of 10 mol% of $ZnCl_2$ or HCl led to lower isolated yields (Entries 5 and 6). A full conversion of starting aminopyrazole **(1)** was achieved, when the reaction was carried out in boiling EtOH without addition of any catalyst (Entry 7).

These results indicated that the MCR can be promoted with a base, the catalyst is not necessary, and the high isolated yield can be reached at slightly elevated temperature (~ 80 °C). Other solvents, MeCN, THF, AcOH and pyridine, were also examined. The reaction in boiling pyridine gave comparable result to

EtOH (Entry 11), while MeCN and THF provided **(4a)** in lower yields (Entries 8 and 9). The complex mixture was obtained, when AcOH was used as a solvent, and only traces of **(4a)** were detected by HPLC-MS. Since the reaction in boiling EtOH without any catalyst gave the highest isolated yield (Entry 7), these conditions were used for the synthesis of pyrazolopyrimidines **(4a-q)**.

Table 1. The optimisation of MCR of pyrazole **(1)**, Medldrum´s acid **(2)** and 4-methoxybenzaldehyde **(3a)**

Entry	Solvent	Catalyst (20 mol%)	T (°C)	Yield[a] (%)
1	EtOH	-	rt	52
2	EtOH	Et_3N	rt	63
3	EtOH	DBU	rt	71
4	EtOH	NaOH	rt	64
5	EtOH	$ZnCl_2$	rt	42
6	EtOH	HCl	rt	49
7	EtOH	-	reflux	86
8	MeCN	-	reflux	37
9	THF	-	reflux	32
10	AcOH	-	reflux	-
11	pyridine	-	reflux	77

[a]Isolated yield of pyrazolopyrimidine **(4a)** after 16 hours.

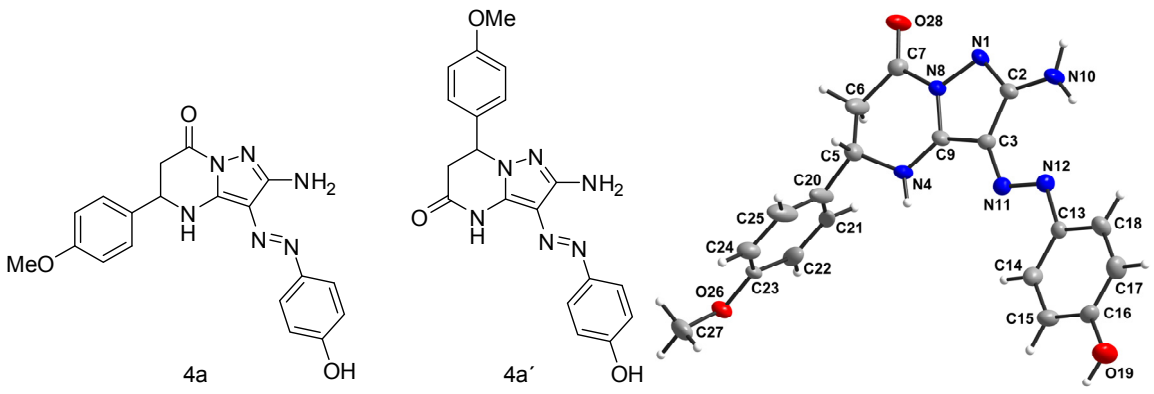
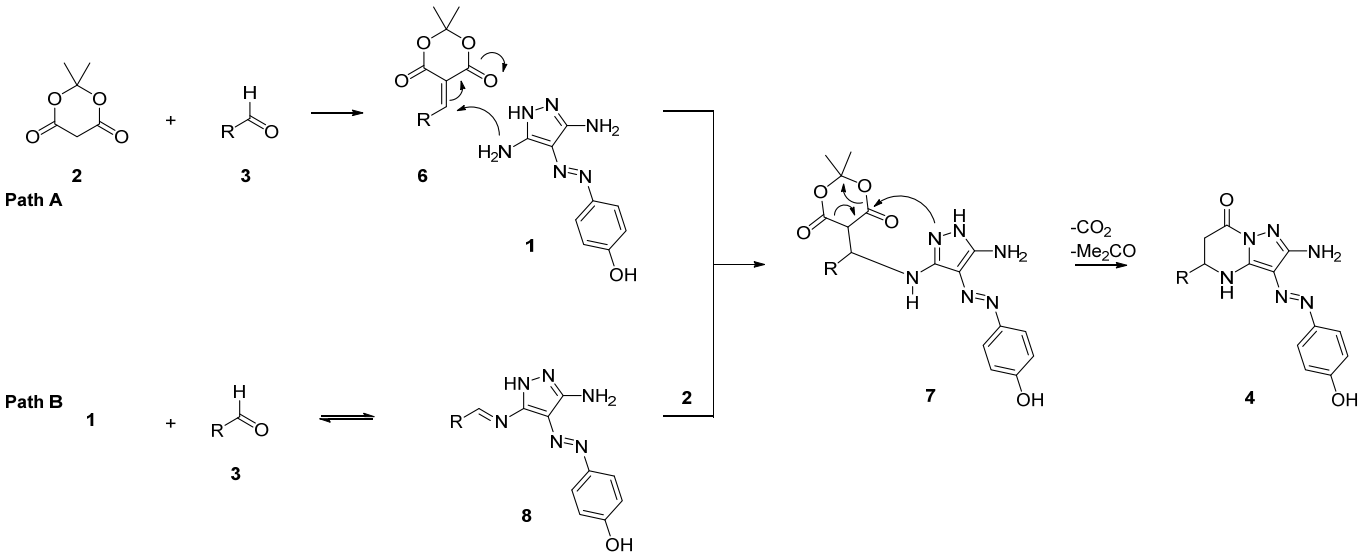


Figure 1.Regioisomeric structures **(4a)** and **(4a´)**. X-Ray structure of **(4a)**; ellipsoids are drawn at the 40% probability level. Only one of two crystallographically independent molecules is shown, the second part of the disordered C_5H moiety is omitted for clarity.

It should be noted, that the compound **(4a)** was isolated as the single regioisomer. Theoretically, the MCR depicted in Scheme 1 could provide two regioisomers **(4a)** and **(4a´)**. The single crystals of the product were grown in pyridine and the structure was assigned by single crystal X-ray analysis as **(4a)** (Figure 1). Plausible mechanism of the presented MCR involves the formation of the arylidene Meldrum´s acid **(6)** (Scheme 3), which was detected in the reaction mixture by HPLC-MS. In the model experiment the cyclocondensation of separately prepared **(6)** with pyrazole **(1)** delivered the same regioisomer **(4a)** as the multicomponent protocol and the yield for both procedures was almost identical. In the next step, Michael addition of the exocyclic amino group to β-carbon of compound **(6)** led to the intermediate **(7)**, which underwent cyclisation with simultaneous elimination of an acetone and carbon dioxide molecule (path A). Alternatively, the first step of the plausible mechanism can be reversible formation of imine **(8)**, path B. However, in the model experiment, aldehyde **(3a)** and pyrazole **(1)** gave only a low amount of imine **(8)**, less then 10%. Moreover, imine **(8)** was not detected in the MCR, therefore pathway B can be excluded.

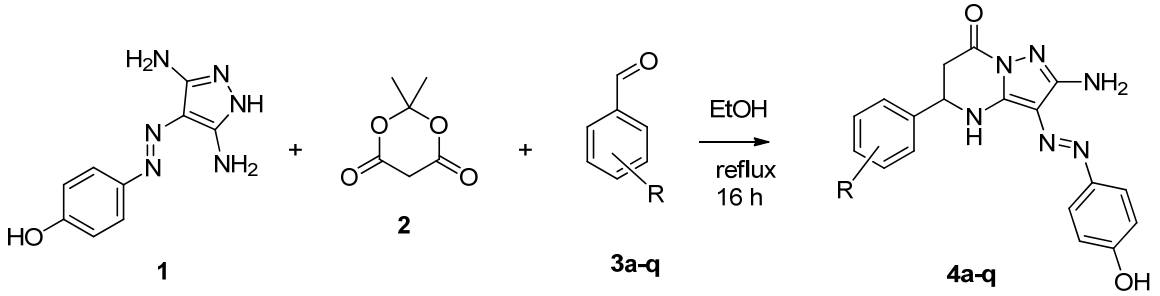


Scheme 3. Proposed mechanism of the MCR

The scope of the optimized MCR with various benzaldehydes **(3a-q)** was extended to the synthesis of seventeen pyrazolopyrimidines **(4a-q)** [Table 2 (reaction shown in Scheme 1)]. All compounds were isolated by simple filtration as single regioisomers in high isolated yields, 79 – 92%. Moreover, the purity of the crude products exceeded 95%, as determined by a combination of ^{1}H NMR and HPLC-MS. The crystallization from EtOH afforded analytically pure samples. All substituents on aldehydes **(3a-q)** (CF_3, NO_2, OMe, OH, F, Cl) were compatible with the reaction. Any significant effect of electron donating or electron withdrawing groups on the reaction rate and yield was not observed. It can be expected, that the dihydropyrazolopyrimidine could be prone to aromatization (oxidation). However, any decomposition or

aromatization of **(4a)** was not detected even after six months standing at room temperature in solid state or in DMF solution.

Table 2. The MCR synthesis of pyrazolopyrimidines **(4a-q)** using benzaldehydes **(3a-q)**



1 2 3a-q 4a-q

Entry	R	Yield[a] (%)	Entry	R	Yield[a] (%)
4a	4-OMe	86	**4j**	4-F	86
4b	2-OMe	83	**4k**	2-Cl, 6-F	82
4c	4-OH, 3-OMe	89	**4l**	2,6-Cl	92
4d	2,4-OMe	85	**4m**	2-CF_3	91
4e	2,4,6-OMe	87	**4n**	4-CF_3	87
4f	3-OH	92	**4o**	3-CF_3	80
4g	2,6-Me	80	**4p**	2-NO_2	84
4h	2-F	88	**4q**	4-NO_2	79
4i	3-F	90			

[a]Isolated yields of pyrazolopyrimidines **(4a-q)** after filtration (purity > 95%).

All prepared dihydropyrazolo[1,5-*a*]pyrimidines **(4a-q)** were assayed for their CDK inhibitory activity as described.[17] However, the results were negative probably due to structural differences from potent CDK inhibitors based on pyrazolo[1,5-*a*]pyrimidines[10b,c] and 3,5-diaminopyrazoles (including CAN508).[17] Although the acylation of the exocyclic aminopyrazole group enhanced CDK inhibition[17b] the formation of partially saturated pyrimidine ring led to conformation where the aryl substituent was oriented more axially with respect to pyrazolopyrimidine system.

In summary, an efficient, regioselective and high yielding MCR protocol for the synthesis of dihydropyrazolo[1,5-*a*]pyrimidines was developed. The regioisomeric outcome of the presented MCR was unambiguously proved by X-ray analysis. All compounds were obtained in high purity as stable crystalline solids, thoroughly characterized and tested for CDK inhibitory activity. Unfortunately, they did not show any significant CDK inhibitory potency probably due to their conformation.

EXPERIMENTAL

All starting materials, solvents and reagents were purchased from commercial suppliers and were used as received without further purification. Pyrazole **(1)** was prepared according the known procedure.[17a] Melting points were determined on a Boetius stage. The HPLC-MS analyses were carried out on an UHPLC-MS system consisting of an Accela UHPLC chromatograph with a photodiode array detector and a TSQ Quantum Access triple quadrupole mass spectrometer (both Thermo Scientific, CA, USA), using a Nucleodur Gravity C18 column (Macherey-Nagel, 1.8 μm, 2.1 x 50 mm, Germany) at 30 °C and a flow rate of 800 μL/min. The APCI source operated at a discharge current of 5 μA, vaporizer temperature of 400 °C and capillary temperature of 200 °C. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 20 °C on a Bruker 400 or 300 FT NMR spectrometer. Elemental analyses were performed using a Flash 2000 CHNS Elemental Analyzer (Thermo Scientific). X-Ray data of **(4a)** were collected on an Xcalibur^{TM}2 diffractometer (Oxford Diffraction Ltd.) equipped with Sapphire2 CCD detector, with Mo Kαradiation (Monochromator Enhance, Oxford Diffraction Ltd.), and at 120 K. Software used for data collection, data reduction, structure solution and refinement, together with crystal data and structure refinement, selected bond lengths and angles, and hydrogen bonds, are given in Supplementary data.

Representative procedure for the synthesis of dihydropyrazolo[1,5-*a*]pyrimidines (4a-q).

A mixture of aminopyrazole **(1)** (0.22 g, 1.0 mmol), Meldrum´s acid **(2)** (0.16 g, 1.1 mmol,) and 4-methoxybenzaldehyde (0.15 g, 1.1 mmol) was stirred in boiling EtOH (4 mL) for 16 h. After the mixture was cooled to a room temperature, the orange solid was collected by filtration, washed with cold EtOH and dried under vacuum to yield pyrazolopyrimidine **(4a)** as an orange solid (0.33 g, 86%).

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-(4-methoxyphenyl)-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4a): orange solid 0.33 g (86%), mp 280-282 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98 (dd, J = 16.4, 7.8 Hz, 1 H), 3.08 (dd, J = 16.4, 5.7 Hz, 1 H), 3.74 (s, 3 H), 5.00 (dd, J = 7.8, 5.7 Hz, 1 H), 6.28 (br. s, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 7.67 (d, J = 8.8 Hz, 2 H), 8.74 (br. s, 1 H), 9.78 (br. s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 39.2, 53.3, 55.2, 112.0, 114.1, 115.4, 122.8, 127.6, 132.4, 145.9, 146.0, 153.4, 158.2, 159.0, 160.4. Anal.Calcd for $C_{19}H_{18}N_6O_3$ (378.14); C, 60.31; H, 4.79; N, 22.21. Found: C, 60.24; H, 4.90; N, 22.34.

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-(2-methoxyphenyl)-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4b): Prepared according to the representative procedure using aldehyde **(3b)**. Yellow solid 0.31 g (83%), mp 268-270 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.87 (dd, J = 16.6, 5.5 Hz, 1 H), 3.25 (dd, J = 16.6, 6.4 Hz, 1 H), 3.85 (s, 3 H), 5.23 (t, J = 5.6 Hz, 1 H), 6.26 (br. s, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.96 (t, J = 7.3 Hz, 1 H), 7.07 (d, J = 8.2 Hz, 1 H), 7.16 (d, J = 7.3 Hz, 1 H), 7.3 (t, J = 7.3 Hz, 1 H), 7.68 (d, J = 8.7 Hz, 2 H), 8.72 (br. s, 1 H), 9.80 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6)

δ ppm 36.9, 48.8, 55.6, 111.3, 111.9, 115.5, 120.6, 122.7, 125.9, 128.0, 129.3, 145.0, 146.0, 154.0, 156.1, 158.2, 160.3. Anal.Calcd for $C_{19}H_{18}N_6O_3$ (378.14); C, 60.31; H, 4.79; N, 22.21. Found: C, 60.53; H, 4.56; N, 22.01.

2-Amino-5-(4-hydroxy-3-methoxyphenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo-[1,5-*a*]pyrimidin-7(4*H*)-one (4c): Prepared according to the representative procedure using aldehyde **(3c)**.Yellow solid 0.35 g (89%), mp 284-285 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.00 (dd, J = 17.0, 5.7 Hz, 1 H), 3.09 (dd, J = 17.0, 8.4 Hz, 1 H), 3.77 (s, 3 H), 4.96 (t, J = 6.7 Hz, 1 H), 6.31 (br. s, 2 H), 6.74 - 6.88 (m, 4 H), 7.05 (s, 1 H), 7.70 (d, J = 8.4 Hz, 2 H), 8.93 (br. s, 1 H), 9.77 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 39.4, 53.9, 55.7, 111.0, 112.0, 115.4, 115.5, 118.7, 122.9, 131.1, 146.1, 146.2, 146.5, 147.7, 153.4, 158.2, 160.6. Anal.Calcd for $C_{19}H_{18}N_6O_4$ (394.38); C, 57.86; H, 4,60; N, 21.31. Found: C, 57.66; H, 4.82; N, 21.05.

2-Amino-5-(2,4-dimethoxyphenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4d): Prepared according to the representative procedure using aldehyde **(3d)**. Yellow solid 0.34 g (85%), mp 276-278 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.89 (dd, J = 16.5, 5.5 Hz, 1 H), 3.15 - 3.23 (m, 1 H), 3.74 (s, 3 H), 3.83 (s, 3 H), 5.17 (t, J = 5.3 Hz, 1 H), 6.27 (br. s, 2 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.62 (s, 1 H), 6.84 (d, J = 8.1 Hz, 2 H), 7.09 (d, J = 8.1 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 2 H), 8.69 (br. s, 1 H), 9.79 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 37.2, 48.7, 55.3, 55.7, 98.9, 104.8, 112.0, 115.5, 120.2, 122.8, 126.8, 145.1, 146.1, 154.0, 157.3, 158.2, 160.5, 160.5. Anal.Calcd for: $C_{20}H_{20}N_6O_4$ (408.41); C, 58.82; H, 4.94; N, 20.58. Found: C, 58,63; H, 4.86; N, 20.74.

2-Amino-5-(2,4,6-trimethoxyphenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo-[1,5-*a*]-pyrimidin-7(4*H*)-one (4e): Prepared according to the representative procedure using aldehyde **(3e)**. Yellow solid 0.38 g (87%), mp 295-296 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.88 (dd, J = 16.8, 5.3 Hz, 1 H), 3.12 (dd, J = 16.8, 8.1 Hz, 1 H), 3.72 (s, 6 H), 3.77 (s, 3 H), 5.49 (dd, J = 8.1, 5.3 Hz, 1 H), 6.20 (br. s, 2 H), 6.25 (s, 2 H), 6.78 (d, J = 8.6 Hz, 2 H), 7.61 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 35.7, 44.3, 54.1, 55.5, 91.3, 109.0, 111.5, 115.3, 122.5, 146.1, 146.5, 152.7, 157.7, 158.9, 160.5, 160.9. Anal.Calcd for $C_{21}H_{22}N_6O_5$ (438.44); C, 57.53; H, 5.06; N, 19.17. Found: C, 57.42; H, 5.18; N, 18.91.

2-Amino-5-(3-hydroxyphenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4f): Prepared according to the representative procedure using aldehyde **(3f)**. Yellow solid 0.33 g (92%), mp 312-314 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.92 (dd, J = 16.6, 7.0 Hz, 1 H), 3.16 (dd, J = 16.6, 5.7 Hz, 1 H), 4.98 (t, J = 6.1 Hz, 1 H), 6.30 (br. s, 2 H), 6.72 (d, J = 7.9 Hz, 1 H), 6.76 - 6.87 (m, 4 H), 7.18 (t, J = 7.8 Hz, 1 H), 7.69 (d, J = 8.6 Hz, 2 H), 9.55 (br. s, 1 H), 9.78 (br. s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 39.1, 53.6, 111.9, 112.9, 114.8, 115.4, 116.8, 122.8, 129.8,

142.2, 145.6, 146.1, 153.6, 157.6, 158.2, 160.3. Anal.Calcd for $C_{18}H_{16}N_6O_3$ (364.36); C, 59.34; H, 4.43; N, 23.07. Found: C, 59.30; 4.47; N, 22.78.

2-Amino-5-(2,6-dimethylphenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4g): Prepared according to the representative procedure using aldehyde **(3g)**. Yellow solid 0.30 g (80%), mp 298-300 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.45 (s, 6 H), 2.75 (dd, J = 16.9, 4.9 Hz, 1 H), 3.22 (dd, J = 16.9, 14.3 Hz, 1 H), 5.52 (dd, J = 14.3, 4.9 Hz, 1 H), 6.32 (br. s, 2 H), 6.78 (d, J = 8.6 Hz, 2 H), 7.06 (d, J = 7.0 Hz, 2 H), 7.13 (dd, J = 8.4, 6.4 Hz, 1 H), 7.64 (d, J = 8.6 Hz, 2 H), 8.64 (br. s, 1 H), 9.69 (br. s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 20.7, 35.3, 50.9, 112.1, 115.3, 122.6, 127.6, 129.4, 134.7, 136.7, 145.9, 147.5, 152.6, 157.9, 160.5. Anal.Calcd for $C_{20}H_{20}N_6O_2$ (376.41); C, 63.82; H, 5.36; N, 22.33. Found:C, 63.41; H, 5.34; N, 22.21.

2-Amino-5-(2-fluorophenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4h): Prepared according to the representative procedure using aldehyde **(3h)**. Yellow solid 0.32 g (88%), mp 288-290 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.95 (dd, J = 16.6, 7.7 Hz, 1 H), 3.19 (dd, J = 16.6, 5.9 Hz, 1 H), 5.33 (t, J = 6.7 Hz, 1 H), 6.31 (br. s, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 7.20 - 7.32 (m, 2 H), 7.35 - 7.47 (m, 2 H), 7.68 (d, J = 8.6 Hz, 2 H), 8.80 (br. s, 1 H), 9.79 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 37.7, 48.2 (d, $^3J_{CF}$ = 3.3 Hz), 112.1, 115.4, 115.7 (d, $^2J_{CF}$ = 22.1 Hz), 122.8, 124.8 (d, $^4J_{CF}$ = 3.3 Hz), 127.4 (d, $^2J_{CF}$ = 13.3 Hz), 127.7 (d, $^3J_{CF}$ = 3.3 Hz), 130.0 (d, $^3J_{CF}$ = 7.7 Hz), 145.8, 145.9, 153.4, 158.2, 159.8, 160.0 (d, $^1J_{CF}$ = 245.5 Hz). Anal.Calcd for $C_{18}H_{15}FN_6O_2$ (366.35); C, 59.01; H, 4.13; N, 22.94. Found: C, 58.83; H, 4.03; N, 22.47.

2-Amino-5-(3-fluorophenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4i): Prepared according to the representative procedure using aldehyde **(3i)**. Yellow solid 0.33 g (90%), mp 270-272 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.04 (dd, J = 16.8, 7.9 Hz, 1 H), 3.14 (dd, J = 16.8, 5.7 Hz, 1 H), 5.09 (t, J = 6.6 Hz, 1 H), 6.29 (br. s, 2 H), 6.82 (d,J = 8.6 Hz, 2 H), 7.17 (t, J = 8.4 Hz, 1 H), 7.22 - 7.33 (m, 2 H), 7.40 - 7.52 (m, 1 H), 7.69 (d, J = 8.6 Hz, 2 H), 8.82 (br. s, 1 H), 9.78 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 38.9, 53.4, 112.0, 113.4 (d, $^2J_{CF}$ = 22.1 Hz), 114.8 (d, $^2J_{CF}$ = 21.0 Hz), 115.4, 122.4 (d,$^4J_{CF}$ = 3.3 Hz), 122.8, 130.7 (d, $^3J_{CF}$ = 8.9 Hz), 143.5 (d, $^3J_{CF}$ = 6.6 Hz), 145.8, 145.9, 153.3, 158.2, 160.1, 162.9 (d, $^1J_{CF}$ = 244.4 Hz). Anal.Calcd for $C_{18}H_{15}FN_6O_2$ (366.35); C, 59.01; H, 4.13; N, 22.94. Found: C, 58.82; 3.98; N, 23.37.

2-Amino-5-(4-fluorophenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4j): Prepared according to the representative procedure using aldehyde **(3j)**. Yellow solid 0.31 g (86%), mp 286-288 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.01 (dd, J = 16.7, 8.1 Hz, 1 H), 3.10 (dd, J = 16.7, 5.9 Hz, 1 H), 5.07 (t, J = 6.7 Hz, 1 H), 6.28 (br. s, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 7.24 (t, J = 8.8 Hz, 2 H), 7.47 (dd, J = 8.1, 5.7 Hz, 2 H), 7.68 (d, J = 8.6 Hz, 2 H), 8.78 (br. s, 1 H), 9.77 (br. s, 1

H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 39.1, 53.2, 112.0, 115.3, 115.4 (d, $^{2}J_{CF}$ = 21.0 Hz), 122.8, 128.6 (d, $^{3}J_{CF}$ = 8.9 Hz), 136.7 (d, $^{4}J_{CF}$ = 3.3 Hz), 145.8, 145.9, 153.3, 158.2, 160.1, 161.2 (d, $^{1}J_{CF}$ = 244.4 Hz). Anal.Calcd for $C_{18}H_{15}FN_6O_2$ (366.35); C, 59.01; H, 4.13; N, 22.94. Found: C, 58.69; H, 4.11; N, 22.73.

2-Amino-5-(2-chloro-6-fluorophenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo-[1,5-*a*]pyrimidin-7(4*H*)-one (4k): Prepared according to the representative procedure using aldehyde **(3k)**. Orange solid 0.33 g (82%), mp 295-297 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.12 (d, *J* = 8.0 Hz, 2 H), 5.64 (t, *J* = 8.0 Hz, 1 H), 6.32 (br. s, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 7.19 - 7.35 (m, 1 H), 7.36 - 7.51 (m, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 8.86 (br. s, 1 H), 9.74 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 35.3, 48.7, 112.0, 115.4, 115.8 (d, $^{2}J_{CF}$ = 23.2), 122.6, 125.0 (d, $^{2}J_{CF}$ = 14.4), 126.2 (d, $^{4}J_{CF}$ = 3.3 Hz), 130.8 (d, $^{3}J_{CF}$ = 11.1 Hz), 133.6 (d, $^{3}J_{CF}$ = 5.5 Hz), 145.8, 146.6, 152.8, 158.1, 159.6, 161.5 (d, $^{1}J_{CF}$ = 251.0). Anal.Calcd for $C_{18}H_{14}ClFN_6O_2$ (400.79); C, 53.94; H, 3.52; N, 20.97. Found: C, 53.69; H, 3.74; N, 20.62.

2-Amino-5-(2,6-dichlorophenyl)-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5,6-dihydropyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-one (4l): Prepared according to the representative procedure using aldehyde **(3l)**. Red solid 0.38 g (92%), mp 302-304 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) 2.93 (dd, *J* = 17.0, 6.5 Hz, 1 H), 3.34 (dd,*J* = 17.0, 11.9 Hz, 1 H), 5.92 (dd, *J* = 11.9, 6.5 Hz, 1 H), 6.38 (br. s, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 7.41 (t, *J* = 7.9 Hz, 1 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 7.63 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 34.1, 51.0, 112.3, 115.4, 122.5, 129.9, 130.6, 133.6, 134.7, 145.6, 147.1, 152.7, 158.0, 159.4. Anal.Calcd for $C_{18}H_{14}Cl_2N_6O_2$ (417.25); C, 51.81; H, 3.38; N, 20.14. Found: C, 51.46; H, 3.23; N, 20.18.

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-[2-(trifluoromethyl)phenyl]-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4m):Prepared according to the representative procedure using aldehyde **(3m)**. Yellow solid 0.38 g (91%), mp 289-291 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 (dd, *J* = 16.5, 5.5 Hz, 1 H), 3.05 (dd, *J* = 16.5, 9.8 Hz, 1 H), 5.36 (dd, *J* = 9.8, 5.5 Hz, 1 H), 6.36 (br. s, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 7.59 (t, *J* = 7.7 Hz, 1 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.73 - 7.83 (m, 2 H), 7.92 (d, *J* = 7.7 Hz, 1 H), 8.82 (br. s, 1 H), 9.77 (br. s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 39.6, 50.8, 112.1, 115.4, 122.9, 124.1 (q, $^{1}J_{CF}$ = 274.0 Hz), 125.8 (q, $^{3}J_{CF}$ = 5.5 Hz), 126.2 (q, $^{2}J_{CF}$ = 29.9 Hz), 128.6, 128.7, 133.3, 139.4, 145.9, 147.4, 152.8, 158.3, 159.5. Anal.Calcd for $C_{19}H_{15}F_3N_6O_2$ (416.36); C, 54.81; H, 3.36; N, 20.18. Found: C, 54.61; H, 3.58; N, 19.96.

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-[4-(trifluoromethyl)phenyl]-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4n): Prepared according to the representative procedure using aldehyde **(3n)**. Yellow solid 0.36 g (87%), mp 283-285 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.04 (dd, *J* = 16.6, 8.2 Hz, 1 H), 3.17 (dd, *J* = 16.6, 5.7 Hz, 1 H), 5.18 (t, *J* = 6.6 Hz, 1 H), 6.31 (br. s, 2 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 7.60 - 7.73 (m, 4 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 8.86 (br. s, 1 H), 9.79 (br. s, 1 H); ^{13}C NMR (75

MHz, DMSO-d_6) δ ppm 38.8, 53.6, 112.1, 115.4, 122.9, 124.2 (q, $^1J_{CF}$= 272.5 Hz), 125.6 (q, $^3J_{CF}$ = 3.8 Hz), 127.39, 127.40, 128.47 (q, $^2J_{CF}$ = 31.9 Hz), 145.4, 145.9, 153.4, 158.3, 160.0. Anal.Calcd for $C_{19}H_{15}F_3N_6O_2$ (416.36); C, 54.81; H, 3.36; N, 20.18. Found: C, 54.62; H, 3.55; N, 20.23.

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-[3-(trifluoromethyl)phenyl]-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4o): Prepared according to the representative procedure using aldehyde **(3o)**. Orange solid 0.33 g (80%), mp 274-276 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.11 (d, J = 6.9 Hz, 2 H), 5.19 (t, J = 6.9 Hz, 1 H), 6.33 (br. s, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 7.60 – 7.80 (m, 3 H), 7.68 (d, J = 8.6 Hz, 2 H), 7.84 (s., 1 H), 8.83 (br. s, 1 H), 9.80 (br. s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm (one signal overlap by DMSO), 53.7, 112.1, 115.4, 122.9, 123.6 (q, $^1J_{CF}$ = 3.9 Hz), 124.3 (q, $^1J_{CF}$ = 272.5 Hz), 124.8 (q, $^3J_{CF}$ = 3.1 Hz), 129.3 (q, $^2J_{CF}$ = 31.9 Hz), 129.9, 130.7, 142.0, 145.9, 146.4, 153.2, 158.3, 160.1. Anal.Calcd for $C_{19}H_{15}F_3N_6O_2$ (416.36); C, 54.81; H, 3.36; N, 20.18. Found: C, 54.51; H, 3.64; N, 20.24.

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-(2-nitrophenyl)-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4p): Prepared according to the representative procedure using aldehyde **(3p)**. Orange solid 0.33 g (84%), mp 278-280 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.05 (dd, J=16.6, 8.8 Hz, 1 H), 3.28 (dd, J = 16.6, 5.7 Hz, 1 H), 5.49 (dd, J = 8.8, 5.7 Hz, 1 H), 6.32 (br. s, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 7.56 - 7.71 (m, 3 H), 7.74 - 7.84 (m, 2 H), 8.04 (d, J = 7.9 Hz, 1 H), 8.73 (br. s, 1 H), 9.79 (br.s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 38.2, 50.2, 112.4, 115.4, 122.7, 124.7, 128.4, 129.4, 134.1, 135.4, 145.4, 145.6, 148.2, 153.8, 158.3, 159.5. Anal.Calcd for $C_{18}H_{15}N_7O_4$ (393.36); C, 54.96; H, 3.84; N, 24.93. Found: C, 54.61; H, 3.83; N, 24.74.

2-Amino-3-[(*E*)-(4-hydroxyphenyl)diazenyl]-5-(4-nitrophenyl)-5,6-dihydropyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (4q): Prepared according to the representative procedure using aldehyde **(3q)**. Orange solid 0.31 g (79%), mp 332-334 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.03 (dd, J = 16.5, 7.9 Hz, 1 H), 3.19 (dd, J=16.5, 5.8 Hz, 1 H), 5.24 (dd, J = 7.9, 5.8 Hz, 1 H), 6.30 (br. s, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 7.68 (d, J = 7.8 Hz, 2 H), 7.71 (d, J = 7.8 Hz, 2 H), 8.28 (d, J = 8.6 Hz, 2 H), 8.91 (br. s, 1 H), 9.80 (br. s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm (one signal overlap by DMSO) 53.4, 112.2, 115.4, 122.8, 123.8, 127.8, 145.6, 145.8, 147.1, 148.2, 153.4, 158.3, 159.8. Anal.Calcd for $C_{18}H_{15}N_7O_4$ (393.36); C, 54.96; H, 3.84; N, 24.93. Found: C, 55.51; H, 3.74; N, 25.17.

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