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Synthesis and Molecular Docking Studies of *N*,*N*-Dimethyl Arylpyranopyrimidinedione Derivatives

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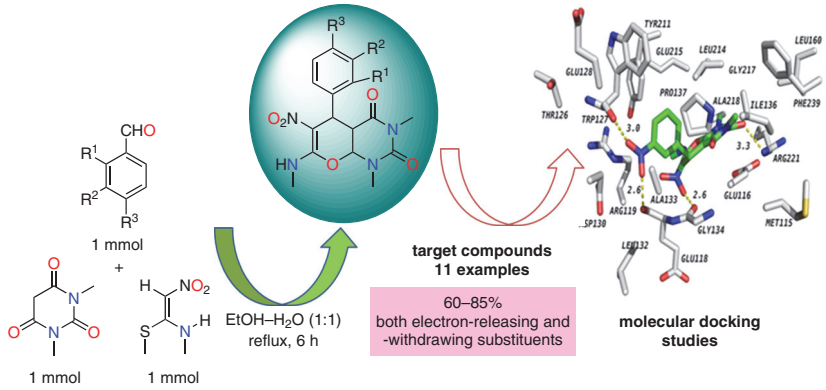

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Abstract The synthesis of *N*,*N*-dimethyl arylpyranopyrimidinedione derivatives from aromatic aldehydes, *N*-methyl-1-(methylthio)-2-nitroethamine (NMSM) and 1,3-dimethyl barbituric acid, in the presence of piperidine as a catalyst, is reported. The reaction mechanism involves a Knoevenagel condensation, followed by Michael addition and intramolecular O-cyclization reaction sequence. The synthesized compounds were docked with human kinesin Eg5 protein to calculate binding energy, inhibition constant and H-bond interaction. All the compounds show good binding affinity towards the protein, with significant docking score.

Keywords *N*,*N*-dimethyl arylpyranopyrimidinedione, Knoevenagel condensation, Michael addition, O-cyclization, docking studies

Heterocyclic compounds are central to a wide range of bioactive molecules.[1] Multicomponent reactions have attracted much attention from medicinal chemists due to the potential for rapid synthesis of complex molecules without isolation of intermediates.[2] Furthermore, there is much interest in joining two privileged heterocyclic moieties into one molecular framework with the aim of obtaining a compound with combined bioresponses.[3] This strategy has potential to lead to polyfunctional heterocycles in a green chemistry paradigm.[4] The major challenge in such a synthetic approach is to construct complex molecules with diverse functionality in as few synthetic steps as possible.[5]

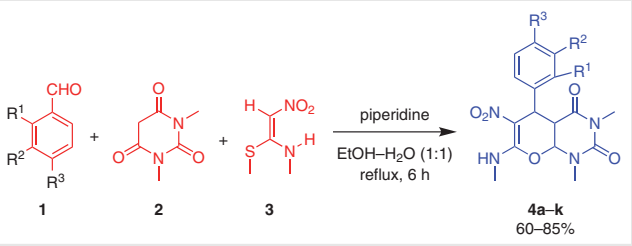
The pyran heterocyclic moiety is present in natural products such as carbohydrates, alkaloids, antibiotics and pheromones.[6] Based on these facts, and in continuation of our work on heterocyclic chemistry,[7] it was decided to fuse a pyran moiety with a pyrimidine ring system with the aim of minimizing the number of synthetic and purification steps. *N*-Methyl-1-(methylthio)-2-nitroethamine (NMSM) is a versatile building block in organic synthesis as the presence of both electron-donating as well as electron-withdrawing groups leads to unique chemical properties that are highly useful for the preparation of a range of heterocyclic rings.[8] For example, NMSM is used in the preparation of the pharmaceutically important drugs Nizatidine® and Ranitidine®.[9]

Barbituric acid, which contains a pyrimidine ring system, acts as a key construction building block for the synthesis of drugs such as hypnotics, sedatives, and CNS depressants.[10] It is proposed that the combination of a barbituric acid moiety with another heterocycle may yield new heterocyclic scaffolds with enhanced biological effects.[11] Similarly, chromenes and related heterocycles are present in various natural as well as synthetic products with promising bioactivities.[12]

Shehab et al. have reported nanoparticle-catalysed synthesis and biological application of pyranopyrimidine derivatives and their nucleoside analogues.[13] Reddy et al. reported the synthesis, antiproliferative activity and docking studies of thiazole/benzothiazole-fused pyranopyrimidine derivatives.[14] Ouf et al. have studied the anticancer activity of novel pyrano[2,3-*d*][1,2,3]triazine derivatives using 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethenone.[15] Inspired by these reports, we were encouraged to use NMSM to construct hybrid heterocyclic scaffolds with barbituric acid.[16]

Compounds containing the pyranopyrimidine nucleus exhibit anticancer,[17] antioxidant,[18] antimicrobial, and[19] antiviral properties.[20] Hence, it was planned to explore their anticancer activities by molecular docking. Kinesin Eg5, also known as KIF 11, is a protein that plays a pivotal role in mitosis.[21] These proteins act as nano-motors that move

along microtubule tracks in the cell.[22] To date, 70 kinesin 5 proteins have been identified to play key roles in mitotic spindle dynamics such as chromosome positioning, centrosome separation, and arrangement of the bipolar spindle during mitosis. At the cellular level, Eg5 is involved in stabilization of microtubule bundles, chromosome movement, and microtubule polymerization during cell division.[23] The mitotic spindles are assembled and organized in a bipolar manner so that segregation of chromosomes can be achieved in a systematic way. In addition, kinesin 5 acts as a molecular brake that regulates microtubule motions.



Scheme 1 Synthesis of arylpyranopyrimidinediones

Based on literature precedent on multicomponent one-pot reactions, we proposed that the NMSM scaffold could be a precursor to the target arylpyranopyrimidinediones by adopting a one-pot multicomponent reaction (MCR) using a mixture of aromatic aldehyde, 1,3-dimethyl barbituric acid and *N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) and piperidine as an organic base (Scheme 1).

Initially, the reaction was carried out under neat conditions in a mortar and pestle without any solvent or catalyst, but this resulted in no yield (Table 1, entry 1). Hence, we performed the next experiment using methanol as solvent, at reflux without base for 24 hours. Again, the reaction did not yield any product (entry 2). It was then decided to carry out the reaction with piperidine as base at room temperature (RT) stirring for 24 h, but the result was again disappointing, leading to no product (entry 3). We then modified the reaction conditions regarding temperature and time, using methanol as solvent and piperidine as base. This resulted in the product being obtained in 60% yield (entry 4). We further optimized the reactions by using ethanol as solvent and piperidine as base. When the reaction mixture was heated at reflux for 12 h, the desired product was obtained in 70% yield (entry 5), and the same yield was obtained when the reaction time was reduced to 6h (entry 6). Subsequently, it was decided to use a water/methanol (1:1) solvent combination and piperidine as base. The reaction mixture was heated to reflux for 6 h at 75 °C but the resultant yield was 60% (entry 7). Variations led to no improvements (entries 8 and 9), but, by increasing the temperature to 80 °C, the desired product was isolated in 85% yield (entry 10). Using sodium ethoxide as base under the same reaction conditions reduced the yield to 50% (entry 11). Similarly, when sodium carbonate and potassium carbonate were used as bases, no significant improvement in the yield was observed (entries 12 and 13). It was clearly observed that strong bases such as NaOH and KOH drastically reduced the yield of product to 20 and 30%, respectively (entries 14 and 15). Using water as solvent, the reaction did not proceed efficiently, presumably due to the poor solubility of the reactants (entry 16). With polar solvents such as DMF, DMSO, acetone, THF, and dioxane, poor, or no yield, of product was observed (entries 18–22). In the absence of any base, the reaction did not proceed (entry 23).

With the optimized reaction conditions established, the procedure was applied to synthesize various derivatives using different aromatic aldehydes (Figure 1). Six products were synthesized using aromatic aldehydes with electron-donating groups, amongst which compounds **4d** and **4e** were obtained in 85% yield, and **4b**, **4c**, **4f** and **4g** in 70–75% yield. From the results it can be concluded that an electron-

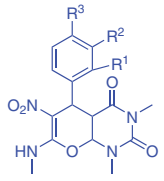
Table 1 Optimization of Reaction Conditions for the Synthesis of Phenylpyranopyrimidinedione **4a**[a]

Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Isolated yield (%)[b]
1	no solvent	no catalyst	RT	3	–
2	MeOH	no catalyst	RT	24	–
3	MeOH	piperidine	RT	24	–
4	MeOH	piperidine	65	12	60
5	EtOH	piperidine	75	12	70
6	EtOH	piperidine	75	6	70
7	MeOH/H_2O[c]	piperidine	75	6	60
8	MeOH/H_2O[c]	piperidine	80	6	60
9	EtOH/H_2O[c]	piperidine	70	6	70
10	EtOH/H_2O[c]	piperidine	80	6	85
11	EtOH/H_2O[c]	NaOEt	80	6	50
12	EtOH/H_2O[c]	Na_2CO_3	80	6	50
13	EtOH/H_2O[c]	K_2CO_3	80	6	50
14	EtOH/H_2O[c]	NaOH	80	6	20
15	EtOH/H_2O[c]	KOH	80	6	30
16	H_2O	piperidine	90	6	–
17	no solvent	no catalyst	85	1	–
18	THF	piperidine	50	6	20
19	1,4-dioxane	piperidine	80	6	10
20	acetone	piperidine	50	6	–
21	DMF	piperidine	90	6	–
22	DMSO	piperidine	85	6	–
23	EtOH/H_2O[c]	no catalyst	80	6	–

[a] Reaction conditions: aldehyde **1** (1.0 mmol), 1,3-dimethylbarbituric acid **2** (1.0 mmol), *N*-methyl-1-(methylthio)-2-nitroethenamine **3** (1.0 mmol) in presence of base (0.2 mmol) and solvent (5 mL) as indicated reflux condition for 6 h.
[b] Isolated yield.
[c] 1:1 ratio v/v.

donating group at the *para*-position of the aldehyde improves the yield, presumably due to reduced steric hindrance. The reaction conditions were also applied to synthesize derivatives using aromatic aldehyde precursors with electron-withdrawing groups (F, Cl and NO_2). Derivatives **4h** and **4i** were obtained in 75% yield, whereas **4j** and **4k**, derived from 2-nitrobenzaldehyde and 3-nitrobenzaldehyde, respectively, resulted in 60% yield of the desired product.

From these observations, it can be concluded that the use of aldehyde precursors possessing electron-donating groups result in better yields.



4	R^1	R^2	R^3	Yield (%)
4a	H	H	H	80
4b	Me	H	H	70
4c	H	Me	H	70
4d	H	H	Me	85
4e	H	H	Et	85
4f	OMe	H	H	70
4g	H	H	OMe	75
4h	F	H	H	75
4i	Cl	H	H	75
4j	NO_2	H	H	60
4k	H	NO_2	H	60

Figure 1 Arylpyranopyrimidinedione derivatives synthesized

Eleven analogues of the arylpyranopyrimidinedione derivatives were subjected to docking studies to ascertain the binding affinity of the individual compounds. Human kinesin Eg 5 was used as the macromolecular target, docking was performed using Autodock 4.2® software, and images were obtained using Pymol® software. The human kinesis Eg5 structure was obtained from the PDB data bank (PDB id 2x7d) with 2.3 Å resolution. The X-ray crystal structure of the protein is shown in Figure 2.[23] The docking studies yielded parameters such as binding energy, estimated inhibition constant, and H-bonding interactions.

AutoDock Tools (ADT) was used to carry out molecular docking, and the scoring functions were obtained by using a novel algorithm that executes a machine learning approach. The structures of **4a–k** in the PDBQT file format were obtained using ADT. The three-dimensional structure of the a human kinesin Eg5 protein (PDB ID: 2X7D), was downloaded from the Protein Data Bank. Before docking, the structures of each ligand **4a–k** with 2X7D, downloaded from Protein Data Bank, were optimized. Water molecules were removed from the 3D structure of the protein 2X7D. The ligand and protein optimizations include addition of Gasteiger charges, Kollman charges, and polar hydrogen bonds. The docked complexes resulting from the conformation with highest negative binding energy were converted into a 2D structure. Using this, interactions between the ligands and the binding site of 2X7D were analysed.

The conformational changes for the library of 11 compounds were generated by exploring the torsional space of the ligand. A 3D grid was generated with spacing of 0.375 Å.

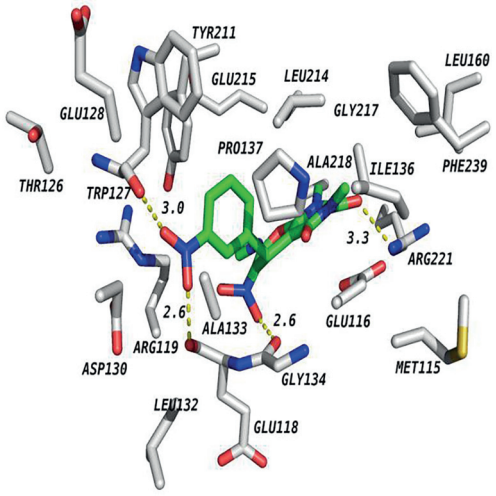


Figure 2 Molecular docking of active compounds (Binding energy –7.9 kcal M^{-1}) with target protein

Then the docking was continued with a search algorithm to establish the best conformer. The docking results are shown in Table 2. Using these results, consideration of hydrogen bond generation between ligand and protein allowed identification of the binding pocket.

Almost all the compounds showed significant binding affinity towards the target protein (Table 2). However, compounds **4e**, **4j** and **4k** showed very good binding affinity –7.28, –7.41, and –7.95 kcal M^{-1}, respectively. Hence further exploitation of these derivatives may pave the way to design potent compounds with significant anticancer properties.

We have demonstrated the synthesis of a series of arylpyranopyrimidinedione derivatives by using a one-pot multicomponent procedure. The derivatives were submitted to docking score analysis and showed noticeable binding affinity with Human kinesin Eg 5; compounds **4e**, **4j** and **4k** resulted in most efficient binding scores on the target protein.

Melting points were determined in a capillary and are uncorrected. FTIR spectra were recorded with a Nicolet iS5 spectrometer using KBr pellets. NMR spectra were recorded with a Bruker (Avance) 500 MHz spectrometer. Tetramethylsilane (TMS) was used as internal standard, and $CDCl_3$ or DMSO-d_6 was used as solvent; chemical shifts are in parts per million (δ-scale) and coupling constants are given in Hertz. Mass spectra were recorded with a 6.450 XT Agilent spectrometer, using ESI. All the chemicals were purchased from Sigma-Aldrich, much used eluent for the purpose of TLC (silica-G plates-Merck) was a hexane/ethyl acetate (90:20) mixture.

General Procedure

To a solution of aromatic aldehyde **1** (0.106 g, 1.0 mmol), *N*,*N*-dimethyl barbituric acid **2** (0.156 g, 1.0 mmol), and *N*-methyl-1-(methylthio)-2-nitroethenamine **3** (0.148 g, 1.0 mmol) in ethanol/H_2O

Table 2 Docking of Arylpyranopyrimidinedione Derivatives

Compd	Binding energy (kcal/M)	Inhibition constant IC_{50} (μM)	Amino acid and type of hydrogen-bond (D–H···A)	Distance (Å)	Binding residues
4a	–6.47	18.07	(ARG221) N–H···O (GLY117) O–H···O	3.2 3.0	MET115 GLU116
4b	–6.77	10.97	(ARG-221) N–H···O (Gly-117) O–H···O	3.2 2.6	MET115 GLU116
4c	–6.91	8.55	(ILE136) O–H···O (ARG221) N–H···O	2.5 3.3	MET115 GLU116
4d	–6.71	12.07	(GLY117) O–H···O (ARG221) N–H···O	2.9 3.3	MET115 GLU116
4e	–7.28	4.58	(GLU116) O–H···O (GLY117) O–H···O (ARG221) N–H···O	2.8 2.9 3.3	MET115 GLU116 GLY117
4f	–6.56	15.58	(GLY117) O–H···O (ARG221) N–H···O	2.6 3.3	MET115 GLU116
4g	–6.38	21.12	(GLY116) O–H···O (GLY117) O–H···O (ARG221) N–H···O	2.8 2.8 3.2	MET115 GLU116 GLY117 GLU118
4h	–6.43	19.40	(GLY117) O–H···O (ARG221) N–H···O	2.7 3.2	MET115 GLU116
4i	–6.52	16.68	(GLY117) O–H···N (ARG221) N–H···O	2.7 3.2	GLU116 GLY117
4j	–7.41	3.70	(GLU116) O–H···O (TRP127) O–H···O (LEU214) O–H···N (ARG221) N–H···O	2.8 2.9 3.4 3.2	GLU116 GLY117 GLU118 ARG119
4k	–7.95	1.48	(GLY117) O–H···O (GLU118) O–H···O (TRP127) O–H···O	3.0 2.6 2.6	MET115 GLU116 GLY117

(1:1.5 mL), piperidine (0.017 g, 0.2 mmol) was added and the mixture was heated to reflux for 6 h. The progress of the reaction was monitored by TLC and the resultant precipitate was filtered and washed with EtOH to give a white solid that was purified by recrystallization from EtOH to afford colorless crystals.

1,3-Dimethyl-7-(methylamino)-6-nitro-5-phenyl-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4a)

Yield: 0.276 g (80%); white solid; mp 150–152 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.01 (d, *J* = 4.8 Hz, 1 H), 7.35 (dd, *J* = 8.2, 1.1 Hz, 2 H), 7.30–7.26 (m, 2 H), 7.23–7.18 (m, 1 H), 5.24 (s, 1 H), 3.57 (s, 3 H), 3.27 (s, 3 H), 3.24 (d, *J* = 5.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.33, 156.95, 150.13, 149.05, 141.17, 128.33, 128.16, 127.44, 109.78, 93.12, 36.48, 29.53, 28.63, 28.49.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_4O_5$: 345.1199; found: 345.1198.

1,3-Dimethyl-7-(methylamino)-6-nitro-5-(*o*-tolyl)-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4b)

Yield: 0.251 g (70%); white solid; mp 160–162 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.06 (d, *J* = 4.3 Hz, 1 H), 7.12 (d, *J* = 6.4 Hz, 1 H), 7.08–7.05 (m, 2 H), 6.88 (d, *J* = 7.7 Hz, 1 H), 5.38 (s, 1 H), 3.59 (s, 3 H), 3.26 (d, *J* = 2.6 Hz, 6 H), 2.82 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.50, 156.93, 150.03, 148.97, 139.36, 127.16, 127.05, 125.87, 110.70, 94 .08, 32.47, 29.57, 28.61, 28.49, 19.43.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_4O_5$: 359.1355; found: 359.1354.

1,3-Dimethyl-7-(methylamino)-6-nitro-5-(*m*-tolyl)-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4c)

Yield: 0.251 g (70%); white solid; mp 162–164 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.00 (d, *J* = 4.9 Hz, 1 H), 7.17–7.14 (m, 2 H), 7.13 (s, 1 H), 7.01 (d, *J* = 7.0 Hz, 1 H), 5.20 (s, 1 H), 3.57 (s, 3 H), 3.27 (s, 3 H), 3.23 (d, *J* = 5.2 Hz, 3 H), 2.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.35, 157.08, 150.14, 149.04, 140.90, 137.89, 128.81, 128.29, 125.26, 109.85, 93.18, 36.37, 29.53, 28.63, 28.49, 21.50.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_4O_5$: 359.1355; found: 359.1356.

1,3-Dimethyl-7-(methylamino)-6-nitro-5-(*p*-tolyl)-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4d)

Yield: 0.289 g (85%); white solid; mp 164–166 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.01 (d, *J* = 4.9 Hz, 1 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.08 (d, *J* = 7.8 Hz, 2 H), 5.20 (s, 1 H), 3.56 (s, 3 H), 3.26 (s, 3 H), 3.24 (d, *J* = 5.2 Hz, 3 H), 2.27 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.37, 157.03, 150.13, 148.96, 138.09, 137.10, 129.04, 128.00, 109.86, 94.24, 36.08, 30.97, 29.51, 28.61, 28.48, 21.13.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_4O_5$: 359.1355; found: 359.1352.

5-(4-Ethylphenyl)-1,3-dimethyl-7-(methylamino)-6-nitro-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4e)

Yield: 0.300 g (85%); white solid; mp 168–170 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.00 (d, *J* = 4.9 Hz, 1 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 5.21 (s, 1 H), 3.56 (s, 3 H), 3.27 (s, 3 H), 3.23 (d, *J* = 5.2 Hz, 3 H), 2.56 (q, *J* = 7.6 Hz, 2 H), 1.18 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.37, 157.03, 150.13, 148.96, 138.09, 137.10, 129.04, 128.00, 109.86, 93.24, 36.08, 30.97, 28.61, 28.48, 21.13.

HRMS (ESI): *m*/*z* [M + H]$^+$ for $C_{18}H_{20}N_4O_5$: 372.1434; found: 372.2603.

5-(2-Methoxyphenyl)-1,3-dimethyl-7-(methylamino)-6-nitro-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4f)

Yield: 0.265 g (70%); white solid; mp 160–162 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.02 (d, *J* = 5.0 Hz, 1 H), 7.26 (d, *J* = 6.6 Hz, 2 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 5.19 (s, 1 H), 3.75 (s, 3 H), 3.56 (s, 3 H), 3.27 (s, 3 H), 3.26 (d, *J* = 5.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.39, 158.76, 156.97, 150.13, 148.89, 133.13, 129.17, 113.13, 109.93, 93.27, 55.24, 35.70, 30.98, 29.50, 28.61, 28.48.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_4O_6$: 375.1305; found: 375.1305.

5-(4-Methoxyphenyl)-1,3-dimethyl-7-(methylamino)-6-nitro-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4g)

Yield: 0.282 g (75%); white solid; mp 162–164 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.23 (d, *J* = 4.1 Hz, 1 H), 7.60–7.58 (m, 1 H), 7.21–7.17 (m, 1 H), 6.96 (dt, *J* = 7.5, 3.7 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 5.22 (s, 1 H), 3.71 (s, 3 H), 3.57 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.48, 157.97, 157.45, 154.91, 150.44, 150.31, 149.43, 133.24, 128.81, 126.74, 120.68, 111.15, 108.76, 91.08, 55.45, 35.23, 29.42, 28.44, 28.37, 28.30.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_4O_6$: 375.1305; found: 375.1303.

5-(2-Fluorophenyl)-1,3-dimethyl-7-(methylamino)-6-nitro-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4h)

Yield: 0.272 g (75%); white solid; mp 170–172 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.15 (s, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.22–7.18 (m, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 6.93–6.89 (m, 1 H), 5.25 (s, 1 H), 3.58 (s, 3 H), 3.28 (s, 3 H), 3.27 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.41, 157.33, 150.16, 149.42, 133.15, 133.11, 129.27 (d, J_{CF} = 8.75 Hz), 126.72, 126.64, 123.91, 115.67 (d, J_{CF}=21.25 Hz), 108.29, 90.86, 33.80, 29.49, 28.58, 28.43.

^{19}F NMR (125 MHz, $CDCl_3$): δ = –121.28.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}FN_4O_6$: 363.1105; found: 363.1103.

5-(2-Chlorophenyl)-1,3-dimethyl-7-(methylamino)-6-nitro-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4i)

Yield: 0.282 g (75%); white solid; mp 180–182 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.21 (d, *J* = 4.3 Hz, 1 H), 7.58 (d, *J* = 7.0 Hz, 1 H), 7.45 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.31–7.28 (m, 1 H), 7.12–7.06 (m, 1 H), 5.42 (s, 1 H), 3.59 (s, 2 H), 3.28 (d, *J* = 5.2 Hz, 2 H), 3.26 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.31, 157.17, 150.15, 149.37.137.49, 133.72, 129.30, 129.10, 127.02, 108.11, 90.51, 33.67, 29.59, 28.66, 28.44.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClN_4O_6$: 379.0809; found: 379.0805.

1,3-Dimethyl-7-(methylamino)-6-nitro-5-(2-nitrophenyl)-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4j)

Yield: 0.389 g (60%); white solid; mp 188–190 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.10 (d, *J* = 4.9 Hz, 1 H), 8.10–8.07 (m, 1 H), 8.01 (t, *J* = 1.9 Hz, 1 H), 7.95–7.92 (m, 1 H), 5.31 (s, 1 H), 3.61 (s, 3 H), 3.33 (d, *J* = 5.2 Hz, 3 H), 3.27 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.29, 157.77, 149.93, 148.34, 143.18, 136.32, 128.29, 122.64, 122.09, 108.71, 91.61, 36.79, 29.70, 28.80, 28.53.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_5O_7$: 390.1050; found: 390.1044.

1,3-Dimethyl-7-(methylamino)-6-nitro-5-(3-nitrophenyl)-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4k)

Yield: 235 g (60%); white solid; mp 188–190 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.24 (s, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.66 (s, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.37 (t, *J* = 7.7 Hz, 1 H), 5.82 (s, 1 H), 3.60 (s, 3 H), 3.30 (s, 3 H), 3.26 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.29, 157.77, 149.93, 148.34, 143.18, 136.24, 128.98, 122.64, 122.64, 122.09, 108.71, 91.61, 36.79, 29.70, 28.80, 28.53.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_5O_7$: 390.1050; found: 390.1158.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719869. ^{1}H, ^{13}C and Dept-135 NMR and HR-MS spectroscopic data of **4a–k** and docking images are included.

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