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A Simple Synthesis of Furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine Derivatives through Multicomponent Reactions in Water

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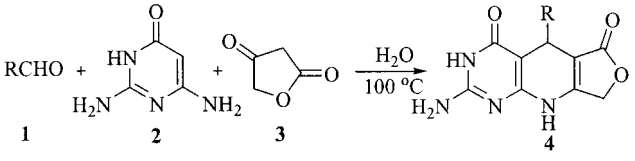
A series of furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine and indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derivatives were synthesized by three-component reactions involving an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one, and either tetronic acid or indane-1,3-dione in water, under microwave irradiation and traditional heating conditions, without use of any catalyst. This protocol has the advantages of higher yields, lower cost, reduced environmental impact, and convenience of procedure. The synthesis of a class of important compounds in aqueous medium has been achieved.

Introduction

Multicomponent reactions, in which multiple reactions are combined into one synthetic operation, have been extensively used in synthetic chemistry for the formation of carbon–carbon and carbon–heteroatom bonds.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings both of solvents and of reagents. The use of water as a solvent has many advantages in organic synthesis, both from economic and from environmental points of view.[2] Water has therefore become an attractive medium for many organic reactions, not only as the need for drying reactants, expensive catalysts, and solvents can be circumvented, but also for its unique reactivity and selectivity.[3,4] Many important types of heterocyclic compounds, such as triazines,[5] acridines,[6] quinolines,[7] pyridines,[8] indoles,[9] pyrazines,[10] furans,[11] and pyrimidines,[12] have been synthesized in aqueous media. The synthesis of new and important types of heterocyclic compounds in water continues to attract wide attention among synthetic chemists.

Furopyridine is one of the most important "privileged medicinal scaffolds," which are molecular frameworks used for the development of pharmaceutical agents for diverse applications. Compounds incorporating this motif show a wide range of pharmacological activities such as antipsychotic,[13] antianaphylactic,[14] antiproliferative,[15] anticonvulsant,[16] and anthelmintic[17] activities, and can also be used as calcium influx promoters,[18] HIV-1 nonnucleoside reverse transcriptase inhibitors,[19] and acetylcholinesterase inhibitors.[20] Uracil derivatives have been reported to be versatile building blocks for the synthesis of a wide range of heterocyclic motifs, including pyrazolopyridines,[21] pyridopyrimidines,[22] and pyrazolopyrimidines.[23] Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, which include antitumor,[24] antibacterial,[25] anti-inflammatory,[26] antifungal,[27] and antileishmaniasis[28] properties, and also act as cyclin-dependent kinase 4 inhibitors.[29]

Furopyridines[30] and pyrido[2,3-*d*]pyrimidines[31] have been reported widely in the literature, but the synthesis of the compounds incorporating both pyrido[2,3-*d*]pyrimidine and furo[3,4-*b*]pyridine motifs has been neglected. Here we describe a simple multicomponent reaction involving an aldehyde **1**, 2,6-diaminopyrimidine-4(3*H*)-one (**2**), and tetronic acid (**3**) in water under microwave irradiation and conventional heating conditions without use of any catalyst to synthesize the furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **4** (Scheme 1).



1 2 3 4

Scheme 1. Synthesis of **4** in water.

Results and Discussion

Choosing an appropriate solvent is of crucial importance for a successful organic synthesis. To search for the optimal solvent, the microwave-assisted reaction between 4-fluorobenzaldehyde (**1d**), 2,6-diaminopyrimidine-4(3*H*)-one (**2**),

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and tetronic acid (**3**) was examined in water, ethylene glycol, *N*,*N*-dimethylformamide, glacial acetic acid, and ethanol as solvents, at 70 °C. All the reactions were carried out at the maximum power of 300 W and the results are summarized in Table 1.

Table 1. Solvent optimization for the synthesis of **4d** at 70 °C under microwave irradiation conditions.

Entry	Solvent	Power [W]	Time [min]	Yield [%]
1	glycol	300	6	85
2	H_2O	300	6	84
3	AcOH	300	8	74
4	DMF	300	10	70
5	EtOH	300	12	63

As can be seen in Table 1, the reactions with glycol or water as the solvent gave higher yields and required shorter reaction times than those with AcOH, DMF, or EtOH (Table 1, Entries 1 and 2). Water was thus chosen as the solvent for all further reactions, as it is environmentally friendly and allows toxic organic reagents to be avoided.

To optimize the reaction temperature, the same three reagents were allowed to react in water at temperatures ranging from 70 to 120 °C, with an increment of 10 °C each time. The results are shown in Table 2.

Table 2. Temperature optimization for the synthesis of **4d** in water under microwave irradiation conditions.

Entry	*T* [°C]	Power [W]	Time [min]	Yield [%]
1	70	300	6	84
2	80	300	5	89
3	90	300	4	93
4	100	300	2	95
5	110	300	2	95
6	120	300	2	95

The yield of product **4d** was increased and the reaction time was shortened as the temperature was increased from 70 °C to 100 °C (Table 2, Entries 1–4). The yield leveled off when the temperature was further increased to 110 and 120 °C (Table 2, Entries 5 and 6), so a reaction temperature of 100 °C was considered to be most suitable.

The power of microwave irradiation was optimized by carrying out the same reaction for the synthesis of **4d** at 50, 100, 150, 200, 250 and 300 W, in water as the solvent (Table 3).

Table 3. Power optimization for the synthesis of **4d** in water under microwave irradiation conditions.

Entry	Power [W]	Time [min]	Yield [%]
1	50	2	82
2	100	2	90
3	150	2	95
4	200	2	95
5	250	2	95
6	300	2	95

At 50 and 100 W, the times taken for the temperature to reach 100 °C were too long. Microwave irradiation at 150 W generated the highest yield, with the highest temperature reached during the whole reaction being 102 °C (Table 3, Entry 3). The yields leveled off when the power of microwave irradiation was further increased to 200, 250 and 300 W, so a microwave power of 150 W was chosen as the optimal power.

Furthermore, the volume of water was also found to be important for the yields of the reactions. The synthesis of **4d** in different volumes of water was tested at 100 °C under microwave irradiation conditions. The yield was found to be the highest when 2.0 mL of water was used as solvent for the reaction [with use of 4-fluorobenzaldehyde (**1d**, 1 mmol), 2,6-diaminopyrimidine-4(3*H*)-one (**2**, 1 mmol), tetronic acid (**3**, 1 mmol)].

Under these optimized reaction conditions [water (2.0 mL), 100 °C, 150 W], a series of furo[3′,4′:5,6]pyrido-[2,3-*d*]pyrimidine derivatives **4** were synthesized. The results are summarized in Table 4.

In order to expand the scope of the method, the replacement of tetronic acid **3** with indane-1,3-dione (**5**) was also examined. This is particularly attractive because compounds containing the indenopyridine motif show a wide range of biological activities, such as calcium antagonistic,[32] antioxidant,[33] antihistamine, and antidepressant[34]

Table 4. Synthesis of **4** in water at 100 °C.

Entry	**4**	**1**	R	Time [min]		Yield [%]		M.p. [°C]
				MW[a]	SC[b]	MW[a]	SC[b]	
1	**4a**	**1a**	4-ClC_6H_4	2	180	96	89	>300
2	**4b**	**1b**	4-BrC_6H_4	3	210	97	85	>300
3	**4c**	**1c**	4-$CH_3OC_6H_4$	2	210	93	83	>300
4	**4d**	**1d**	4-FC_6H_4	2	150	95	88	>300
5	**4e**	**1e**	C_6H_5	4	210	91	87	>300
6	**4f**	**1f**	2-ClC_6H_4	3	180	93	84	>300
7	**4g**	**1g**	3-$NO_2C_6H_4$	2	180	95	88	>300
8	**4h**	**1h**	4-$NO_2C_6H_4$	3	210	96	86	>300
9	**4i**	**1i**	3,4-$OCH_2OC_6H_3$	4	150	90	82	>300
10	**4j**	**1j**	2,4-$Cl_2C_6H_3$	3	210	92	82	>300
11	**4k**	**1k**	3-CH_3O-4-OHC_6H_3	3	240	95	80	>300
12	**4l**	**1l**	*n*Bu	4	270	90	75	>300
13	**4m**	**1m**	thiophen-2-yl	4	240	91	82	>300
14	**4n**	**1n**	4-(benzo[*d*]oxazol-2-yl)C_6H_4	3	150	96	88	>300

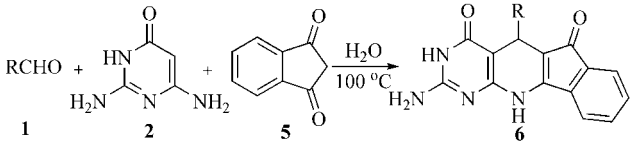
[a] The time and yields under microwave irradiation conditions. [b] The time and yields under standard heating conditions.

Table 5. Synthesis of **6** in water at 100 °C.

Entry	6	1	R	Time [min] MW[a]	Time [min] SC[b]	Yield [%] MW[a]	Yield [%] SC[b]	M.p. [°C]
1	**6a**	**1a**	4-ClC_6H_4	3	150	94	88	>300
2	**6b**	**1b**	4-BrC_6H_4	5	180	95	87	>300
3	**6c**	**1c**	4-$CH_3OC_6H_4$	4	150	92	83	>300
4	**6d**	**1d**	4-FC_6H_4	2	210	93	85	>300
5	**6e**	**1e**	C_6H_5	3	180	96	83	>300
6	**6f**	**1g**	3-$NO_2C_6H_4$	5	180	94	85	>300
7	**6g**	**1j**	2,4-$Cl_2C_6H_3$	4	210	92	81	>300
8	**6h**	**1l**	*n*Bu	6	240	90	72	>300
9	**6i**	**1m**	thiophen-2-yl	6	240	91	80	>300
10	**6j**	**1n**	4-(benzo[*d*]oxazol-2-yl)C_6H_4	4	150	94	88	>300
11	**6k**	**1o**	2,3-$(CH_3O)_2C_6H_3$	3	150	93	85	>300

[a] The time and yields under microwave irradiation conditions. [b] The time and yields under standard heating conditions.

properties, and also act as phosphodiesterase (PDE) inhibitors[35] and as NK-1 and dopamine receptor ligands.[36] To our delight, the reactions proceeded smoothly under the above optimized conditions and a series of indeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrimidines **6** was obtained in excellent yields (Scheme 2). The results are summarized in Table 5.



Scheme 2. Synthesis of **6** in water.

As shown in Table 4 and Table 5, this methodology can be applied not only to aromatic aldehydes either with electron-withdrawing groups (such as nitro or halide groups) or with electron-donating groups (such as alkoxyl groups), but also to heterocyclic and aliphatic aldehydes with excellent yields under same conditions, so we conclude that the electronic nature of the substituents has no significant effect on this reaction.

Moreover, we performed the synthesis of **4** and **6** in water at 100 °C under classical heating conditions, and those results are also summarized in Table 4 and Table 5, respectively. We found that microwave irradiation efficiently promoted the reactions and resulted both in the dramatic reduction of the reaction times – from hours to minutes – and in increases in yields.

Structure Determination

All the products in this study were characterized by mp and by IR and ^1H NMR and ^{13}C NMR spectroscopy, as well as by elemental analysis. The structure of **6k** was further confirmed by X-ray diffraction analysis.[37] The molecular structure of **6k** is shown in Figure 1.

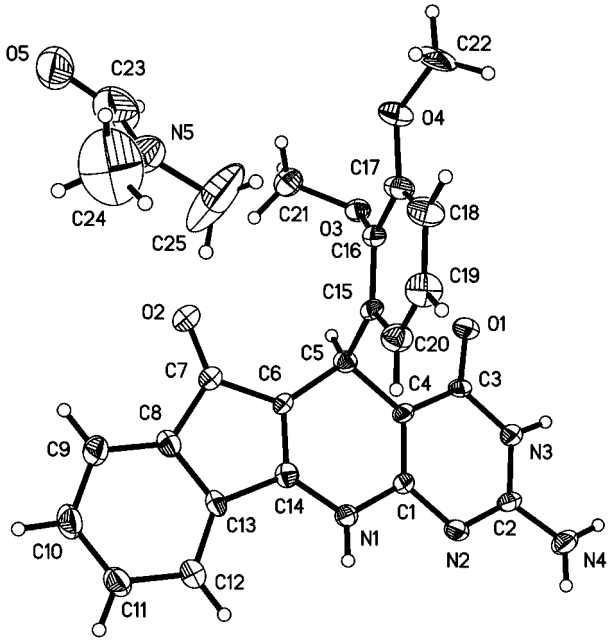
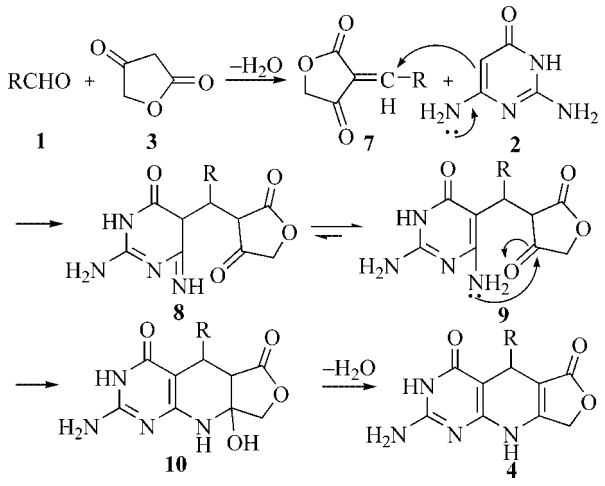


Figure 1. ORTEP diagram showing **6k**.

Proposed Reaction Mechanism

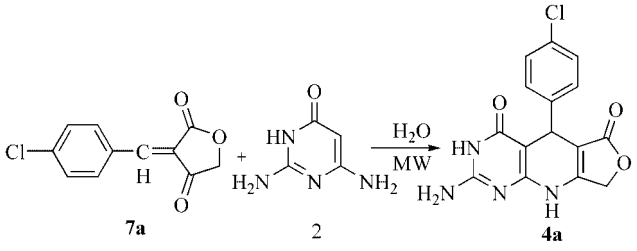
Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of furo-[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **4** could be explained by a reaction sequence as presented in Scheme 3. We proposed that the reaction might proceed through a reaction sequence of condensation, addition, cyclization, and dehydration. Firstly, a condensation between aldehyde **1** and tetronic acid **3** would give the intermediate product **7**. The addition of **7** to 2,6-diaminopyrimidine-4(3*H*)-one (**2**) would then furnish the intermediate product **9**, which upon intermolecular cyclization and dehydration would give rise to **4**.

Evidence supporting this proposed mechanism was provided by the observation that when **7a** and **2** were subjected



Scheme 3. Proposed reaction mechanism.

to the same conditions, the expected product **4a** was obtained in a yield similar to that obtained in the one-pot reaction (Scheme 4).



Scheme 4. The reaction between **7a** and **2** in water under microwave irradiation conditions.

Conclusions

In conclusion, we have developed simple three-component reactions involving an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one, and either tetronic acid or indane-1,3-dione for the synthesis of furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine and indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derivatives in water under microwave irradiation and traditional heating conditions. Particularly valuable features of this method include the excellent yields of the products, reduced environmental impact, and the straightforwardness of the procedure. The synthesis of a type of important compounds has been achieved in aqueous medium and it is hoped that new classes of compounds for biomedical screening have been provided. This work is currently in progress and the results will be reported in due course.

Experimental Section

General: Microwave irradiation was carried out with an Emrys™ Creator microwave oven from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken with a FT-IR-Tensor 27 spectrometer in KBr pellets and are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were measured with a Bruker DPX 400 MHz spectrometer in [D_6]DMSO with chemical shifts (δ) given in ppm relative to TMS as internal standard. Element analysis was determined with a Perkin–Elmer 240c elemental analysis instrument. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General Procedure for the Synthesis of Furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine Derivatives 4 and Indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine Derivatives 6 in Water under Microwave Irradiation Conditions: Typically, an aldehyde **1** (1 mmol), 2,6-diaminopyrimidine-4(3*H*)-one (**2**, 1 mmol), either tetronic acid (**3**, 1 mmol) or indane-1,3-dione (**5**, 1 mmol), and H_2O (2 mL) were mixed in a 10 mL Emrys™ reaction vial, which was then capped. The mixture was irradiated at 150 W at 100 °C for a given time. The reaction mixture was allowed to cool to room temp. and filtered to give the crude product, which was further purified by recrystallization (DMF/EtOH) to give the pure furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **4** or indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidin derivatives **6**.

General Procedure for the Synthesis of Furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine Derivatives 4 and Indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine Derivatives 6 in Water under Standard Heating Conditions: A solution of aldehyde **1** (1 mmol), 2,6-diaminopyrimidine-4(3*H*)-one (**2**, 1 mmol) and either tetronic acid (**3**, 1 mmol) or indane-1,3-dione (**5**, 1 mmol) in water (10 mL) was heated at 100 °C with stirring for the given time before being allowed to cool down to room temperature. The reaction mixture was filtered to give the crude product, which was further purified by recrystallization (DMF/EtOH) to give the pure furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **4** or indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidin derivatives **6**.

The Procedure for the Synthesis of 7a under Microwave Irradiation Conditions: 4-Chlorobenzaldehyde (**1a**, 2 mmol), tetronic acid (**3**, 2 mmol), and water (3 mL) were mixed in a 10 mL Emrys™ reaction vial, which was then capped. The mixture was irradiated at 150 W and at 100 °C for 2 min. The reaction mixture was allowed to cool to room temp. and filtered to give the crude product, which was further purified by recrystallization from EtOH to give pure 3-(4-chlorobenzylidene)furan-2,4(3*H*,5*H*)-dione (**7a**).

The Procedure for the Reaction between 7a and 2,6-Diaminopyrimidine-4(3*H*)-one (2): 3-(4-Chlorobenzylidene)furan-2,4(3*H*,5*H*)-dione (**7a**, 1 mmol), 2,6-diaminopyrimidine-4(3*H*)-one (**2**, 1 mmol), and water (2 mL) were mixed in a 10 mL Emrys™ reaction vial, which was then capped. The mixture was irradiated at 150 W and at 100 °C for 2 min. The reaction mixture was allowed to cool to room temp. and filtered to give the crude product, which was further purified by recrystallization (DMF/ethanol) to give pure 2-amino-5-(4-chlorophenyl)-5,9-dihydrofuro[3′,4′:5,6]pyrido[2,3-*d*]-pyrimidine-4,6(3*H*,8*H*)-dione (**4a**).

Compound 4a: ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 10.51 (s, 1 H, NH), 9.86 (s, 1 H, NH), 7.28 (d, J = 8.4 Hz, 2 H, ArH), 7.21 (d, J = 8.4 Hz, 2 H, ArH), 6.52 (s, 2 H, NH_2), 4.89–4.80 (m, 2 H, CH_2), 4.63 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 171.68, 161.95, 158.42, 154.78, 154.64, 144.75, 130.67, 129.63, 127.90, 99.43, 90.76, 65.45, 34.12 ppm. IR: $\tilde{\nu}$ = 3470, 3355, 3030, 2935, 1728, 1679, 1558, 1518, 1488, 1018, 844, 593 cm^{-1}. $C_{15}H_{11}ClN_4O_3$ (330.73): calcd. C 54.47, H 3.35, N 16.94; found: C 54.51, H 3.32, N 17.01.

Compound 4b: ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 10.54 (s, 1 H, NH), 9.88 (s, 1 H, NH), 7.42 (d, J = 8.4 Hz, 2 H, ArH), 7.16 (d, J = 8.4 Hz, 2 H, ArH), 6.54 (s, 2 H, NH_2), 4.89–4.78 (m, 2 H, CH_2), 4.61 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 171.70, 161.91, 158.51, 154.82, 154.59, 144.61, 130.58,

129.53, 127.89, 99.37, 90.31, 65.37, 34.10 ppm. IR: ṽ = 3379, 3211, 2929, 1773, 1733, 1653, 1515, 1419, 1236, 1012, 839 cm^{-1}. $C_{15}H_{11}BrN_4O_3$ (375.18): calcd. C 48.02, H 2.96, N 14.93; found: C 48.15, H 2.85, N 14.82.

Compound 4c: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.51 (s, 1 H, NH), 9.95 (s, 1 H, NH), 7.39 (d, J = 8.0 Hz, 2 H, ArH), 7.18 (d, J = 8.0 Hz, 2 H, ArH), 6.59 (s, 2 H, NH_2), 4.92–4.79 (m, 2 H, CH_2), 4.65 (s, 1 H, CH), 3.36 (s, 3 H, OCH_3) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.72, 162.00, 158.31, 154.82, 154.59, 151.30, 144.32, 129.28, 114.36, 99.62, 91.11, 65.38, 56.10, 34.21 ppm. IR: ṽ = 3480, 3209, 1744, 1654, 1520, 1420, 790, 767, 766 cm^{-1}. $C_{16}H_{14}N_4O_4$ (326.31): calcd. C 58.89, H 4.32, N 17.17; found: C 59.01, H 4.25, N 17.06.

Compound 4d: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.52 (s, 1 H, NH), 9.87 (s, 1 H, NH), 7.23–7.20 (m, 2 H, ArH), 7.04 (t, J = 9.2 Hz, 2 H, ArH), 6.53 (s, 2 H, NH_2), 4.89–4.77 (m, 2 H, CH_2), 4.63 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.74, 162.00, 159.61, 158.30, 154.75, 154.59, 142.02, 130.27, 114.69, 99.74, 91.05, 65.42, 33.83 ppm. IR: ṽ = 3472, 3346, 3072, 1722, 1718, 1519, 1420, 1369, 862, 754, 598 cm^{-1}. $C_{15}H_{11}FN_4O_3$ (314.27): calcd. C 57.33, H 3.53, N 17.83; found: C 57.46, H 3.42, N 17.75.

Compound 4e: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.50 (s, 1 H, NH), 9.84 (s, 1 H, NH), 7.24–7.19 (m, 3 H, ArH), 7.13–7.10 (m, 2 H, ArH), 6.51 (s, 2 H, NH_2), 4.89–4.62 (m, 2 H, CH_2), 4.67 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.76, 161.99, 158.24, 154.80, 154.53, 145.80, 127.98, 127.86, 126.12, 99.95, 91.14, 65.37, 34.42 ppm. IR: ṽ = 3566, 3435, 3332, 3231, 1715, 1655, 1522, 1171, 1073, 756, 599 cm^{-1}. $C_{15}H_{12}N_4O_3$ (296.28): calcd. C 60.81, H 4.08, N 18.91; found: C 60.92, H 4.00, N 18.82.

Compound 4f: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.53 (s, 1 H, NH), 9.89 (s, 1 H, NH), 7.33–7.29 (m, 2 H, ArH), 7.20–7.13 (m, 2 H, ArH), 6.53 (s, 2 H, NH_2), 4.90–4.81 (m, 2 H, CH_2), 4.62 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.72, 161.91, 158.42, 154.82, 154.47, 144.45, 132.50, 130.56, 128.81, 127.62, 126.53, 99.38, 91.14, 65.43, 34.34 ppm. IR: ṽ = 3486, 3358, 2881, 1746, 1682, 1646, 1524, 1195, 830 cm^{-1}. $C_{15}H_{11}ClN_4O_3$ (330.73): calcd. C 54.47, H 3.35, N 16.94; found: C 54.56, H 3.25, N 16.82.

Compound 4 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.56 (s, 1 H, NH), 10.00 (s, 1 H, NH), 8.04 (d, J = 8.0 Hz, 1 H, ArH), 7.96 (s, 1 H, ArH), 7.70 (d, J = 8.0 Hz, 1 H, ArH), 7.55 (t, J = 8.0 Hz, 1 H, ArH), 6.60 (s, 2 H, NH_2), 4.94–4.81 (m, 2 H, CH_2), 4.80 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.62, 161.97, 158.87, 155.00, 154.85, 147.82, 147.73, 134.73, 129.56, 122.17, 121.37, 98.84, 90.19, 65.60, 34.81 ppm. IR: ṽ = 3566, 3353, 3209, 2939, 1747, 1663, 1523, 1519, 1350, 826, 739, 682 cm^{-1}. $C_{15}H_{11}N_5O_5$ (341.28): calcd. C 52.79, H 3.25, N 20.52; found: C 52.86, H 3.12, N 20.41.

Compound 4h: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.53 (s, 1 H, NH), 9.90 (s, 1 H, NH), 7.93–7.80 (m, 2 H, ArH), 7.63–7.53 (m, 2 H, ArH), 6.58 (s, 2 H, NH_2), 4.92–4.80 (m, 2 H, CH_2), 4.75 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.61, 161.95, 158.87, 154.98, 154.85, 147.82, 143.73, 129.56, 122.16, 98.81, 90.19, 65.60, 34.81 ppm. IR: ṽ = 3447, 3337, 3071, 2933, 1724, 1680, 1647, 1519, 1281, 1107, 861 cm^{-1}. $C_{15}H_{11}N_5O_5$ (341.28): calcd. C 52.79, H 3.25, N 20.52; found: C 52.90, H 3.26, N 20.45.

Compound 4i: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.51 (s, 1 H, NH), 9.83 (s, 1 H, NH), 6.77–6.73 (m, 2 H, ArH), 6.65–6.62 (m, 1 H, ArH), 6.51 (s, 2 H, NH_2), 5.94 (s, 2 H, CH_2), 4.90–4.76 (m, 2 H, CH_2), 4.55 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.75, 161.99, 158.13, 154.63, 154.50, 146.95, 145.55, 140.13, 120.59, 108.35, 107.76, 100.78, 99.94, 91.30, 65.36, 34.05 ppm. IR: ṽ = 3432, 3230, 3154, 2897, 1726, 1670, 1603, 1278, 1181, 1037, 1013 cm^{-1}. $C_{16}H_{12}N_4O_5$ (340.29): calcd. C 56.47, H 3.55, N 16.46; found: C 56.58, H 3.48, N 16.35.

Compound 4j: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.47 (s, 1 H, NH), 9.95 (s, 1 H, NH), 7.33 (d, J = 8.4 Hz, 1 H, ArH), 7.23–7.19 (m, 2 H, ArH), 6.58 (s, 2 H, NH_2), 5.04 (s, 1 H, CH), 4.88–4.79 (m, 2 H, CH_2) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.64, 161.99, 158.75, 154.88, 154.77, 146.71, 135.57, 133.51, 130.91, 129.70, 128.25, 98.80, 90.22, 65.56, 34.26 ppm. IR: ṽ = 3567, 3193, 1770, 1731, 1657, 1582, 1519, 1473 cm^{-1}. $C_{15}H_{10}Cl_2N_4O_3$ (365.14): calcd. C 49.34, H 2.76, N 15.34; found: C 49.48, H 2.63, N 15.28.

Compound 4k: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.61 (s, 1 H, OH), 10.52 (s, 1 H, NH), 9.77 (s, 1 H, NH), 6.75–6.72 (m, 1 H, ArH), 6.67–6.60 (m, 2 H, ArH), 6.50 (s, 2 H, NH_2), 4.87–4.76 (m, 2 H, CH_2), 4.54 (s, 1 H, CH), 3.40 (s, 3 H, OCH_3) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.72, 162.00, 158.31, 154.82, 154.59, 150.67, 144.17, 142,89, 122.45, 119.21, 114.52, 99.62, 91.11, 65.38, 56.10, 34.21 ppm. IR: ṽ = 3432, 3195, 1768, 1720, 1682, 1473, 1362, 1179, 1027 cm^{-1}. $C_{16}H_{14}N_4O_5$ (342.31): calcd. C 56.14, H 4.12, N 16.37; found: C 56.28, H 4.05, N 16.25.

Compound 4l: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.53 (s, 1 H, NH), 9.82 (s, 1 H, NH), 6.51 (s, 2 H, NH_2), 4.90–4.70 (m, 2 H, CH_2), 4.70 (s, 1 H, CH), 1.54–1.49 (m, 2 H, CH_2), 1.43–1.37 (m, 4 H, $2CH_2$), 0.96–0.89 (m, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.68, 161.95, 158.42, 154.78, 154.58, 99.43, 90.76, 65.45, 34.12, 33.28, 29.57, 23.29, 14.01 ppm. IR: ṽ = 3233, 3105, 2959, 2859, 1765, 1674, 1579, 1530, 1277, 1092, 825, 683 cm^{-1}. $C_{13}H_{16}N_4O_3$ (276.29): calcd. C 56.51, H 5.84, N 20.28; found: C 56.64, H 5.72, N 20.12.

Compound 4m: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.51 (s, 1 H, NH), 9.90 (s, 1 H, NH), 7.21–7.13 (m, 2 H, ArH), 7.08–7.02 (m, 1 H, ArH), 6.53 (s, 2 H, NH_2), 4.90–4.82 (m, 2 H, CH_2), 4.68 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.76, 161.99, 158.24, 154.80, 154.53, 144.39, 126.90, 126.44, 123.34, 99.95, 91.14, 65.37, 34.42 ppm. IR: ṽ = 3320, 3152, 1767, 1720, 1678, 1577, 1474, 1341, 1291, 1040 cm^{-1}. $C_{13}H_{10}N_4O_3S$ (302.31): calcd. C 51.65, H 3.33, N 18.53, S 10.61; found: C 51.78, H 3.20, N 18.41, S 10.65.

Compound 4n: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.57 (s, 1 H, NH), 9.95 (s, 1 H, NH), 8.09 (d, J = 8.0 Hz, 2 H, ArH), 7.81–7.78 (m, 2 H, ArH), 7.45 (d, J = 8.4 Hz, 2 H, ArH), 7.42–7.38 (m, 2 H, ArH), 6.58 (s, 2 H, NH_2), 4.93–4.74 (m, 2 H, CH_2), 4.48 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 171.69, 162.61, 162.56, 158.58, 154.99, 154.74, 150.37, 149.80, 141.76, 128.92, 127.21, 125.05, 124.93, 124.44, 120.01, 111.09, 99.33, 90.62, 62.99, 34.89 ppm. IR: ṽ = 3431, 3310, 1717, 1676, 1600, 1476, 1346, 1164, 1109, 1060, 1025, 865 cm^{-1}. $C_{22}H_{15}N_5O_4$ (413.39): calcd. C 63.92, H 3.66, N 16.94; found: C 64.02, H 3.52, N 16.81.

Compound 6a: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.79 (s, 1 H, NH), 10.66 (s, 1 H, NH), 7.76 (d, J = 6.8 Hz, 1 H, ArH), 7.59 (m, 1 H, ArH), 7.41 (t, J = 7.2 Hz, 1 H, ArH), 7.33 (t, J = 7.2 Hz, 1 H, ArH), 7.29–7.22 (m, 4 H, ArH), 6.49 (s, 2 H, NH_2), 4.72 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.71, 161.95, 155.94, 154.82, 154.46, 145.53, 136.44, 133.59, 131.83, 130.45, 130.33, 129.61, 127.92, 120.35, 119.97, 107.60,

93.08, 35.94 ppm. IR: ṽ = 3247, 2927, 1715, 1680, 1634, 1519, 1499, 1090, 1075, 905, 826, 767 cm^{-1}. $C_{20}H_{13}ClN_4O_2$ (376.80): calcd. C 63.75, H 3.48, N 14.87; found: C 63.87, H 3.36, N 14.72.

Compound 6b: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.78 (s, 1 H, NH), 10.66 (s, 1 H, NH), 7.76 (d, J = 7.2 Hz, 1 H, ArH), 7.61–7.54 (m, 2 H, ArH), 7.43–7.38 (m, 3 H, ArH), 7.33 (t, J = 7.2 Hz, 1 H, ArH), 6.79–6.72 (m, 1 H, ArH), 6.48 (s, 2 H, NH$_2$), 4.70 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.71, 161.97, 155.94, 154.83, 154.47, 145.86, 136.43, 133.59, 131.82, 130.84, 130.33, 130.05, 120.35, 119.98, 118.95, 107.54, 93.03, 35.94 ppm. IR: ṽ = 3446, 3161, 2926, 1716, 1636, 1570, 1554, 1072, 1011, 906, 780, 747 cm^{-1}. $C_{20}H_{13}BrN_4O_2$ (421.25): calcd. C 57.02, H 3.11, N 13.30; found: C 57.14, H 3.01, N 13.18.

Compound 6c: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.81 (s, 1 H, NH), 10.71 (s, 1 H, NH), 7.88 (d, J = 7.2 Hz, 1 H, ArH), 7.78–7.71 (m, 1 H, ArH), 7.61–7.56 (m, 2 H, ArH), 7.19 (d, J = 8.4 Hz, 2 H, ArH), 6.90 (d, J = 8.4 Hz, 2 H, ArH), 6.50 (s, 2 H, NH$_2$), 4.70 (s, 1 H, CH), 3.83 (s, 3 H, OCH$_3$) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.51, 161.81, 156.02, 154.89, 152.11, 146.62, 140.00, 137.12, 133.83, 131.61, 130.02, 123.25, 122.34, 120.48, 120.05, 109.11, 95.32, 56.33, 30.02 ppm. IR: ṽ = 3230, 3129, 2836, 1723, 1682, 1607, 1482, 1293, 1022, 883, 754 cm^{-1}. $C_{21}H_{16}N_4O_3$ (372.38): calcd. C 67.73, H 4.33, N 15.05; found: C 67.86, H 4.21, N 14.92.

Compound 6d: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.74 (s, 1 H, NH), 10.62 (s, 1 H, NH), 7.76 (d, J = 7.2 Hz, 1 H, ArH), 7.40 (t, J = 7.6 Hz, 1 H, ArH), 7.32 (t, J = 7.6 Hz, 1 H, ArH), 7.26–7.22 (m, 3 H, ArH), 7.01 (t, J = 8.8 Hz, 2 H, ArH), 6.52 (s, 2 H, NH$_2$), 4.73 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.77, 161.97, 161.89, 159.49, 155.85, 154.42, 142.65, 136.50, 133.62, 131.81, 130.28, 129.46, 129.38, 120.33, 119.92, 114.70, 114.48, 107.94, 93.38, 33.43 ppm. IR: ṽ = 3468, 3264, 3081, 2927, 1754, 1665, 1601, 1517, 1481, 1447, 907, 858, 745 cm^{-1}. $C_{20}H_{13}FN_4O_2$ (360.34): calcd. C 66.66, H 3.64, N 15.55; found: C 66.78, H 3.54, N 15.42.

Compound 6e: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.84 (s, 1 H, NH), 10.69 (s, 1 H, NH), 7.78 (d, J = 7.2 Hz, 1 H, ArH), 7.48–7.40 (m, 5 H, ArH), 7.34 (t, J = 7.2 Hz, 1 H, ArH), 7.24 (d, J = 6.8 Hz, 1 H, ArH), 7.19 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H, ArH), 6.53 (s, 2 H, NH$_2$), 4.73 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.76, 161.97, 155.82, 154.81, 154.36, 146.55, 136.53, 133.66, 131.78, 130.23, 128.00, 127.71, 125.93, 120.30, 119.84, 108.21, 93.47, 34.00 ppm. IR: ṽ = 3469, 3333, 3249, 3080, 2929, 1731, 1661, 1599, 1514, 1448, 1042, 899 cm^{-1}. $C_{20}H_{14}N_4O_2$ (342.35): calcd. C 70.17, H 4.12, N 16.37; found: C 70.28, H 4.01, N 16.28.

Compound 6f: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.90 (s, 1 H, NH), 10.70 (s, 1 H, NH), 8.04–7.99 (m, 2 H, ArH), 7.80 (d, J = 7.2 Hz, 1 H, ArH), 7.71 (d, J = 8.0 Hz, 1 H, ArH), 7.53 (t, J = 8.0 Hz, 1 H, ArH), 7.42 (t, J = 8.0 Hz, 1 H, ArH), 7.34 (t, J = 7.6 Hz, 1 H, ArH), 7.24 (d, J = 7.2 Hz, 1 H, ArH), 6.58 (s, 2 H, NH$_2$), 4.88 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.77, 161.97, 159.48, 155.85, 154.76, 151.31, 142.68, 136.49, 135.21, 133.61, 131.81, 130.28, 129.46, 124.35, 120.33, 119.93, 114.70, 107.93, 93.37, 35.94 ppm. IR: ṽ = 3465, 3293, 3083, 2923, 1717, 1660, 1602, 1523, 1448, 899, 827, 780, 766, 739 cm^{-1}. $C_{20}H_{13}N_5O_4$ (387.35): calcd. C 62.01, H 3.38, N 18.08; found: C 62.15, H 3.28, N 17.96.

Compound 6g: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.44 (s, 1 H, NH), 10.39 (s, 1 H, NH), 7.35 (s, 1 H, ArH), 7.68–7.60 (m, 1 H, ArH), 7.27–7.22 (m, 1 H, ArH), 7.20–7.17 (m, 4 H, ArH), 6.03 (s, 2 H, NH$_2$), 4.82 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.72, 161.98, 156.35, 155.21, 154.82, 145.49, 136.50, 133.59, 131.83, 130.45, 130.33, 129.91, 129.38, 120.35, 119.97, 115.34, 114.43, 107.60, 93.08, 35.89 ppm. IR: ṽ = 3310, 3135, 1720, 1667, 1562, 1480, 1377, 1294, 1170, 1081, 1041, 942, 871, 748 cm^{-1}. $C_{20}H_{12}Cl_2N_4O_2$ (411.24): calcd. C 58.41, H 2.94, N 13.62; found: C 58.59, H 2.87, N 13.51.

Compound 6h: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.21 (s, 1 H, NH), 10.81 (s, 1 H, NH), 7.85–7.83 (m, 1 H, ArH), 7.74–7.67 (m, 2 H, ArH), 7.62–7.59 (m, 1 H, ArH), 6.65 (s, 2 H, NH$_2$), 4.92 (s, 1 H, CH), 1.55–1.49 (m, 2 H, CH$_2$), 1.45–1.39 (m, 4 H, 2CH$_2$), 0.96–0.91 (m, 3 H, CH$_3$) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.71, 161.95, 158.34, 155.94, 154.82, 154.62, 146.31, 139.72, 136.44, 133.69, 131.83, 107.87, 93.08, 35.94, 32.12, 28.67, 23.36, 13.89 ppm. IR: ṽ = 3273, 3203, 3071, 1960, 1735, 1644, 1486, 1369, 920, 606 cm^{-1}. $C_{18}H_{18}N_4O_2$ (322.36): calcd. C 67.07, H 5.63, N 17.38; found: C 67.15, H 5.52, N 17.25.

Compound 6i: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.81 (s, 1 H, NH), 10.71 (s, 1 H, NH), 7.76 (d, J = 7.2 Hz, 2 H, ArH), 7.61 (s, 1 H, ArH), 7.42 (t, J = 7.2 Hz, 1 H, ArH), 7.35 (t, J = 7.2 Hz, 1 H, ArH), 7.29 (d, J = 7.2 Hz, 1 H, ArH), 7.18 (t, J = 7.2 Hz, 1 H, ArH), 6.50 (s, 2 H, NH$_2$), 5.04 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.76, 161.97, 155.82, 154.81, 154.36, 146.55, 136.53, 133.66, 131.78, 130.23, 126.97, 126.73, 123.67, 120.30, 119.84, 108.21, 93.47, 34.00 ppm. IR: ṽ = 3442, 3245, 2923, 1730, 1669, 1599, 1514, 1419, 1037, 902, 663 cm^{-1}. $C_{18}H_{12}N_4O_2S$ (348.38): calcd. C 62.06, H 3.47, N 16.08, S 9.20; found: C 62.18, H 3.38, N 15.91, S 9.18.

Compound 6j: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.79 (s, 1 H, NH), 10.63 (s, 1 H, NH), 8.06 (d, J = 8.4 Hz, 2 H, ArH), 7.78–7.71 (m, 3 H, ArH), 7.47 (d, J = 8.4 Hz, 2 H, ArH), 7.40–7.36 (m, 3 H, ArH), 7.32–7.28 (m, 1 H, ArH), 7.21 (d, J = 6.8 Hz, 1 H, ArH), 6.46 (s, 2 H, NH$_2$), 4.84 (s, 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 191.69, 162.61, 162.01, 161.11, 158.52, 155.31, 150.41, 142.71, 141.81, 136.61, 133.65, 131.85, 130.31, 129.01, 127.34, 125.05, 124.93, 124.51, 120.51, 120.01, 119.89, 111.12, 108.11, 93.42, 33.51 ppm. IR: ṽ = 3419, 3252, 2932, 1716, 1655, 1630, 1558, 1516, 1482, 1359, 1282, 1241, 1153, 1055, 871 cm^{-1}. $C_{27}H_{17}N_5O_3$ (459.46): calcd. C 70.58, H 3.73, N 15.24; found: C 70.69, H 3.65, N 15.13.

Compound 6k: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.64 (s, 1 H, NH), 10.47 (s, 1 H, NH), 7.74 (d, J = 7.2 Hz, 1 H, ArH), 7.37 (t, J = 7.2 Hz, 1 H, ArH), 7.29 (t, J = 7.2 Hz, 1 H, ArH), 7.17 (d, J = 7.2 Hz, 1 H, ArH), 6.86 (t, J = 7.6 Hz, 1 H, ArH), 6.76 (d, J = 7.6 Hz, 1 H, ArH), 6.71 (d, J = 7.6 Hz, 1 H, ArH), 6.39 (s, 2 H, NH$_2$), 4.96 (s, 1 H, CH), 3.76 (s, 3 H, OCH$_3$), 3.74 (s, 3 H, OCH$_3$) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 190.49, 161.73, 155.93, 154.91, 154.21, 152.26, 146.54, 140.03, 136.67, 133.79, 131.59, 130.09, 123.11, 122.04, 120.30, 119.71, 110.29, 108.11, 94.32, 59.62, 55.58, 29.46 ppm. IR: ṽ = 3463, 3268, 2931, 1664, 1603, 1519, 1481, 1001, 906, 729 cm^{-1}. $C_{22}H_{18}N_4O_4$ (402.40): calcd. C 65.66, H 4.51, N 13.92; found: C 65.78, H 4.40, N 13.85.

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[37] The single crystal was grown in EtOH/DMF at room temp. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer (graphite monochromator, Mo-K_α radiation $\lambda = 0.71073$ Å). Crystal data for **6k**: empirical formula $C_{22}H_{18}N_4O_4.C_3H_7NO$, yellow, crystal dimensions $0.14 \times 0.11 \times 0.08$ mm, monoclinic, space group *P21/c*, $a = 11.642(7)$ Å, $b = 19.256(11)$ Å, $c = 11.975(7)$ Å, $\alpha = 90°$, $\beta = 118.172(11)°$, $\gamma = 90°$, $V = 2367(2)$ Å^3, $Mr = 475.50$, $Z = 4$, $Dc = 1.335$ Mgm^{-3}, $\lambda = 0.71073$ Å, μ (Mo-K_α) = 0.095 mm^{-1}, $F(000) = 1000$, $S = 0.973$, $R_1 = 0.075$, $wR_2 = 0.1448$. CCDC-632190 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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