6-Carbohydrazonamidepurines: Convenient Precursors for 4,8-Disubstituted Pyrimido[5,4-*d*]pyrimidines

Ashly Rocha, Ana H. Bacelar, Joana Fernandes, M. Fernanda Proenca, M. Alice Carvalho*

Centro de Química, Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal
Fax +351(253)604382; E-mail: mac@quimica.uminho.pt

Received: 25.09.2013; Accepted after revision: 09.11.2013

Abstract: A series of 4-arylamino-8-(alkyl or aryl)hydrazidepyrimido[5,4-*d*]pyrimidines was obtained efficiently from 6-carbohydrazonamidepurines by reaction with piperidine. The 6-carbohydrazonamidepurines were generated selectively by the reaction of 6-imidatopurine with hydrazides under acidic conditions.

Key words: rearrangement, ring opening, ring closure, substituent effects, fused-ring systems, heterocycles

Tuberculosis affects much of the world population and it is estimated that 9.2 million new cases appear each year, from which many lead to death.[1] The emergence of multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) has added urgency to the search for new antitubercular agents[2] and, since the last decade of the 20th century, the scientific community has undertaken intensive research in this area.[3] Recently, in our research group, the pyrimido[5,4-*d*]pyrimidines (Figure 1) were identified as a promising new class of antitubercular agents.[4] The new compounds showed high potency that depends on the substituents R^1 and R^2. Furthermore, the new compounds have no structural similarity to any other compounds active against *Mycobacterium tuberculosis* and may have a different mechanism of action in relation to drugs currently on the market. Therefore a research program was started in order to develop new methods for the efficient synthesis of new pyrimido[5,4-*d*]pyrimidines derivatives **3** (Scheme 1) for structure–activity relationship studies.

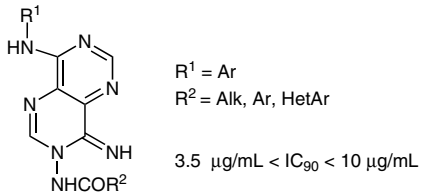
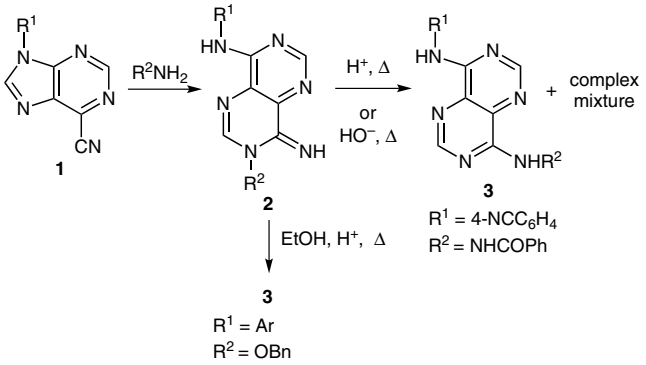


Figure 1 A new class of antitubercular agents

In the literature, the pyrimido[5,4-*d*]pyrimidine core structure has been prepared from a substituted pyrimidine, upon reaction with an appropriate electrophile or nucleophile.[5] Amino substituents are usually incorporated into the heteroaromatic ring by nucleophilic substitution of chlorine atoms by amines.[6] The 6-cyanopurines have also been used as precursors of substituted pyrimido[5,4-*d*]pyrimidines, as the reaction with amines leads to the desired structure by an ANRORC-type mechanism.[7] This approach has been used in our group for the efficient synthesis of compounds **2** (Scheme 1).[4,8–10] According to the literature, structure **2** can be used to generate the aromatic analogue **3** by Dimroth rearrangement, in the presence of acid or base catalysis.[11] Furthermore, our studies on the reactivity of the pyrimidopyrimidine derivatives **2** (R^2 = OBn) have proved that the conversion of **2** (R^2 = OBn) into **3** (R^2 = OBn) occurs efficiently under acid conditions although other products may also be formed (Scheme 1).[10] In the present work, compounds **2** were considered to be convenient precursors of the aromatic pyrimido[5,4-*d*]pyrimidines **3** (R^2 = NHCOR[3]).



Scheme 1 Synthesis of **2**, its conversion into **3** (R^2 = OBn) and attempts to generate new derivatives **3** (R^1 = 4-NCC_6H_4, R^2 = NHCOR[3]).

Herein we report our attempts to convert pyrimido[5,4-*d*]pyrimidine **2** (R^2 = NHCOR[3]) into **3** (R^2 = NHCOR[3]) and the new synthetic strategy designed to generate derivatives **3** starting from 6-carbohydrazonamidepurines **4** that have proved to be valuable precursors for the target compounds **3**.

Compound **2** (R^1 = 4-NCC_6H_4, R^2 = NHCOPh) was prepared by reaction of the 6-cyanopurine **1** (R^1 = 4-NCC_6H_4) with benzoic hydrazide according to a previously described procedure.[4] Attempts to perform the Dimroth rearrangement of **2** (R^1 = 4-NCC_6H_4, R^2 = NHCOPh) under reflux conditions using ethanol and hydrochloric acid led to a complex mixture (evidence by TLC) and the product was isolated as a yellow solid when the starting material was no longer present. The ^{1}H NMR of the solid con-

SYNLETT 2014, 25, 0343–0348
Advanced online publication: 19.12.2013
DOI: 10.1055/s-0033-1340344; Art ID: ST-2013-D0911-L

firmed the formation of a complex mixture, where the signals for the desired product **3** could be identified as the major component (Scheme 1). A similar result was obtained when sulfuric acid or trifluoroacetic acid were used as catalysts. The conversion of **2** (R^2 = NHCOR^3) into **3** (Scheme 1) was also attempted under basic conditions using ethanol as solvent and aqueous sodium hydroxide. Again, complex mixtures resulted from these reactions and the desired product **3** was only identified by ^{1}H NMR analysis of the isolated solids as a minor component. The reactivity of compound **2** was clearly affected by the nature of the substituent R^2 as the presence of the amide group resulted in complex reaction mixtures under the experimental conditions normally used for the Dimroth rearrangement. Thus, efficient formation of pyrimido[5,4-*d*]pyrimidines **3** required an alternative approach and a new synthetic strategy was designed (Scheme 2).

6-Cyanopurines **1** had been previously used to generate 6-imidatopurines **6**,[12] and reaction of these compounds with hydrazides was carried out in the presence of acid catalysis, aiming to prepare the 6-amidinopurines **4**. Previous results on the reactivity of the purine ring, under basic conditions and in the presence of nucleophiles, indicated that attack on C8 was the major pathway,[8–10] leading to pyrimidopyrimidines **2**. The use of a catalytic amount of sulfuric acid, when a suspension of compound **6a** in dimethylsulfoxide was combined with acetic hydrazide **7a**, prevented the competitive formation of product **2**.

The mixture was stirred at room temperature and, when TLC showed the absence of starting material, addition of water led to the isolation of a solid product identified as **4a**, in 51% yield[13] (Table 1, entry 1). Similar reaction conditions were applied to the reactions of **6a–c** with other alkyl (**7b**), aryl (**7c**,**e**) and heteroaryl hydrazides (**7d**). The products **4a–j** were isolated in excellent yields by simple filtration of the reaction mixture (Table 1, entries 2–10).

The conversion of 6-amidinopurines **4** into the pyrimido[5,4-*d*]pyrimidines **3** was performed in the presence of piperidine using ethanol or ethanol–DMF, when the reagents were observed to be poorly soluble in ethanol alone. Piperidine is a powerful nucleophile that attacks C8 of the purine ring **4** readily leading to the substituted pyrimidine **5**. The bulkiness of the piperidine group presumably prevents nucleophilic attack at the starred carbon by the sterically congested amidrazone nitrogen (blue nitrogen atom) in intermediate **5** (Scheme 2). Cyclization occurred preferentially through the primary amine (red nitrogen atom), leading to **3**. The reactions were performed under reflux conditions, and the products were isolated in good to excellent yield after 17–30 hours (Table 1, entries 11–20),[14] following removal of solvent by rotary evaporator and addition of water. The structures of all new compounds were supported by analytical and spectroscopic data.[15]

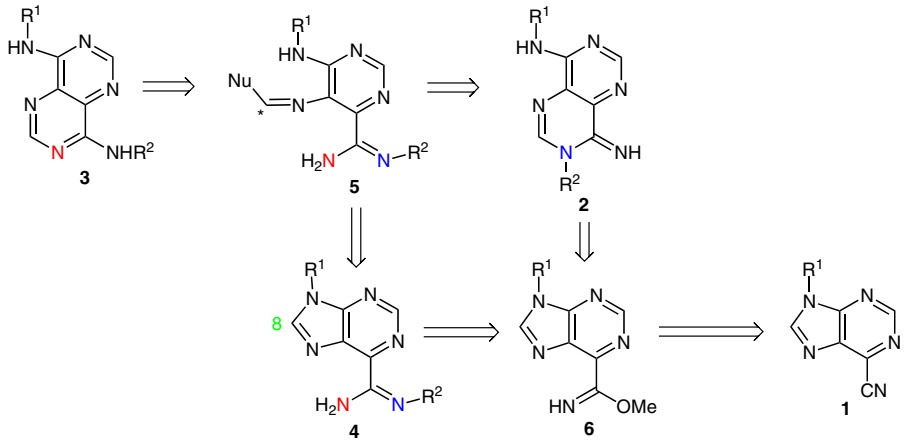
In conclusion, we have described a new and efficient method to generate 4,8-disubstituted pyrimido[5,4-*d*]yrimidines **3** (R^2 = NHCOR^3) starting from novel 6-carbohydrazonamidepurines **4**. Purines **4** were obtained from 6-imidatopurines **6** by reaction with hydrazides under acidic conditions. The reaction proceeds smoothly when R^1 is an aryl group while amidrazone substituent R^3 can be alkyl, aryl or heteroaryl groups. We have also demonstrated that pyrimido[5,4-*d*]pyrimidines **2** (R^2 = NHCOR^3) are not convenient precursors of the new derivatives **3** as compounds **2** (R^2 = NHCOR^3) generated complex mixtures when submitted to reaction conditions normally leading to Dimroth rearrangement.

Acknowledgment

Thanks are due to the University of Minho and *Fundação para a Ciência e Tecnologia* (FCT) for financial support [project nºF-COMP-01-0124-FEDER-022716 (ref. FCT PEst-/QUI/UI0686/2011) FEDER-COMPETE, FCT-Portugal, a PhD grant awarded to Ana Bacelar (SRFH/BD/24959/2005)]. The NMR spectrometer (Bruker 400 Avance III) is part of the National NMR Network supported with funds from FCT.

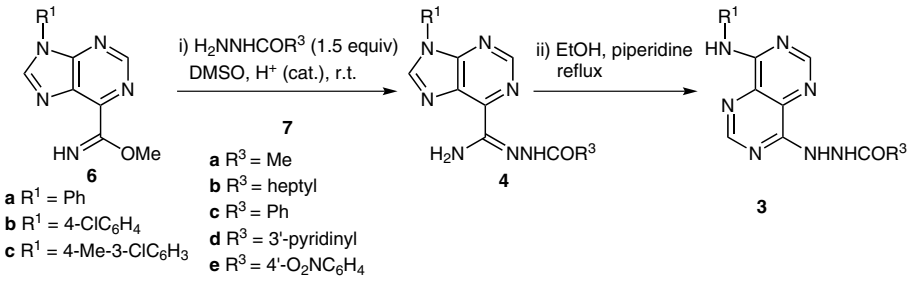
References and Notes

(1) (a) Dye, C. *Nat. Rev. Microbiol.* **2009**, *7*, 81. (b) Tomioka, H.; Tatano, Y.; Yasumoto, K.; Shimizu, T. *Expert Rev. Respir. Med.* **2008**, *2*, 455.



Scheme 2 Disconnection of pyrimido[5,4-*d*]pyrimidine **3** (R^2 = NHCOR^3)

Table 1 Synthesis of 6-Carbohydrazonamidepurines **4** and 4,8-Disubstituted Pyrimido[5,4-*d*]pyrimidines **3**



Entry	Reagent	R^1		R^3	Reaction conditions	Product	Yield (%)
1	**6a** (0.75 mmol)	Ph	**7a**	Me	i) DMSO (1.2 mL), 1 h	**4a**	51
2	**6a** (1.59 mmol)	Ph	**7b**	heptyl	i) DMSO (2.5 mL), 10 min	**4b**	97
3	**6a** (0.60 mmol)	Ph	**7c**	Ph	i) DMSO (2.0 mL), 1 h	**4c**	85
4	**6a** (0.99 mmol)	Ph	**7d**	3′-pyridinyl	i) DMSO (2.0 mL), 10 min	**4d**	83
5	**6b** (0.92 mmol)	4-ClC_6H_4	**7b**	heptyl	i) DMSO (2.2 mL), 15 min	**4e**	99
6	**6b** (0.86 mmol)	4-ClC_6H_4	**7e**	4′-$O_2NC_6H_4$	i) DMSO (2.0 mL), 15 min	**4f**	98
7	**6b** (1.01 mmol)	4-ClC_6H_4	**7d**	3′-pyridinyl	i) DMSO (2.0 mL), 10 min	**4g**	94
8	**6c** (1.27 mmol)	4-Me-3-ClC_6H_3	**7b**	heptyl	i) DMSO (2.2 mL), 10 min	**4h**	99
9	**6c** (1.20 mmol)	4-Me-3-ClC_6H_3	**7e**	4′-$O_2NC_6H_4$	i) DMSO (2.0 mL), 18 min	**4i**	83
10	**6c** (0.82 mmol)	4-Me-3-ClC_6H_3	**7d**	3′-pyridinyl	i) DMSO (2.4 mL), 20 min	**4j**	79
11	**4a** (1.20 mmol)	Ph		Me	ii)[a] 24 h	**3a**	63
12	**4b** (0.49 mmol)	Ph		heptyl	ii)[b] 24 h	**3b**	76
13	**4c** (0.28 mmol)	Ph		Ph	ii)[c] 30 h	**3c**	51
14	**4d** (0.60 mmol)	Ph		3′-pyridinyl	ii)[c] 24 h	**3d**	54
15	**4e** (0.61mmol)	4-ClC_6H_4		heptyl	ii)[b] 18 h	**3e**	75
16	**4f** (0.51 mmol)	4-ClC_6H_4		4′-$O_2NC_6H_4$	ii)[b] 23 h	**3f**	81
17	**4g** (1.22 mmol)	4-ClC_6H_4		3′-pyridinyl	ii)[b] 22 h	**3g**	72
18	**4h** (1.35 mmol)	4-Me-3-ClC_6H_3		heptyl	ii)[b] 20 h	**3h**	86
19	**4i** (0.92 mmol)	4-Me-3-ClC_6H_3		4′-$O_2NC_6H_4$	ii)[b] 17 h	**3i**	82
20	**4j** (0.48 mmol)	4-Me-3-ClC_6H_3		3′-pyridinyl	ii)[b] 24 h	**3j**	99

[a] EtOH (10 mL), piperidine (0.6 mL).
[b] EtOH (10 mL), piperidine (0.5 mL).
[c] EtOH (10 mL), DMF (0.4 mL), piperidine (0.5 mL).

(2) (a) Chhabria, M.; Jani, M.; Patel, S. *Mini-Rev. Med. Chem.* **2009**, 401. (b) Showalter, H. D.; Denny, W. *Tuberculosis* **2008**, *88*, S3. (c) Goldman, R.; Plumley, K. V.; Laughon, B. E. *Infect. Disord. Drug Targets* **2007**, *7*, 73. (d) Nguyen, L.; Thompson, C. J. *Trends Microbiol.* **2006**, *14*, 304. (e) Shi, R.; Itagaki, N.; Sugawara, I. *Mini-Rev. Med. Chem.* **2007**, *7*, 1177.

(3) (a) Ballell, L.; Field, R. A.; Duncan, K.; Young, R. J. *Antimicrob. Agents Chemother.* **2005**, 2153. (b) Nayyar, A.; Jain, R. *Curr. Med. Chem.* **2005**, *12*, 1873. (c) Tangallapally, R. P.; Yendapally, R.; Daniels, A. J.; Lee, R. E. B. *Curr. Top. Med. Chem.* **2007**, *7*, 509.

(4) Bacelar, A. H.; Carvalho, M. A.; Proença, M. F. *Eur. J. Med. Chem.* **2010**, 3234.

(5) (a) Rewcastle, G. W.; Bridges, A. J.; Fry, D. W.; Rubin, J. R.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 1820. (b) Rewcastle, G. W.; Denny, W. A.; Showalter, D. H. *Curr. Org. Chem.* **2000**, *4*, 679. (c) Al-Azmi, A. *J. Chem. Res., Synop.* **2005**, *8*, 530.

(6) (a) Sanghvi, Y. S.; Larson, S. B.; Matsumoto, S. S.; Nord, L. D.; Smee, D. F.; Willis, R. C.; Avery, T. L.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1989**, *32*, 629. (b) Curtin, N. J.; Barlow, H. C.; Bowman, K. J.; Calvert, A. H.; Davison, R.; Golding, B. T.; Huang, B.; Loughlin, P. J.; Newell, D. R.; Smith, P. G.; Griffin, R. J. *J. Med. Chem.* **2004**, *47*, 4905. (c) Northen, J. S.; Boyle, F. T.; Clegg, W.; Curtin, N. J.; Edwards, A. J.; Griffin, R. J.; Golding, B. T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 108. (d) El-Araby, M.; Pottorf, R. S.;

Player, M. R. *Comb. Chem. High Throughput Screening* **2004**, *7*, 413.
(7) (a) Srivastava, P. C.; Revankar, G. R.; Robins, R. K.; Rousseau, R. J. *J. Med. Chem.* **1981**, *24*, 393. (b) Cook, P. D.; Berry, D. A. US Patent US4801698, **1989**; *Chem. Abstr.* **1989**, 109: 110861h (c) Mabry, T. E.; Jones, C. D.; Chou, T. S.; Colacino, J. M.; Grindey, G. B.; Worzalla, J. F.; Pearce, H. L. *Nucleosides Nucleotides* **1994**, *13*, 1125. (d) Berman, H. M.; Rousseau, R. J.; Mancuso, R. W.; Kreishman, G. P.; Robins, R. K. *Tetrahedron Lett.* **1973**, 3099. (e) Westover, J. D.; Revankar, G. R.; Robins, R. K.; Madsen, R. D.; Ogden, J. R.; North, J. A.; Mancuso, R. W.; Rousseau, R. J.; Stephen, E. L. *J. Med. Chem.* **1981**, *24*, 941. (f) Rao, T. S.; Revankar, G. R. *Nucleosides Nucleotides* **1995**, *14*, 1601. (g) Al-Azmi, A.; Kumari, K. A. *Heterocycles* **2009**, *78*, 2245.
(8) Al-Azmi, A.; Booth, B. L.; Carpenter, R. A.; Carvalho, M. A.; Marrelec, E.; Pritchard, R. G.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2532.
(9) Carvalho, M. A.; Esperança, S.; Esteves, T.; Proença, M. F. *Eur. J. Org. Chem.* **2007**, 1324.
(10) Ribeiro, A.; Carvalho, M. A.; Proença, M. F. *Eur. J. Org. Chem.* **2009**, 4867.
(11) *Mechanisms of Molecular Migration*; Vol. 1; Thyagarajan, B. S., Ed.; Interscience Publishers: USA, **1968**, 209.
(12) Carvalho, M. A.; Esteves, T. M.; Proença, M. F.; Booth, B. L. *Org. Biomol. Chem.* **2004**, 1019.
(13) **Experimental Procedure for the Synthesis of 6-Carbohydrazonamidepurine 4a**: The 6-imidatopurines **6a** (0.19 g, 0.75 mmol) and hydrazide **7a** (0.08g, 1.3 mmol, 1.5 equiv) were combined in a round-bottom flask using DMSO (1.2 mL) as solvent and sulfuric acid (25 μL) as catalyst. The reaction was stirred at r.t. until TLC analysis showed the absence of starting material (1 h) and H_2O (10 mL) was added to the reaction mixture. The yellow suspension was filtered, washed with H_2O, EtOH and Et_2O and identified as 6-carbohydrazonamidepurine **4a** (0.12 g, 0.38 mmol, 51%); mp 235–237 °C. IR (nujol mull): 3459, 3363, 3203, 3057, 1680, 1655, 1590, 1576, 1567 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.27 (s, 2 H, NH_2, D_2O exch.), 9.44 (s, 1 H, CH), 9.29 (s, 1 H, CH), 7.93 (d, *J* = 7.8 Hz, 2 H, Ar), 7.68 (t, *J* = 7.8 Hz, 2 H, Ar), 7.57 (t, *J* = 7.8 Hz, 1 H, Ar), 2.03 (s, 3 H, Me). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.7, 158.6, 153.4, 152.3, 149.4, 139.6, 133.6, 131.9, 129.8, 128.9, 124.0, 21.0. Anal. Calcd for $C_{14}H_{13}N_7O$: C, 56.94; H, 4.44; N, 33.20. Found: C, 56.77; H, 4.55; N, 33.02.
(14) **Experimental Procedure for the Synthesis of Pyrimido[5,4,-*d*]pyrimidine 3a**: A solution of 6-carbohydrazonamidepurine **4a** (0.35 g, 1.2 mmol) in EtOH (10 mL) and piperidine (0.6 mL) was heated to reflux for 24 h, when TLC showed the absence of starting material. The suspension was concentrated to dryness and H_2O was added to the residue. The resulting off-white solid was filtered, washed with H_2O and EtOH and identified as the pyrimido[5,4-*d*]pyrimidine **3a** (0.22 g, 0.76 mmol, 63%); mp 181–182 °C. IR (nujol mull): 3360, 3225, 3048, 1610, 1590, 1551, 1528 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.19 (br s, 1 H, NH, D_2O exch.), 10.16 (br s, 1 H, NH, D_2O exch.), 8.65 (s, 1 H, CH), 8.61 (s, 1 H, CH) 7.97 (d, *J* = 7.5 Hz, 2 H, Ar), 7.38 (t, *J* = 7.5 Hz, 2 H, Ar), 7.14 (t, *J* = 7.5 Hz, 1 H, Ar), 1.96 (s, 3 H, Me). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 168.4, 157.9, 156.5, 154.2, 153.5, 138.3, 131.8, 131.0, 128.6, 124.2, 121.9, 20.7. Anal. Calcd for $C_{14}H_{13}N_7O$: C, 56.94; H, 4.44; N, 33.20. Found: C, 56.77; H, 4.55; N, 33.57.
(15) Analytical and spectroscopic data for compounds **3b**–**j** and **4b**–**j**:

Compound 3b: yield: 76%; crème solid; mp 142–144 °C. IR (nujol mull): 3365, 3237, 1678, 1597, 1576, 1524 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.11 (s, 1 H, NH, D_2O exch.), 10.08 (s, 1 H, NH, D_2O exch.), 8.64 (s, 1 H, CH), 8.58 (s, 1 H, CH), 7.99 (d, *J* = 7.5 Hz, 2 H, Ar), 7.38 (t, *J* = 7.5 Hz, 2 H, Ar), 7.13 (t, *J* = 7.5 Hz, 1 H, Ar), 2.21 (t, *J* = 7.2 Hz, 2 H), 1.55–1.58 (m, 2 H), 1.28 (m, 8 H), 0.84–0.86 (m, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 171.4, 158.3, 156.4, 154.1 (2 ×), 138.4, 131.9, 131.0, 128.6, 124.0, 121.9, 33.3, 31.3, 28.6, 28.5, 25.1, 22.1, 14.0. Anal. Calcd for $C_{20}H_{25}N_7O$: C, 63.30; H, 6.64; N, 25.84. Found: C, 63.33; H, 6.86; N, 25.85.
Compound 3c: yield: 51%; yellow solid; mp >300 °C. IR (nujol mull): 3315, 3169, 1670, 1680, 1539, 1530 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 10.69 (br s, 1 H, NH, D_2O exch.), 10.41 (br s, 1 H, NH, D_2O exch.), 10.06 (s, 1 H, NH, D_2O exch.), 8.67 (s, 1 H, CH), 8.59 (s, 1 H, CH), 8.01 (d, *J* = 7.8 Hz, 2 H, Ar), 7.96 (d, *J* = 7.2 Hz, 2 H, Ar), 7.60 (t, *J* = 7.2 Hz, 1 H, Ar), 7.52 (t, *J* = 7.2 Hz, 2 H, Ar), 7.39 (t, *J* = 7.8 Hz, 2 H, Ar), 7.13 (t, *J* = 7.8 Hz, 1 H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.4, 158.7, 156.3, 154.4, 154.1, 132.5, 132.1, 131.8, 131.1, 128.6, 128.5, 127.5, 123.3, 121.6. Anal. Calcd for $C_{19}H_{15}N_7O$: C, 63.86; H, 4.23; N, 27.44. Found: C, 63.58; H, 4.32; N, 27.53.
Compound 3d: yield: 54%; yellow solid; mp 255–257 °C. IR (nujol mull): 3315, 3248, 3105, 1640, 1601, 1591, 1568, 1527 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.95 (s, 1 H, NH, D_2O exch.), 10.10 (s, 1 H, NH, D_2O exch.), 9.14 (d, *J* = 1.6 Hz, 1 H), 8.81 (dd, *J* = 1.6, 5.2 Hz, 1 H, HetAr), 8.69 (s, 1 H, CH), 8.63 (s, 1 H, CH), 8.35 (dd, *J* = 1.6, 6.0 Hz, 1 H, HetAr), 8.01 (d, *J* = 7.6 Hz, 2 H, Ar), 7.64 (dd, *J* = 5.2, 6.0 Hz, 1 H, HetAr), 7.39 (t, *J* = 7.6 Hz, 2 H, Ar), 7.14 (t, *J* = 7.6 Hz, 1 H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 164.4, 158.8, 156.5, 154.5, 154.3, 152.1, 148.1, 138.4, 136.0, 132.2, 131.1, 128.6, 128.4, 124.0 (2 ×), 121.7. Anal. Calcd for $C_{18}H_{14}N_8O$: C, 60.33; H, 3.94; N, 31.27. Found: C, 60.09; H, 4.00; N, 31.13.
Compound 3e: yield: 75%; off-white solid; mp 165–167 °C. IR (nujol mull): 3357, 3251, 1679, 1654, 1615, 1603, 1595, 1569, 1547 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.23 (s, 1 H, NH, D_2O exch.), 10.05 (s, 1 H, NH, D_2O exch.), 8.65 (s, 1 H, CH), 8.58 (s, 1 H, CH), 8.07 (d, *J* = 8.9 Hz, 2 H, Ar), 7.42 (d, *J* = 8.9 Hz, 2 H, Ar), 2.21 (t, *J* = 7.5 Hz, 2 H), 1.54–1.59 (m, 2 H), 1.26–1.29 (m, 8 H), 0.84–0.86 (m, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 171.4, 158.6, 156.4, 154.4, 153.9, 137.5, 132.0, 131.1, 128.4, 127.5, 123.2, 33.3, 31.2, 28.6, 28.5, 25.0, 22.1, 14.0. Anal. Calcd for $C_{20}H_{24}ClN_7O$: C, 58.04; H, 5.84; N, 23.69. Found: C, 58.15; H, 5.95; N, 23.43.
Compound 3f: yield: 81%; orange solid; mp >300 °C. IR (nujol mull): 3310, 3218, 1693, 1666, 1604, 1594, 1570, 1537 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.08 (s, 1 H, NH, D_2O exch.), 10.29 (s, 1 H, NH, D_2O exch.), 8.71 (s, 1 H, CH), 8.63 (s, 1 H, CH), 8.38 (d, *J* = 8.9 Hz, 2 H, Ar), 8.18 (d, *J* = 8.9 Hz, 2 H, Ar), 8.08 (d, *J* = 8.9 Hz, 2 H, Ar), 7.43 (d, *J* = 8.9 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 164.1, 158.7, 156.5, 154.5, 154.2, 149.5, 138.1, 137.5, 132.2, 131.2, 129.1, 128.4, 127.6, 123.8, 123.3. Anal. Calcd for $C_{19}H_{13}ClN_8O_3$: C, 52.24; H, 3.00; N, 25.65. Found: C, 51.99; H, 3.27; N, 25.42.
Compound 3g: yield 72%; light yellow solid; mp 282–284 °C. IR (nujol mull): 3347, 3209, 1684, 1642, 1614, 1580, 1544, 1505 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6–TFA): δ = 10.99 (br s, 1 H, NH, D_2O exch.), 10.27 (s, 1 H, NH, D_2O exch.), 9.14 (d, *J* = 1.6 Hz, 1 H, HetAr), 8.83 (s, 1 H, CH), 8.71 (s, 1 H, CH), 8.82 (dd, *J* = 2.0, 4.8 Hz, 1 H, HetAr), 8.37 (dt, *J* = 2.0, 8.0 Hz, 1 H, HetAr), 8.08 (d, *J* = 8.8 Hz, 2 H,

Ar), 7.66 (dd, *J* = 4.8, 8.0 Hz, 1 H, HetAr), 7.43 (d, *J* = 8.8 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, DMSO-d_6–TFA): δ = 163.9, 158.8, 156.5, 154.8, 154.1, 151.8, 147.8, 137.5, 136.3, 132.2, 131.2, 128.5, 128.4, 127.6, 124.2, 123.2. Anal. Calcd for $C_{18}H_{13}ClN_8O$: C, 55.04; H, 3.34; N, 28.53. Found: C, 55.14; H, 3.54; N, 28.74.

Compound 3h: yield: 86%; yellow solid; mp 165–167 °C. IR (nujol mull): 3360, 3225, 1674, 1599, 1525 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6–TFA): δ = 10.10 (s, 1 H, NH, D_2O exch.), 10.07 (s, 1 H, NH, D_2O exch.), 8.68 (s, 1 H, CH), 8.58 (s, 1 H, CH), 8.24 (d, *J* = 1.5 Hz, 1 H, Ar), 7.84 (dd, *J* = 1.5, 8.1 Hz, 1 H, Ar), 7.31 (d, *J* = 8.1 Hz, 1 H, Ar), 2.30 (s, 3 H, Me), 2.26 (t, *J* = 7.2 Hz, 2 H), 1.54–1.58 (m, 2 H), 1.26–1.29 (m, 8 H), 0.84–0.86 (m, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6–TFA): δ = 171.4, 158.4, 156.4, 154.1, 154.0, 137.7, 132.8, 131.9, 131.0, 130.9, 130.6, 121.4, 120.3, 33.3, 31.1, 28.6, 28.5, 25.1, 22.1, 14.0. HRMS (ESI): *m*/*z* [M$^+$ + 1] calcd for $C_{21}H_{27}ClN_7O$: 428.93838; found: 428.93840.

Compound 3i: yield: 82%; orange solid; mp >300 °C. IR (nujol mull): 3311, 3215, 1665, 1591, 1533, 1522 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6–TFA): δ = 11.06 (s, 1 H, NH, D_2O exch.), 10.22 (s, 1 H, NH, D_2O exch.), 8.74 (s, 1 H, CH), 8.63 (s, 1 H, CH), 8.39 (d, *J* = 8.8 Hz, 2 H, Ar), 8.27 (d, *J* = 2.0 Hz, 1 H, Ar), 8.18 (d, *J* = 8.8 Hz, 2 H, Ar), 7.87 (dd, *J* = 2.0, 8.4 Hz, 1 H, Ar), 7.34 (d, *J* = 8.4 Hz, 1 H, Ar), 2.31 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6–TFA): δ = 164.0, 158.8, 156.4, 154.6, 154.2, 149.5, 138.1, 137.7, 132.8 (2 ×), 131.1, 130.9, 130.4, 129.1, 123.8, 121.4, 120.3, 19.0. HRMS (ESI): *m*/*z* [M$^+$ + 1] calcd for $C_{20}H_{16}ClN_8O_3$: 451.84584; found: 451.84583.

Compound 3j: yield: 99%; yellow solid; mp 300–302 °C. IR (nujol mull): 3438, 3358, 3199, 1683, 1652, 1604, 1584, 1540 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6–TFA): δ = 11.05 (s, 1 H, NH, D_2O exch.), 10.23 (s, 1 H, NH, D_2O exch.), 9.18 (d, *J* = 1.6 Hz, 1 H, HetAr), 8.88 (dd, *J* = 1.6, 5.2 Hz, 1 H, HetAr), 8.74 (s, 1 H, CH), 8.62 (s, 1 H, CH), 8.48 (dd, *J* = 1.6, 8.0 Hz, 1 H, HetAr), 8.26 (d, *J* = 2.0 Hz, 1 H, Ar), 7.86 (dd, *J* = 2.0, 8.6 Hz, 1 H, Ar), 7.75 (dd, *J* = 5.2, 8.0 Hz, 1 H, HetAr), 7.34 (d, *J* = 8.6 Hz, 1 H, Ar), 2.31 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.5, 159.0, 156.5, 154.4, 154.2, 150.8, 146.9, 137.6 (2 ×), 132.8, 132.2, 131.2, 130.9, 130.6, 128.9, 124.7, 121.5, 120.3, 19.0. Anal. Calcd for $C_{19}H_{15}ClN_8O$: C, 56.09; H, 3.72; N, 27.54. Found: C, 56.22; H, 3.82; N, 27.88.

Compound 4b: yield: 97%; crème solid; mp 208–210 °C. IR (nujol mull): 3430, 3351, 3291, 3224, 3108, 3066, 3048, 1666, 1647, 1581, 1556, 1506 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6–TFA): δ = 10.80 (s, 1 H, NH, D_2O exch.), 10.24 (s, 2 H, NH_2, D_2O exch.), 9.46 (s, 1 H, CH), 9.31 (s, 1 H, CH), 7.94 (d, *J* = 7.6 Hz, 2 H, Ar), 7.69 (t, *J* = 7.6 Hz, 2 H, Ar), 7.58 (t, *J* = 7.6 Hz, 1 H, Ar), 2.30 (t, *J* = 7.2 Hz, 2 H), 1.58–1.60 (m, 2 H), 1.28–1.30 (m, 8 H), 0.86 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 171.5, 158.7, 153.3, 152.3, 149.3, 139.6, 133.6, 131.9, 129.8, 128.9, 124.0, 33.3, 31.2, 28.6, 28.5, 24.3, 22.1, 13.9. Anal. Calcd for $C_{20}H_{25}N_7O$: C, 63.30; H, 6.64; N, 25.84. Found: C, 63.27; H, 6.56; N, 25.74.

Compound 4c: yield: 85%; yellow solid; mp 236–240 °C. IR (nujol mull): 3378, 3316, 3181, 3097, 1650, 1600, 1590, 1573, 1532, 1509 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6–TFA): δ = 9.63 (br s, 2 H, NH_2, D_2O exch.), 9.39 (s, 1 H, CH), 9.27 (s, 1 H, CH), 8.01 (d, *J* = 7.2 Hz, 2 H, Ar), 7.95 (d, *J* = 7.8 Hz, 2 H, Ar), 7.69 (t, *J* = 7.8 Hz, 2 H, Ar), 7.57 (m, 4 H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 165.3, 157.3, 153.1, 152.2, 148.7, 141.5, 132.5, 132.1, 131.7, 128.4, 128.8, 128.0, 124.0. Anal. Calcd for $C_{19}H_{15}N_7O$: C, 63.86; H, 4.23; N, 27.44. Found: C, 63.55; H, 4.45; N, 27.17.

Compound 4d: yield: 83%; orange solid; mp >300 °C. IR (nujol mull): δ = 3352, 3180, 1682, 1631, 1583, 1509 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6–TFA): δ = 9.77 (s, 2 H, NH_2, D_2O exch.), 9.43 (s, 1 H, CH), 9.28 (s, 1 H, CH), 9.24 (d, *J* = 1.2 Hz, 1 H, HetAr), 8.63 (dd, *J* = 1.2, 4.8 Hz, 1 H, HetAr), 8.46 (d, *J* = 8.0 Hz, 1 H, HetAr), 7.95 (d, *J* = 7.6 Hz, 2 H, Ar), 7.65–7.70 (m, 3 H, Ar + HetAr), 7.57 (t, *J* = 7.6 Hz, 1 H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 151.0, 163.8, 154.7, 153.1, 151.9, 148.0, 147.3, 145.1, 136.8, 133.7, 131.5, 129.7, 129.6, 128.8, 123.9, 123.8. Anal. Calcd for $C_{18}H_{14}N_8O$: C, 60.33; H, 3.94; N, 31.27. Found: C, 60.49; H, 4.11; N, 30.98.

Compound 4e: yield: 99%; off-white solid; mp 209–211 °C. IR (nujol mull): δ = 3420, 3345, 3283, 3225, 1668, 1646, 1603, 1575, 1553, 1518 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6–TFA): δ = 10.81 (s, 1 H, NH, D_2O exch.), 10.22 (s, 2 H, NH_2, D_2O exch.), 9.45 (s, 1 H, CH), 9.31 (s, 1 H, CH), 8.00 (d, *J* = 8.0 Hz, 2 H, Ar), 7.74 (d, *J* = 8.0 Hz, 2 H, Ar), 2.31 (t, *J* = 7.8 Hz, 2 H), 1.57–1.61 (m, 2 H), 1.24–1.30 (m, 8 H), 0.83–0.88 (m, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 171.7, 158.4, 153.3, 152.3, 149.1, 139.6, 133.3, 132.5, 131.9, 129.8, 125.6, 33.3, 31.2, 28.6, 28.5, 24.3, 22.1, 13.9. Anal. Calcd for $C_{20}H_{24}ClN_7O$: C, 58.04; H, 5.84; N, 23.69. Found: C, 57.95; H, 5.93; N, 23.44.

Compound 4f: yield: 98%; orange solid; mp >300 °C. IR (nujol mull): 3405, 3355, 3298, 3258, 3241, 3210, 3040, 1686, 1671, 1650, 1620, 1590, 1573, 1547, 1509 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.27 (s, 2 H, NH_2, D_2O exch.), 9.48 (s, 1 H, CH), 9.34 (s, 1 H, CH), 8.41 (d, *J* = 8.9 Hz, 2 H, Ar), 8.25 (d, *J* = 8.9 Hz, 2 H, Ar), 8.02 (d, *J* = 8.7 Hz, 2 H, Ar), 7.79 (d, *J* = 8.7 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 157.2, 154.2, 153.3, 152.4, 149.6, 149.2, 139.7, 137.9, 133.3, 132.6, 131.8, 129.8, 129.6, 125.7, 123.6. Anal. Calcd for $C_{19}H_{13}ClN_8O_3$: C, 52.24; H, 3.00; N, 25.65. Found: C, 52.38; H, 3.28; N, 25.80.

Compound 4g: yield: 94%; orange solid; mp >300 °C. IR (nujol mull): 3430, 1680, 1653, 1580 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6–TFA): δ = 9.77 (s, 2 H, NH_2, D_2O exch.), 9.47 (s, 1 H, CH), 9.34 (s, 1 H, CH), 9.24 (d, *J* = 1.5 Hz, 1 H, HetAr), 8.86 (dd, *J* = 1.5, 5.4 Hz, 1 H, HetAr), 8.63 (d, *J* = 8.1 Hz, 1 H, HetAr), 8.02 (d, *J* = 6.9 Hz, 2 H, Ar), 7.73–7.80 (m, 3 H, Ar + HetAr). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 163.7, 156.9, 153.3, 152.4, 150.8, 149.2, 147.5, 139.6, 137.7, 133.3, 132.6, 131.8, 129.8, 129.2, 125.7, 124.4. HRMS (ESI): *m*/*z* [M$^+$ + 1] calcd for $C_{18}H_{14}ClN_8O$: 393.80976; found: 393.80975.

Compound 4h: yield: 99%; white solid; mp 234–236 °C. IR (nujol mull): 3425, 3350, 3288, 3224, 3110, 3048, 1667, 1646, 1602, 1579, 1553, 1506 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.81 (s, 1 H, NH, D_2O exch.), 10.20 (s, 2 H, NH_2, D_2O exch.), 9.46 (s, 1 H, CH), 9.32 (s, 1 H, CH), 8.12 (d, *J* = 2.1 Hz, 1 H, Ar), 7.87 (dd, *J* = 2.1, 8.4 Hz, 1 H, Ar), 7.67 (d, *J* = 8.4 Hz, 1 H, Ar), 2.25 (m, 5 H), 1.50–1.61 (m, 2 H), 1.24–1.29 (m, 8 H), 0.82–0.87 (m, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 171.7, 158.3, 153.3, 152.4, 149.1, 139.7, 136.3, 133.9, 132.6, 132.1, 131.8, 123.9, 122.4, 33.4, 31.2, 28.6, 28.5, 24.3, 22.1, 19.3, 13.9. Anal. Calcd for $C_{21}H_{26}ClN_7O$: C, 58.94; H, 6.12; N, 22.91. Found: C, 59.00; H, 5.98; N, 22.72.

Compound 4i: yield: 83%; orange solid; mp >300 °C. IR (nujol mull): 3389, 3188, 1672, 1657, 1649, 1580, 1521, 1509 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6–TFA): δ = 9.59 (s, 2 H, NH_2, D_2O exch.), 9.38 (s, 1 H, CH), 9.28 (s, 1 H, CH), 8.35 (d, *J* = 8.4 Hz, 2 H, Ar), 8.28 (d, *J* = 8.4 Hz, 2 H, Ar), 8.11 (d, *J* = 2.0 Hz, 1 H, Ar), 7.87 (dd, *J* = 2.0, 8.4 Hz, 1 H, Ar), 7.65 (d, *J* = 8.4 Hz, 1 H, Ar), 2.45 (s, 3 H, Me). ^{13}C

NMR (75 MHz, DMSO-d_6–TFA): δ = 163.2, 156.3, 152.0, 149.4, 149.1, 140.3, 138.1, 136.0, 133.7, 132.4, 131.8, 131.3, 128.7, 124.5, 123.1, 122.1, 18.9. HRMS (ESI): *m*/*z* [M^+ + 1] calcd for $C_{20}H_{16}ClN_8O_3$: 451.84584; found: 451.84583.

Compound 4j: yield: 79%; orange solid; mp >300 °C. IR (nujol mull): 3438, 3358, 3199, 3041, 1683, 1652, 1604, 1584, 1540, 1510 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6–TFA): δ = 10.07 (s, 2 H, NH_2, D_2O exch.), 9.34 (s, 1 H, CH), 9.47 (s, 1 H, CH), 9.23 (d, *J* = 1.5 Hz, 1 H, HetAr), 8.85 (dd, *J* = 1.5, 4.8 Hz, 1 H, HetAr), 8.48 (d, *J* = 7.8 Hz, 1 H, HetAr), 8.13 (d, *J* = 2.1 Hz, 1 H, Ar), 7.89 (dd, *J* = 2.1, 2.4 Hz, 1 H, Ar), 7.66–7.73 (m, 2 H, Ar + HetAr), 2.49 (s, 3 H, Me). ^{13}C NMR (75 MHz, DMSO-d_6–TFA): δ = 163.8, 156.1, 153.2, 152.4, 151.0, 147.8, 139.9, 137.2, 136.3, 133.9, 132.6, 132.1, 131.6, 129.4, 124.2, 124.0, 122.4, 19.3. Anal. Calcd for $C_{19}H_{15}ClN_8O$: C, 56.09; H, 3.72; N, 27.54. Found: C, 56.31; H, 4.00; N, 27.72.

