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# Solid-phase synthesis of tetrasubstituted pyrrolo[2,3-d]pyrimidines<sup>†</sup>

Ji Hoon Lee<sup>*a*</sup> and Hyun-Suk Lim\*<sup>*a,b*</sup>

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A facile solid phase synthesis of 2,4,6,7-tetrasubstituted pyrrolo[2,3-d] pyrimidines is described. The synthesis involves a highly efficient five-step route starting from resin-bound dimeric peptoids. To demonstrate the versatility of our method, a representative library of 108 tetrasubstituted pyrrolo[2,3-d] pyrimidines of high quality was synthesized.

# Introduction

The pyrrolo[2,3-*d*]pyrimidine scaffold is considered a privileged structure<sup>1</sup> and is frequently found in numerous biologically active molecules, including protein kinase inhibitors,<sup>2–7</sup> E1 enzyme inhibitors,<sup>8</sup> insulin-like growth factor 1 receptor inhibitors,<sup>9</sup> antibiotics,<sup>10</sup> STAT6 inhibitors,<sup>11</sup> deazapurine nucleosides,<sup>12</sup> microtubule targeting agents,<sup>13</sup> and neurogenesis-inducing molecules.<sup>14</sup> Consequently, methods that allow for efficient preparation of diversely functionalized pyrrolo[2,3-*d*]-pyrimidines are of great interest in medicinal chemistry and chemical biology. However, in contrast to other structurally related privileged scaffolds,<sup>1</sup> such as pyrrolo[3,2-*d*]pyrimidines,<sup>15,16</sup> purines<sup>17</sup> and indoles,<sup>18</sup> solid-phase methodology for the preparation of pyrrolo[2,3-*d*]pyrimidines has yet to be explored.

We have recently developed a solid-phase synthetic route for 2,6,7-trisubstituted pyrrolo[2,3-*d*]pyrimidine derivatives **1**, which were designed as  $\alpha$ -helix mimetics (Fig. 1).<sup>19</sup> This scaffold has three points of diversification that could mimic the spatial orientation of three key residues (*i*, *i* + 3 or *i* + 4, and *i* + 7) on one face of an  $\alpha$ -helix involved in protein–protein interactions.<sup>20</sup> As a result, suitably functionalized pyrrolo[2,3-*d*]pyrimidine structures could serve as inhibitors of  $\alpha$ -helix-mediated protein–protein interactions. For solid-phase synthesis of the designed scaffold **1**, we utilized as a key intermediate dimeric peptoids **5** (Scheme 1), which can be easily synthesized by a standard submonomer route.<sup>21</sup> The resin-bound peptoids **5** were coupled with 4,6-dichloro-2-(methylthio)pyrimidine–carbalde-hyde **6** to furnish **7**. The formation of bicyclic pyrrolopyrimidine



**Fig. 1** Structures of 2,6,7-trisubstituted (1) and 2,4,6,7-tetrasubstituted (2) pyrrolo[2,3-*d*]pyrimidines.



**Scheme 1** Solid-phase synthesis of 2,6,7-trisubstituted pyrrolo[2,3-*d*] pyrimidines **1**.

ring **8** was achieved by intramolecular aldol reaction and concomitant dimethylamination at position 4. It is known that an activated chloride group on aromatic systems can be displaced with a dimethylamino group by DMF under thermal conditions.<sup>22</sup> Oxidation of the thioether **8** with *m*-chloroperbenzoic acid (*m*CPBA), followed by amine displacement reaction afforded the 2,6,7-trisubstituted pyrrolo[2,3-*d*]pyrimidines **1** in good yields. Using this method, we constructed a 900-member combinatorial library of the trisubstituted pyrrolo[2,3-*d*]pyrimidines **1**, in which a few members of the library were identified as MDM2/ MDMX inhibitors.<sup>19</sup> Despite the utility as  $\alpha$ -helix mimetics, the applicability of trisubstituted pyrrolo[2,3-*d*]pyrimidines **1** is limited; they have three diversification points on the same face. To expand the scope and versatility of the pyrrolo[2,3-*d*]pyrimidine scaffold, herein we report the efficient and convenient solid

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<sup>&</sup>lt;sup>a</sup>Department of Biochemistry and Molecular Biology, and Indiana University Simon Cancer Centre, Indiana University School of

Medicine, Indianapolis, Indiana 46202, USA

<sup>&</sup>lt;sup>b</sup>Department of Chemistry, Pohang University of Science and

Technology (POSTECH), Pohang 790-784, South Korea

*E-mail: hslim@postech.ac.kr; Fax: +82-54-279-3399; Tel: +82-54-279-2131* 

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Scheme 2 Synthesis of 4-substituted pyrrolo[2,3-*d*]pyrimidine intermediate 12.

phase synthesis of 2,4,6,7-tetrasubstituted pyrrolo[2,3-*d*]pyrimidines **2**.

### **Results and discussion**

Our initial synthetic strategy was to synthesize 4-chloropyrrolopyrimidine 10 as an intermediate via cyclization of 7, which can then be converted into 4-substituted pyrrolo[2,3-d]pyrimidines 12 by subsequent amination with  $R_4R_4$ 'NH (Scheme 2). In our previous work (Scheme 1), DMF acts both as a source of dimethylamino group and as a solvent, generating pyrrolopyrimidine ring 8 in one step from 7. Thus, we anticipated that the use of an alternative solvent instead of DMF would provide a cyclized product 10 without dimethylamination. Unexpectedly, however, this cyclization reaction did not proceed under various reaction conditions using different solvents such as DMSO, Nmethylpyrrolidone (NMP), and THF and bases such as 1,8-diazabicyclo[5.5.0]undec-7-ene (DBU), N,N-diisopropylethylamine (DIEA), Et<sub>3</sub>N, NaH, and NaOMe (Scheme 2). Given the fact that cyclization occurs only in the presence of DMF, it is likely that dimethylamine displacement of the chloride takes place first, and the resulting dimethylamino group on the heterocycle then facilitates the cyclization. Hence, we postulated that if an amine is employed in the reaction, the cyclization can be achieved along with the concurrent amination, thereby providing a desired product 12 in one-pot reaction.

To test this hypothesis, we carried out the cyclization reaction in the presence of various amines (R<sub>4</sub>R<sub>4</sub>'NH) to be introduced at position 4 (Table 1). Indeed, treatment of aldehyde intermediate 7a with methoxyethylamine and DBU (as a base) in NMP or NMP-MeOH led to the cyclized product 12. However, the reaction was incomplete, yielding a large amount of remaining starting material 7a (entries 1–2, Table 1). When using DIEA instead of DBU, the yield was dramatically increased (entry 3, Table 1). Encouraged by this result, we examined the reactivity with different amines. However, the reaction with other amines such as isobutylamine and dichlorophenethylamine gave a mixture of aldehydes 11 and imine intermediates 13, with no cyclized products 12 (entries 4-5, Table 1). Elevating the reaction temperature resulted in a somewhat increased ratio of imines 13 over aldehydes 11, but the intended products 12 were not observed (entries 6-7, Table 1). Since the amino portion (dimethylamino group) of DMF in our previous work (Scheme 1)<sup>19</sup> is a secondary amine, it is possible to reason that the cyclized products 12 are formed via a reactive iminium intermediate, but not through less active aldehydes 11 or imines 13 obtained from primary



R<sub>4</sub>' = H when using primary amines (R<sub>4</sub>NH<sub>2</sub>)

Entry	R <sub>4</sub> R <sub>4</sub> ′NH	Conditions <sup>a</sup>	Ratio of products $(\%)^b$			
			7a	12	11	13
1	H <sub>2</sub> N V	DBU/NMP/60 °C	28	72	0	0
2	H <sub>2</sub> N V	DBU/NMP-MeOH/ 60 °C	51	49	0	0
3	H <sub>2</sub> N V	DIEA/NMP/60 °C	0	98	2	0
4	H <sub>2</sub> N	DIEA/NMP/60 °C	0	0	71	29
5		DIEA/NMP/60 °C	0	0	77	23
6	H <sub>2</sub> N	DIEA/NMP/90 °C	0	0	49	51
7		DIEA/NMP/90 °C	0	0	45	55
8	HN	DIEA/NMP/90 °C	0	0	100	0
9	HNO	DIEA/NMP/90 °C	0	0	100	0
10	H <sub>2</sub> N	(i) DIEA/NMP/60 °C (ii) NaOMe/DME/rt	0	100	0	0
11	CI CI H <sub>2</sub> N	(i) DIEA/NMP/60 °C (ii) NaOMe/DMF/rt	0	100	0	0
12	HN	(i) DIEA/NMP/60 °C	0	100	0	0
13		(i) DIEA/NMP/60 °C (ii) NaOMe/DMF/rt	0	100	0	0
14	HN	(i) DIEA/NMP/60 °C (ii) DRU/DME/00 °C	0	100	0	0
15		(i) DIEA/NMP/60 °C (ii) DBU/DME/90 °C	0	100	0	0

<sup>a</sup> All reactions were carried out overnight. <sup>b</sup> Calculated from integrated peak areas recorded by HPLC analysis.

amines (entries 1-7, Table 1). To test this, we employed secondary amines. The reaction with dimethylamine and morpholine showed a similar result, giving aldehydes **11** with no trace of cyclized products **12** or iminium intermediates (entries 8-9, Table 1).

Given that both aldehydes 11 and imines 13 are the precursors of pyrrolo[2,3-*d*]pyrimidines 12, it was envisaged that the use of a stronger base would promote the intramolecular aldol reaction, thereby converting the precursors into the product 12. Indeed, treatment of the mixture of 11 and 13 with NaOMe afforded exclusively 12 without any detectable by-products (entries 10–13, Table 1). Although the desired products 12 were successfully prepared using NaOMe, it remains unclear why in our

 Table 2
 Purities of 4-substituted pyrrolo[2,3-d]pyrimidines 14a-h



previous work cyclization occurred without using a strong base. To investigate this, the precursors (11 and 13) substituted with different amines were subjected to the same reaction conditions (DBU/DMF/90 °C). Remarkably, the reaction with DMF in the presence of DBU furnished 12 in excellent yield (entries 14–15, Table 1). Consequently, in accordance with our hypothesis, synthesis of pyrrolopyrimidines 12 was accomplished by amination and subsequent cyclization with either NaOMe or DBU/DMF.

To further assess the efficiency of this method, we synthesized a series of compounds **14a–h** by employing various amine monomers (Table 2). The crude products released from resin were analysed by LC/MS (ESI,† Fig. S1). Notably, compared to the previous cyclization step (Scheme 1) that entails the production of ~5% of by-products,<sup>19</sup> the new method was remarkably efficient, furnishing the products **14a–h** in almost quantitative yields in all cases (Table 2). The crude compounds were purified by HPLC and further characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (Fig. S2†) and high resolution mass spectrometry (HRMS).

To illustrate the versatility of our synthetic method, we constructed a 108-member combinatorial library of fully tetrasubstituted pyrrolo[2,3-*d*]pyrimidines **15** (Fig. 2) following the method described above. We employed a variety of amines as building blocks (9  $R_4R_4$ 'NH and 12  $R_3R_3$ 'NH) (ESI,† Table S1). Synthesis of the 108 compounds was accomplished by a manual parallel synthesis on MBHA Rink amide resin. After synthesis, the cleaved crude compounds were characterized by LC/MS (Fig. 2). The average purity of the library molecules was 93%



**Fig. 2** Synthesis of 2,4,6,7-tetrasubstituted pyrrolo[2,3-*d*]pyrimidines **15** and representative HPLC traces for crude products **15**.

(ESI,† Table S2), clearly demonstrating the robustness of our solid-phase synthesis method. It is important to note that this method is significantly more efficient in terms of yield and purity, compared to our previous method which generates trisub-stituted pyrrolo[2,3-*d*]pyrimidines in 80% purity on average. Moreover, no detectable by-products were found in our new synthetic strategy, whereas several impurities were inevitably observed in our previous method.<sup>19</sup> Hence, libraries constructed by this method can be directly used for biological testing without further purification.

# Conclusion

In conclusion, we developed a highly efficient and convenient solid-phase synthetic pathway for the preparation of structurally diverse 2,4,6,7-tetrasubstituted pyrrolo[2,3-d]pyrimidine derivatives. This method not only generates the desired compounds in remarkably excellent yields, but also offers a greater diversification at four substitution positions. Importantly, our method uses inexpensive and readily available amines as building blocks, making it suitable for constructing a diversely functionalized pyrrolo[2,3-d]pyrimidine library. Further work involving synthesis of a large combinatorial library and biological testing is currently in progress.

#### Experimental

## General

Unless otherwise noted, all chemicals and reagents were purchased from commercial suppliers and used without further purification. Rink amide MBHA resin (0.75 mmol  $g^{-1}$ ) was purchased from Novabiochem. LC/MS characterization was performed using a C18 reversed phase HPLC column (2  $\mu$ m, 4.6 mm × 50 mm). A gradient elution of 90% A in 2 min followed by 100% B in 14 min was used at flow rate of 0.8 mL min<sup>-1</sup> (solvent A: 95% H<sub>2</sub>O, 5% MeOH, 0.01% TFA; B: MeOH, 0.01% TFA). Reverse-phase HPLC purification was performed with a C18 reversed-phase column (5  $\mu$ m, 21.2 mm × 125 mm) using a linear gradient from 10% B to 100% B by changing solvent composition over 40 minutes. Peptoid synthesis under microwave conditions was performed in a kitchen microwave oven with 10% power. Thermal reactions were carried out in a heating mantle filled with sea sand using 4 ml glass vials.

General procedure 1 for the synthesis of dimeric peptoids (5). Rink amide MBHA resin (100 mg, 75 µmol) was swollen with DMF (2 mL) in a 5 mL fritted syringe for 2 h. The Fmoc protecting group on the resin was removed by treating with 20% piperidine in DMF ( $2 \times 10$  min). Two peptoid residues were added by a standard submonomer route<sup>23</sup> using a microwaveassisted protocol.<sup>24</sup> Briefly, to the resin was added 1.5 mL of 2 M bromoacetic acid in DMF and 1.5 mL of 2 M diisopropylcarbodiimide (DIC) in DMF. The reaction mixture was subjected to microwave irradiation at 10% power ( $2 \times 15$  seconds). The beads were shaken manually for 10 seconds between microwave pulses for proper mixing. At the end of the reaction, the reaction mixture was drained, and the resins were washed with DMF (3  $\times$ 2 mL),  $CH_2Cl_2$  (2 × 2 mL), MeOH (2 × 2 mL), and DMF (3 × 2 mL). To the resin was added 2 mL of an amine (2M in DMF), and the same microwave reaction was carried out. This process was repeated to prepare dimeric peptoids.

General procedure 2 for the synthesis of 4,6,7-trisubstituted 2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidines (14). The peptoidloaded resin (5) was treated with 4,6-dichloro-2-methylthio-5formylaldehyde (6) (5 equiv.) and DIEA (5 equiv.) in THF at room temperature overnight. The reaction mixture was drained and washed with DMF (3  $\times$  2 mL), CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  2 mL), MeOH  $(2 \times 2 \text{ mL})$ , and DMF  $(3 \times 2 \text{ mL})$ . To a suspension of the resinbound aldehyde (7) in DIEA (20 equiv.) and NMP (1 mL) was added an amine (20 equiv.). The mixture was shaken at 60 °C overnight. After thorough washing, to the resin was added a solution of NaOMe (25 wt% in MeOH, 20 equiv.) in DMF (1 mL). The mixture was agitated at room temperature overnight. The resin was filtered and thoroughly washed with DMF ( $3 \times 2$  mL), CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  2 mL), MeOH (2  $\times$  2 mL), and DMF (3  $\times$  2 mL). After cleavage from the resin with a cleavage cocktail (95% TFA, 2.5% TIPS, and 2.5% water) for 2 h at room temperature, the crude products (14) were analysed by LC/MS. For further characterization, the products were purified by HPLC.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(isobutylamino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (14a). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.68 (d, *J* = 6.0 Hz, 6H), 1.73 (m, 1H), 2.53 (s, 3H), 2.80 (br s, 2H), 3.28 (s, 3H), 3.57 (br s, 2H), 4.18 (s, 2H), 4.68(br s, 2H), 4.75 (s, 2H), 5,84 (s, 1H), 6.46 (s, 1H), 6.80 (s, 1H), 7.17–7.40 (m, 5H), 10.97 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  13.4, 19.9, 27.9, 42.5, 49.5, 51.5, 53.4, 59.2, 71.7, 96.4, 100.0, 104.3, 125.6, 128.3, 129.5, 135.8, 149.9, 152.6, 159.3, 164.4, 170.8. HRMS (ESI) calculated for  $C_{24}H_{33}N_6O_3S [M + H]^+$  485.2335, found: 485.2339.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(cyclopentylamino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide<sup>-</sup>TFA (14b). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.36–1.68 (m, 8H), 2.59 (s, 3H), 3.35 (s, 3H), 3.58 (m, 1H), 3.63 (br s, 2H), 4.27 (s, 2H), 4.76 (br s, 2H), 4.83 (s, 2H), 5.88 (s, 1H), 6.54 (s, 1H), 6.87 (s, 1H), 7.24–7.47 (m, 5H), 10.78 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  13.4, 23.7, 32.8, 42.5, 49.7, 53.4, 55.6, 59.2, 71.8, 96.3, 100.0, 104.8, 125.5, 127.9, 129.4, 136.1, 149.8, 151.9, 159.4, 164.5, 170.8. HRMS (ESI) calculated for C<sub>25</sub>H<sub>33</sub>N<sub>6</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 497.2335, found: 497.2338.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((2,4-dichlorophenethyl)amino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (14c). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.60 (s, 3H), 2.94 (br s, 2H), 3.33 (m, 5H), 3.63 (br s, 2H), 4.23 (s, 2H), 4.74 (br s, 2H), 4.82 (s, 2H), 6.53 (s, 1H), 6.60 (s, 1H), 7.05 (s, 1H), 7.14–7.34 (m, 8H), 10.88 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  13.5, 31.9, 42.6, 43.4, 49.4, 53.5, 59.2, 71.7, 96.5, 100.0, 104.2, 125.6, 127.5, 128.1, 129.3, 129.5, 132.1, 133.4, 133.7, 134.5, 135.4, 149.9, 152.4, 159.3, 164.3, 172.2. HRMS (ESI) calculated for C<sub>28</sub>H<sub>31</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 601.1555, found: 601.1557.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(dimethylamino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6carboxamide·TFA (14d). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.56 (s, 3H), 3.07 (s, 6H), 3.28 (s, 3H), 3.60 (br s, 2H), 4.25 (s, 2H), 4.72 (br s, 2H), 4.81 (s, 2H), 6.00 (s, 1H), 6.47 (s, 1H), 7.11 (s, 1H), 7.25–7.42 (m, 5H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 14.2, 39.7, 42.7, 49.7, 53.5, 59.1, 71.9, 98.7, 100.0, 104.8, 125.8, 127.9, 129.3, 136.4, 149.1, 155.5, 163.2, 165.1, 172.0. HRMS (ESI) calculated for  $C_{22}H_{29}N_6O_3S$  [M + H]<sup>+</sup> 457.2022, found: 457.2019.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((3,4-dimethoxybenzyl)amino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (14e). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.78 (br s, 6H), 2.00 (m, 1H), 2.54 (s, 3H), 3.69 (s, 3H), 3.76 (s, 3H), 4.00 (s, 2H), 4.19 (d, *J* = 6.5 Hz, 2H), 4.38 (s, 2H), 4.66 (s, 2H), 5.83 (s, 1H), 5.97 (s, 1H), 6.33 (s, 1H), 6.49 (s, 1H), 6.59 (s, 1H), 6.69 (s, 1H), 7.11–7.36 (m, 5H), 11.42 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  13.5, 20.0, 29.8, 46.7, 48.3, 50.5, 54.3, 55.9, 56.0, 96.0, 100.0, 105.6, 109.9, 111.0, 118.6, 126.5, 128.3, 129.2, 135.6, 148.6, 149.4, 150.5, 153.0, 158.7, 163.8, 170.5, 172.9. HRMS (ESI) calculated for C<sub>30</sub>H<sub>37</sub>N<sub>6</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 577.2597, found: 577.2599.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((2,2-diphenylethyl)amino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (14f). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.87 (d, *J* = 6.5 Hz, 6H), 2.10 (m, 1H), 2.58 (s, 3H), 3.88 (br s, 2H), 4.10 (s, 2H), 4.28 (d, *J* = 7.5 Hz, 2H), 4.33 (br s, 1H), 4.80 (s, 2H), 6.05–6.13 (m, 2H), 6.70 (s, 1H), 7.05–7.30 (m, 15H), 10.70 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  12.3, 18.1, 27.8, 28.0, 46.7, 48.0, 48.6, 52.4, 94.3, 98.1, 102.6, 124.2, 125.3, 126.0, 126.5, 126.9, 127.4, 133.6, 138.7, 150.4, 156.7, 162.2, 168.8. HRMS (ESI) calculated for C<sub>35</sub>H<sub>39</sub>N<sub>6</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 607.2855, found: 607.2863. *N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((4-hydroxyphenethyl)amino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (14g). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.85 (br s, 6H), 2.09 (m, 1H), 2.58 (s, 3H), 2.74 (br s, 2H), 3.34 (br s, 1H), 3.59 (br s, 1H), 4.12 (s, 2H), 4.25 (d, *J* = 6.5 Hz, 2H), 4.79 (s, 2H), 5.99 (s, 1H), 6.34 (s, 1H), 6.69–6.86 (s, 4H), 7.16 (s, 1H), 7.20–7.30 (m, 5H), 10.55 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  8.54, 14.2, 20.0, 29.7, 29.9, 34.6, 45.8, 49.7, 98.9, 100.0, 101.4, 115.7, 125.5, 128.0, 129.0, 129.8, 136.0, 152.6, 155.3, 156.4, 165.3, 166.1, 170.9. HRMS (ESI) calculated for C<sub>29</sub>H<sub>35</sub>N<sub>6</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 547.2491, found: 547.2480.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((4-sulfamoylphenethyl)amino)-7-(2-methoxyethyl)-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (14h). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.79 (br s, 6H), 2.03 (m, 1H), 2.54 (s, 3H), 2.82 (br s, 2H), 3.40 (br s, 2H), 4.10 (s, 2H), 4.18 (d, *J* = 7.0 Hz, 2H), 4.75 (s, 2H), 5.11 (br s, 2H), 6.13 (s, 1H), 6.26 (s, 1H), 6.39 (s, 1H), 7.15–7.33 (m, 7H), 7.70 (d, *J* = 7.0 Hz, 2H), 10.56 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  9.2, 14.2, 20.0, 29.7, 30.0, 35.2, 45.8, 49.7, 99.0, 100.0, 101.5, 125.5, 126.3, 128.0, 128.9, 129.6, 136.0, 140.4, 144.5, 152.3, 156.2, 165.2, 166.2, 171.3. HRMS (ESI) calculated for C<sub>29</sub>H<sub>36</sub>N<sub>7</sub>O<sub>4</sub>S<sub>2</sub> [M + H]<sup>+</sup> 610.2270, found: 610.2279.

General procedure 3 for the synthesis of 2,4,6,7-tetrasubstituted 7*H*-pyrrolo[2,3-*d*]pyrimidines (15). The resin-bound 4,6,7trisubstituted 2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidines (12) were treated with *m*-CPBA (10 equiv.) and NaHCO<sub>3</sub> (15 equiv.) in THF (2 mL)/H<sub>2</sub>O (400  $\mu$ L) at room temperature for 2 h. After washing, to the resin was added a solution of an amine (20 equiv.) and DIEA (100 equiv.) in NMP, and the mixture was shaken at 170 °C overnight. The resin was filtered and washed with DMF (3 × 2 mL), CH<sub>2</sub>Cl<sub>2</sub> (2 × 2 mL), MeOH (2 × 2 mL), and CH<sub>2</sub>Cl<sub>2</sub> (3 × 2 mL). After cleavage from the resin followed by evaporation, the products (15) were analysed by LC/MS. For further characterization, the products were purified by HPLC.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(ethylamino)-7-(2-methoxyethyl)-2-((2-methoxyethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-1A). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 0.87 (br s, 3H), 2.95 (s, 2H), 3.25 (s, 3H), 3.30 (s, 3H), 3.44–3.54 (m, 6H), 4.17 (s, 2H), 4.54 (s, 2H), 4.74 (s, 2H), 5.75 (s, 1H), 6.30 (s, 1H), 6.39 (s, 1H), 6.83 (s, 1H), 7.24–7.44 (m, 5H), 9.27 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 13.9, 38.4, 40.8, 42.0, 49.9, 53.7, 59.1, 70.3, 71.9, 92.4, 104.5, 125.6, 127.9, 129.3, 136.3, 151.5, 151.8, 153.1, 164.8, 171.2. HRMS (ESI) calculated for  $C_{24}H_{34}N_7O_4$  [M + H]<sup>+</sup> 484.2672, found: 484.2674.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-2-(benzylamino)-7-(2-methoxyethyl)-4-((2-methoxyethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide·TFA (15-2B). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ 3.18–3.27 (m, 10H), 3.46 (s, 2H), 4.22 (s, 2H), 4.57 (s, 2H), 4.60 (s, 2H), 4.79 (s, 2H), 5.81 (s, 1H), 6.29 (s, 1H), 6.79 (s, 1H), 7.98 (s, 1H), 7.11–7.34 (m, 10H), 9.06 (s, 1H). <sup>3</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  35.6, 42.3, 43.7, 45.0, 49.8, 53.8, 59.2, 69.9, 71.9, 92.9, 104.8, 126.0, 127.6, 128.1, 128.6, 129.4, 136.5, 138.4, 151.5, 152.5, 153.2, 164.9, 171.6. HRMS (ESI) calculated for  $C_{29}H_{36}N_7O_4$  [M + H]<sup>+</sup> 546.2829, found: 546.2830.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-2-((cyclohexylmethyl)amino)-4-(isobutylamino)-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-3C). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 0.79 (s, 6H), 0.99 (m, 2H), 1.23 (m, 4H), 1.57 (m, 1H), 1.65 (m, 1H), 1.73 (m, 4H), 2.79 (s, 2H), 3.25 (t, *J* = 6.5 Hz, 2H), 3.30 (s, 3H), 3.58 (t, *J* = 4.5 Hz, 2H), 4.21 (s, 2H), 4.60 (t, *J* = 4.0 Hz, 2H), 4.80 (s, 2H), 6.36–6.44 (m, 3H), 7.06 (s, 1H), 7.25–7.47 (m, 5H), 9.05 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 19.8, 25.8, 26.4, 28.4, 30.8, 37.9, 42.0, 47.3, 49.4, 51.3, 53.7, 59.2, 71.9, 92.3, 104.2, 125.6, 127.4, 128.1, 129.4, 135.9, 151.6, 151.8, 153.4, 164.9, 172.4. HRMS (ESI) calculated for C<sub>30</sub>H<sub>44</sub>N<sub>7</sub>O<sub>3</sub> [M + H]<sup>+</sup> 550.3505, found: 550.3508.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(cyclopentylamino)-2-((2,4dichlorophenethyl)amino)-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-4D). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 1.34 (m, 2H), 1.43 (m, 4H), 1.63 (m, 2H), 3.01 (t, *J* = 6.5 Hz, 2H), 3.31 (s, 3H), 3.52 (m, 3H), 3.65 (d, *J* = 6.5 Hz, 2H), 4.24 (s, 2H), 4.60 (br s, 2H), 4.80 (s, 2H), 6.38 (s, 1H), 6.45 (m, 2H), 7.16 (s, 1H), 7.19–7.43 (m, 8H), 8.95 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 23.7, 29.7, 33.0, 33.1, 40.6, 42.0, 49.7, 53.5, 55.2, 59.2, 72.1, 92.4, 104.6, 125.5, 127.4, 127.9, 129.4, 132.0, 133.2, 134.7, 134.8, 136.2, 151.1, 151.4, 153.0, 164.9, 172.0. HRMS (ESI) calculated for  $C_{32}H_{38}Cl_2N_7O_3$ [M + H]<sup>+</sup> 638.2413, found: 638.2400.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((3,4-dimethoxybenzyl)amino)-2-((2,2-diphenylethyl)amino)-7-(2-methoxyethyl)-7*H*pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-5E). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 3.30 (s, 3H), 3.66 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 4.03 (s, 3H), 4.14 (s, 2H), 4.20 (m, 2H), 4.33 (s, 1H), 4.60 (s, 2H), 4.73 (s, 2H), 6.26 (br s, 1H), 6.38 (s, 1H), 6.45 (s, 1H), 6.55 (s, 1H), 6.65 (s, 1H), 6.76 (br s, 1H), 6.95 (s, 1H), 7.19–7.49 (m, 15H), 9.54 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 42.4, 45.9, 47.1, 49.5, 50.5, 53.8, 56.1, 59.4, 72.0, 92.8, 104.7, 110.2, 111.3, 119.0, 126.3, 127.1, 128.0, 129.5, 136.1, 141.7, 149.0, 149.7, 151.5, 152.3, 153.5, 164.8, 172.1. HRMS (ESI) calculated for  $C_{42}H_{46}N_7O_5$  [M + H]<sup>+</sup> 728.3560, found: 728.3555.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-((2,4-dichlorophenethyl)amino)-2-((4-hydroxyphenethyl)amino)-7-(2-methoxyethyl)-7*H*pyrrolo[2,3-*d*]pyrimidine-6-carboxamide<sup>-</sup>TFA (15-6F). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.80 (t, *J* = 7.5 Hz, 2H), 2.85 (br s, 2H), 3.28 (m, 5H), 3.55 (m, 4H), 4.18 (s, 2H), 4.57 (s, 2H), 4.77 (s, 2H), 6.31 (s, 1H), 6.37 (s, 1H) 6.42 (s, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 7.06 (m, 3H), 7.15 (s, 1H), 7.19–7.35 (m, 7H), 9.12 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  32.2, 34.5, 42.1, 43.1, 49.3, 53.6, 59.3, 71.9, 92.6, 115.5, 125.6, 127.5, 128.0, 129.3, 129.6, 129.9, 130.5, 132.1, 133.4, 133.7, 134.5, 135.8, 151.2, 151.7, 153.3, 154.6, 164.8, 171.9. HRMS (ESI) calculated for C<sub>35</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>7</sub>O<sub>4</sub> [M + H]<sup>+</sup> 690.2362, found: 690.2345.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-2-(isobutylamino)-7-(2-methoxyethyl)-4-((naphthalen-2-ylmethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-7G). <sup>1</sup>H-NMR (500 MHz, methanol-d<sub>4</sub>)  $\delta$  0.81 (br s, 6H), 1.81 (m, 1H), 3.27 (m, 5H), 3.71 (br s, 2H), 4.08 (s, 2H), 4.46 (s, 2H), 4.74 (s, 2H), 5.22 (s, 2H), 6.96 (s, 1H), 7.29–7.54 (m, 9H), 7.86–8.09 (m, 3H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  20.3, 28.6, 29.9, 42.3, 45.2, 48.8, 53.7, 59.3, 71.8, 92.5, 100.7, 104.2, 122.3, 125.5, 126.1, 126.4, 127.3, 128.2, 129.3, 130.3, 134.0, 135.3, 136.4, 151.9, 153.0, 153.5, 164.6, 172.0. HRMS (ESI) calculated for C<sub>34</sub>H<sub>40</sub>N<sub>7</sub>O<sub>3</sub> [M + H]<sup>+</sup> 594.3192, found: 594.3189.

*N*-(2-amino-2-oxoethyl)-*N*-benzyl-4-((2,2-diphenylethyl)amino)-7-(2-methoxyethyl)-2-(piperidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-12H). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.62 (s, 6H), 3.33 (s, 3H), 3.58 (s, 2H), 3.64 (s, 4H), 3.73 (s, 2H), 4.18 (s, 2H), 4.31, (s, 1H), 4.56 (t, *J* = 4.5 Hz, 2H), 4.77 (s, 2H), 5.63 (s, 1H), 6.46 (s, 1H), 6.88 (s, 1H), 7.07–7.30 (m, 15H), 9.72 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  24.1, 25.3, 41.9, 46.8, 48.4, 49.4, 49.7, 53.5, 59.2, 71.7, 92.1, 103.4, 125.5, 127.1, 128.0, 128.4, 128.8, 129.2, 135.7, 140.7, 150.5, 152.2, 153.0, 164.8, 170.7. HRMS (ESI) calculated for C<sub>40</sub>H<sub>46</sub>N<sub>7</sub>O<sub>3</sub> [M + H]<sup>+</sup> 646.3506, found: 646.3508.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-7-(2-methoxyethyl)-2-((naphthalen-1-ylmethyl)amino)-4-((3-(2-oxopyrrolidin-1-yl)propyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide<sup>-</sup>TFA (15-9I). <sup>1</sup>H-NMR (500 MHz, methanol-d<sub>4</sub>)  $\delta$  1.86 (m, 4H), 2.23 (m, 2H), 2.99–3.27 (m, 6H), 3.40 (s, 3H), 3.71 (s, 2H), 4.04 (s, 2H), 4.41 (s, 2H), 4.71 (br s, 2H), 5.12 (s, 2H), 6.86 (s, 1H), 7.29–7.54 (m, 9H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  14.3, 17.7, 22.8, 29.8, 30.9, 40.3, 42.3, 42.9, 47.8, 55.3, 58.9, 71.0, 92.8, 100.0, 106.3, 123.3, 125.3, 125.4, 125.9, 126.6, 128.5, 129.0, 130.1, 131.4, 133.9, 151.1, 151.9, 153.1, 164.7, 172.1, 176.9. HRMS (ESI) calculated for C<sub>37</sub>H<sub>43</sub>N<sub>8</sub>O<sub>4</sub> [M + H]<sup>+</sup> 663.3407, found: 663.3399.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(ethylamino)-7-(2-methoxyethyl)-2-((4-sulfamoylphenethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide<sup>•</sup>TFA (15-10A). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.96 (m, 3H), 2.98 (t, *J* = 6.5 Hz, 2H), 3.04 (s, 2H), 3.32 (s, 3H), 3.54 (s, 2H), 3.70 (m, 2H), 4.25 (s, 2H), 4.52 (s, 2H), 4.81 (s, 2H), 5.00 (br s, NH<sub>2</sub>), 6.09 (s, 1H), 6.36 (s, 1H), 6.70 (s, 1H), 6.92 (s, 1H), 7.24–7.47 (m, 7H), 7.81 (d, *J* = 8.5 Hz, 2H), 8.87 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  13.8, 29.6, 35.7, 38.3, 41.9, 49.7, 53.4, 59.1, 71.1. 92.4, 104.5, 125.5, 126.5, 127.8, 129.2, 129.5, 136.2, 140.3, 144.2, 151.2, 151.5, 153.0, 163.1, 170.9. HRMS (ESI) calculated for C<sub>29</sub>H<sub>37</sub>N<sub>8</sub>O<sub>5</sub>S [M + H]<sup>+</sup> 609.2607, found: 609.2602.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-7-(2-methoxyethyl)-4-((2-methoxyethyl)amino)-2-morpholino-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide TFA (15-11B). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 3.25 (m, 5H), 3.35 (m, 5H), 3.61 (s, 2H), 3.77–3.81 (m, 8H), 4.26 (s, 2H), 4.63 (s, 2H), 4.83 (s, 2H), 5.87 (s, 1H), 6.50 (s, 1H), 6.89 (s, 1H), 7.26–7.46 (m, 5H), 9.89 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>) δ 29.7, 42.0, 43.8, 45.8, 49.7, 53.5, 58.9, 59.1, 66.2, 29.6, 71.7, 92.8, 104.8, 125.8, 127.9, 128.9, 129.3, 136.3, 150.9, 152.4, 152.6, 164.7, 171.0. HRMS (ESI) calculated for C<sub>26</sub>H<sub>36</sub>N<sub>7</sub>O<sub>5</sub> [M + H]<sup>+</sup> 526.2778, found: 526.2776.

*N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(isobutylamino)-7-(2-methoxyethyl)-2-((3-(2-oxopyrrolidin-1-yl)propyl)amino)-7*H*-pyrrolo-[2,3-*d*]pyrimidine-6-carboxamide<sup>-</sup>TFA (15-8C). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.76 (s, 6H), 1.76 (s, 1H), 1.86 (m, 2H), 2.05 (m, 2H), 2.41 (m, 2H), 2.82 (s, 2H), 3.33 (s, 3H), 3.37 (t, *J* = 7.0 Hz, 2H), 3.43 (m, 4H), 3.59 (s, 2H), 4.22 (s, 2H), 4.62 (s, 2H), 4.82 (s, 2H), 5.69 (s, 1H), 6.40 (s, 1H), 6.76 (2, 1H), 6.91 (s, 1H), 7.25–7.44 (m, 5H), 9.00 (s, 1H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  17.9, 19.8, 26.9, 28.0, 30.9, 38.8, 40.4, 42.0, 47.3, 49.6, 51.1, 53.4, 59.1, 71.9, 92.4, 104.0, 125.6, 128.0, 129.4, 136.1, 151.3, 153.5, 164.7, 170.8, 175.5. HRMS (ESI) calculated for C<sub>30</sub>H<sub>43</sub>N<sub>8</sub>O<sub>4</sub> [M + H]<sup>+</sup> 579.3407, found: 579.3401.

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