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PAPER

Solid-phase synthesis of tetrasubstituted pyrrolo[2,3-*d*]pyrimidines†

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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[1] and is frequently found in numerous biologically active molecules, including protein kinase inhibitors,[2–7] E1 enzyme inhibitors,[8] insulin-like growth factor 1 receptor inhibitors,[9] antibiotics,[10] STAT6 inhibitors,[11] deazapurine nucleosides,[12] microtubule targeting agents,[13] and neurogenesis-inducing molecules.[14] 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,[1] such as pyrrolo[3,2-*d*]pyrimidines,[15,16] purines[17] and indoles,[18] 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 α-helix mimetics (Fig. 1).[19] 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 α-helix involved in protein–protein interactions.[20] As a result, suitably functionalized pyrrolo[2,3-*d*]pyrimidine structures could serve as inhibitors of α-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.[21] The resin-bound peptoids **5** were coupled with 4,6-dichloro-2-(methylthio)pyrimidine–carbaldehyde **6** to furnish **7**. The formation of bicyclic pyrrolopyrimidine

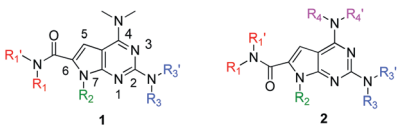
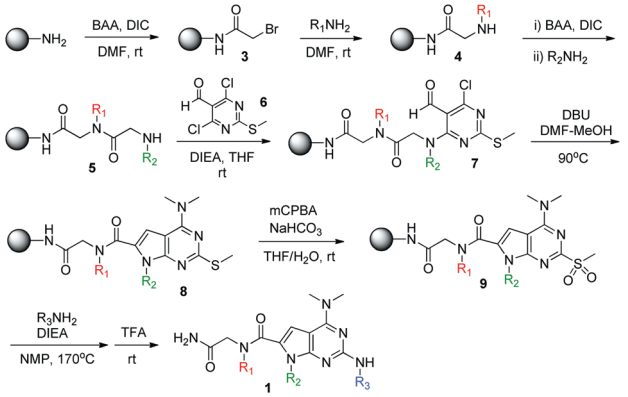


Fig. 1 Structures of 2,6,7-trisubstituted (**1**) and 2,4,6,7-tetrasubstituted (**2**) pyrrolo[2,3-*d*]pyrimidines.



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.[22] 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.[19] Despite the utility as α-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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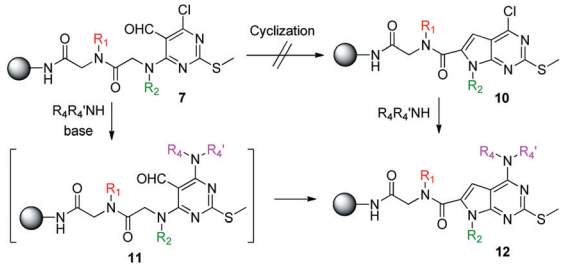
† Electronic supplementary information (ESI) available: Characterization data of compounds **14** and **15**. See DOI: 10.1039/c2ob06899k



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

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

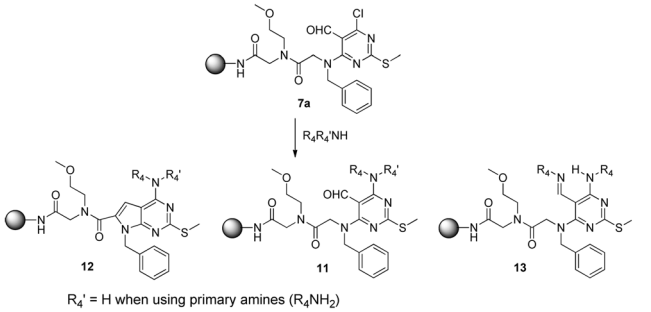
Results and discussion

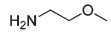
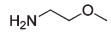
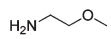
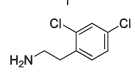
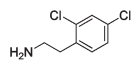
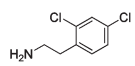
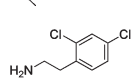
Our initial synthetic strategy was to synthesize 4-chloropyrrolopyrimidine **10** as an intermediate *via* cyclization of **7**, which can then be converted into 4-substituted pyrrolo[2,3-*d*]pyrimidines **12** by subsequent amination with $R_4R_4'NH$ (Scheme 2). In our previous work (Scheme 1), DMF 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, *N*-methylpyrrolidone (NMP), and THF and bases such as 1,8-diazabicyclo[5.5.0]undec-7-ene (DBU), *N*,*N*-diisopropylethylamine (DIEA), Et_3N, 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 ($R_4R_4'NH$) 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)[19] 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 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 1 Results of cyclization



Entry	$R_4R_4'NH$	Conditions[a]	Ratio of products (%)[b] 7a	12	11	13
1		DBU/NMP/60 °C	28	72	0	0
2		DBU/NMP-MeOH/ 60 °C	51	49	0	0
3		DIEA/NMP/60 °C	0	98	2	0
4		DIEA/NMP/60 °C	0	0	71	29
5		DIEA/NMP/60 °C	0	0	77	23
6		DIEA/NMP/90 °C	0	0	49	51
7		DIEA/NMP/90 °C	0	0	45	55
8		DIEA/NMP/90 °C	0	0	100	0
9		DIEA/NMP/90 °C	0	0	100	0
10		(i) DIEA/NMP/60 °C (ii) NaOMe/DMF/rt	0	100	0	0
11		(i) DIEA/NMP/60 °C (ii) NaOMe/DMF/rt	0	100	0	0
12		(i) DIEA/NMP/60 °C (ii) NaOMe/DMF/rt	0	100	0	0
13		(i) DIEA/NMP/60 °C (ii) NaOMe/DMF/rt	0	100	0	0
14		(i) DIEA/NMP/60 °C (ii) DBU/DMF/90 °C	0	100	0	0
15		(i) DIEA/NMP/60 °C (ii) DBU/DMF/90 °C	0	100	0	0

[a] All reactions were carried out overnight. [b] Calculated from integrated peak areas recorded by HPLC analysis.

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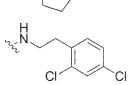
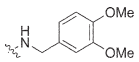
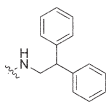
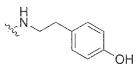
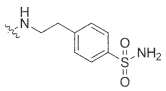
Table 2 Purities of 4-substituted pyrrolo[2,3-*d*]pyrimidines **14a–h**

Compd	R_2	$-NR_4R_4'$	Purity (%)[a]
14a			99
14b			99
14c			97
14d			98
14e			96
14f			98
14g			98
14h			98

[a] Purity of crude products assessed by HPLC.

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,[19] 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 ^1H and ^{13}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%

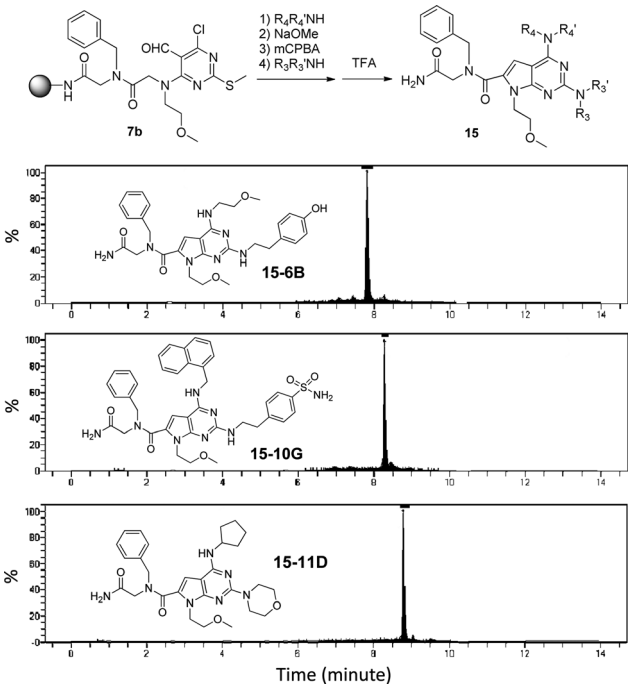


Fig. 2 Synthesis of 2,4,6,7-tetrasubstituted pyrrolo[2,3-*d*]pyrimidines **15** and representative HPLC traces for crude products **15**.

(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 trisubstituted 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.[19] 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

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purchased from Novabiochem. LC/MS characterization was performed using a C18 reversed phase HPLC column (2 μm, 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^{-1} (solvent A: 95% H_2O, 5% MeOH, 0.01% TFA; B: MeOH, 0.01% TFA). Reverse-phase HPLC purification was performed with a C18 reversed-phase column (5 μm, 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 × 10 min). Two peptoid residues were added by a standard submonomer route[23] using a microwave-assisted protocol.[24] 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 × 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 × 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)-7*H*-pyrrolo[2,3-*d*]pyrimidines (14). The peptoid-loaded resin (**5**) was treated with 4,6-dichloro-2-methylthio-5-formylaldehyde (**6**) (5 equiv.) and DIEA (5 equiv.) in THF at room temperature overnight. The reaction mixture was drained and washed with DMF (3 × 2 mL), CH_2Cl_2 (2 × 2 mL), MeOH (2 × 2 mL), and DMF (3 × 2 mL). To a suspension of the resin-bound 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 × 2 mL), CH_2Cl_2 (2 × 2 mL), MeOH (2 × 2 mL), and DMF (3 × 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).** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 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·TFA (14b).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{25}H_{33}N_6O_3S$ $[M + H]^+$ 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).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{28}H_{31}Cl_2N_6O_3S$ $[M + H]^+$ 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-6-carboxamide·TFA (14d).** ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{22}H_{29}N_6O_3S$ $[M + H]^+$ 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).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{30}H_{37}N_6O_4S$ $[M + H]^+$ 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).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{35}H_{39}N_6O_2S$ $[M + H]^+$ 607.2855, found: 607.2863.

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***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).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{29}H_{35}N_6O_3S$ $[M + H]^+$ 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).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{29}H_{36}N_7O_4S_2$ $[M + H]^+$ 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 4,6,7-trisubstituted 2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidines (**12**) were treated with *m*-CPBA (10 equiv.) and $NaHCO_3$ (15 equiv.) in THF (2 mL)/H_2O (400 μL) 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_2Cl_2 (2 × 2 mL), MeOH (2 × 2 mL), and CH_2Cl_2 (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).** ^{1}H-NMR (500 MHz, $CDCl_3$) 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). ^{13}C-NMR (126 MHz, $CDCl_3$) 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 $C_{24}H_{34}N_7O_4$ $[M + H]^+$ 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).** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 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). ^{3}C-NMR (126 MHz, $CDCl_3$) δ 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 $C_{29}H_{36}N_7O_4$ $[M + H]^+$ 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).** ^{1}H-NMR (500 MHz, $CDCl_3$) 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). ^{13}C-NMR (126 MHz, $CDCl_3$) 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 $C_{30}H_{44}N_7O_3$ $[M + H]^+$ 550.3505, found: 550.3508.

***N*-(2-Amino-2-oxoethyl)-*N*-benzyl-4-(cyclopentylamino)-2-((2,4-dichlorophenethyl)amino)-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidine-6-carboxamide·TFA (15-4D).** ^{1}H-NMR (500 MHz, $CDCl_3$) 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). ^{13}C-NMR (126 MHz, $CDCl_3$) 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 $C_{32}H_{38}Cl_2N_7O_3$ $[M + H]^+$ 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).** ^{1}H-NMR (500 MHz, $CDCl_3$) 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). ^{13}C-NMR (126 MHz, $CDCl_3$) 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 $C_{42}H_{46}N_7O_5$ $[M + H]^+$ 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·TFA (15-6F).** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 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 $C_{35}H_{38}Cl_2N_7O_4$ $[M + H]^+$ 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).** ^{1}H-NMR (500 MHz, methanol-d_4) δ 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),

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6.96 (s, 1H), 7.29–7.54 (m, 9H), 7.86–8.09 (m, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 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 $C_{34}H_{40}N_7O_3$ $[M + H]^+$ 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).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{40}H_{46}N_7O_3$ $[M + H]^+$ 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·TFA (15-9I).** ^{1}H-NMR (500 MHz, methanol-d_4) δ 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). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 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 $C_{37}H_{43}N_8O_4$ $[M + H]^+$ 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·TFA (15-10A).** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 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_2), 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). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 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 $C_{29}H_{37}N_8O_5S$ $[M + H]^+$ 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).** ^{1}H-NMR (500 MHz, $CDCl_3$) 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). ^{13}C-NMR (126 MHz, $CDCl_3$) 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 $C_{26}H_{36}N_7O_5$ $[M + H]^+$ 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·TFA (15-8C).** ^{1}H-NMR (500 MHz, $CDCl_3$) δ 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). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 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 $C_{30}H_{43}N_8O_4$ $[M + H]^+$ 579.3407, found: 579.3401.

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