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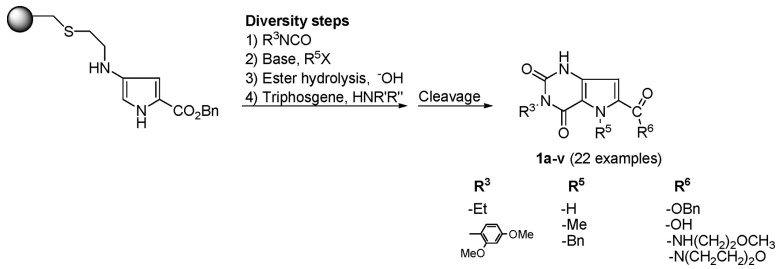

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Deazapurine Solid-Phase Synthesis: Combinatorial Synthesis of a Library of N3,N5,C6-Trisubstituted Pyrrolo[3,2-*d*]pyrimidine Derivatives on Cross-Linked Polystyrene Bearing a Cysteamine Linker

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Solid-phase methodology for the preparation of pyrrolo[3,2-*d*]pyrimidine-6-carboxylates with diversity at the N3 pyrmidine nitrogen has now been elaborated to allow for the generation of pyrrolopyrimidine libraries with members possessing diversity at the N3, N5, and C6 positions. The diversification of the N5 position was achieved by treating the parent resin-bound pyrrolo[3,2-*d*]pyrimidines **3** with an alkyl halide in the presence of Cs_2CO_3 in DMF. Modification of the C6 carboxylate of resin-bound pyrrolopyrimidines **3**−**5** was first achieved by hydrolysis of the benzyl ester using LiOH in a mixture of THF/H_2O/MeOH. Further alteration of the C6 position of resin-bound pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acids **6**−**8** was then performed by activation with triphosgene and treatment with an amine to furnish resin-bound pyrrolo[3,2-*d*]pyrimidine-6-amides. Twenty-two pyrrolo[3,2-*d*]pyrimidines **1a**−**v** with different substituents at the N3, N5, and C6 positions were obtained in yields of 21−83% and purities of 61−98% after cleavage from the solid support.

Introduction

Pyrrolo[3,2-*d*]pyrimidines are a class of deazapurine derivatives with many potential medicinal applications. Among other activities, compounds of this type were found to act as antagonists toward adenosine receptor subtypes[1,2] and inhibitors of enzymes, such as purine nucleoside phosphorylase,[3] phosphodiesterase,[4] and matrix metalloproteinases.[5] Solid-phase methodology for the combinatorial preparation of libraries of these biologically active heterocycles has, however, yet to be developed. Ideally, such methodology should provide opportunities for adding a variety of pharmacophores at each of the ring positions such that diverse libraries can be generated for SAR studies.

We have recently presented an effective method for the solid-phase preparation of pyrrolo[3,2-*d*]pyrimidine-6-carboxylates with different substituents at the N3 pyrimidine nitrogen. By starting from Merrifield resin bearing a cysteamine traceless safety-catch[6−8] linker and 4-oxo-*N*-(PhF) proline benzyl ester (PhF = 9-(9-phenylfluorenyl)) as a 4-amino pyrrole precursor, four pyrrolo[3,2-*d*]pyrimidines with alkyl and aryl substituents at the N3 position were synthesized in overall yields of 42−50% and purities of 90−100%.[9]

In principle, elaboration of this methodology may permit the synthesis of libraries of pyrrolo[3,2-*d*]pyrimidines possessing up to six diversity elements around the heterocycle. For example, by utilizing 3-alkyl-4-oxo-*N*-(PhF)prolines as the 4-amino pyrrole precursor, diversity may be incorporated at the eventual C7 position (Scheme 1).[10] Diversity at the C4 position may be achieved by modifying the cyclization protocol. For example, in solution, pyrrolo[3,2-*d*]pyrimidines with alkyl and aryl substituents at the C4 position have been synthesized in our laboratory by a Pictet−Spengler condensation between aldehydes and ureido pyrroles under acidic conditions.[11] N-Alkylation of the pyrrole nitrogen should permit the introduction of diversity at the N5 position.[12] Benzyl ester hydrolysis and subsequent amide bond formation could be used to modify the C6 position. Finally, different substituents may be incorporated at the N1 position by alkylation of the anion generated during cleavage of the pyrrolopyrimidine from the resin.

In the present manuscript, we demonstrate the addition of diversity at three of the six potential positions enumerated above. The preparation of a pyrrolo[3,2-*d*]pyrimidine library composed of 22 derivatives has been achieved by adding diverse substituents at the N3, N5 and C6 positions. In particular, chemical modification of resin-bound N3-substituted pyrrolo[3,2-*d*]pyrimidines has been achieved by alkylation of the pyrrole nitrogen and derivatization of the C6 carboxylate.

Results and Discussion

Library synthesis commenced with the preparation of resin-bound N3-modified pyrrolo[3,2-*d*]pyrimidines **3a** and **3b**, possessing hydrogen at the N5 position and a benzyl ester at the C6 position, by employing our recently reported methodology.[9] Merrifield resin **2** bearing a cysteamine traceless safety-catch linker was treated with 4-oxo-*N*-(PhF)-

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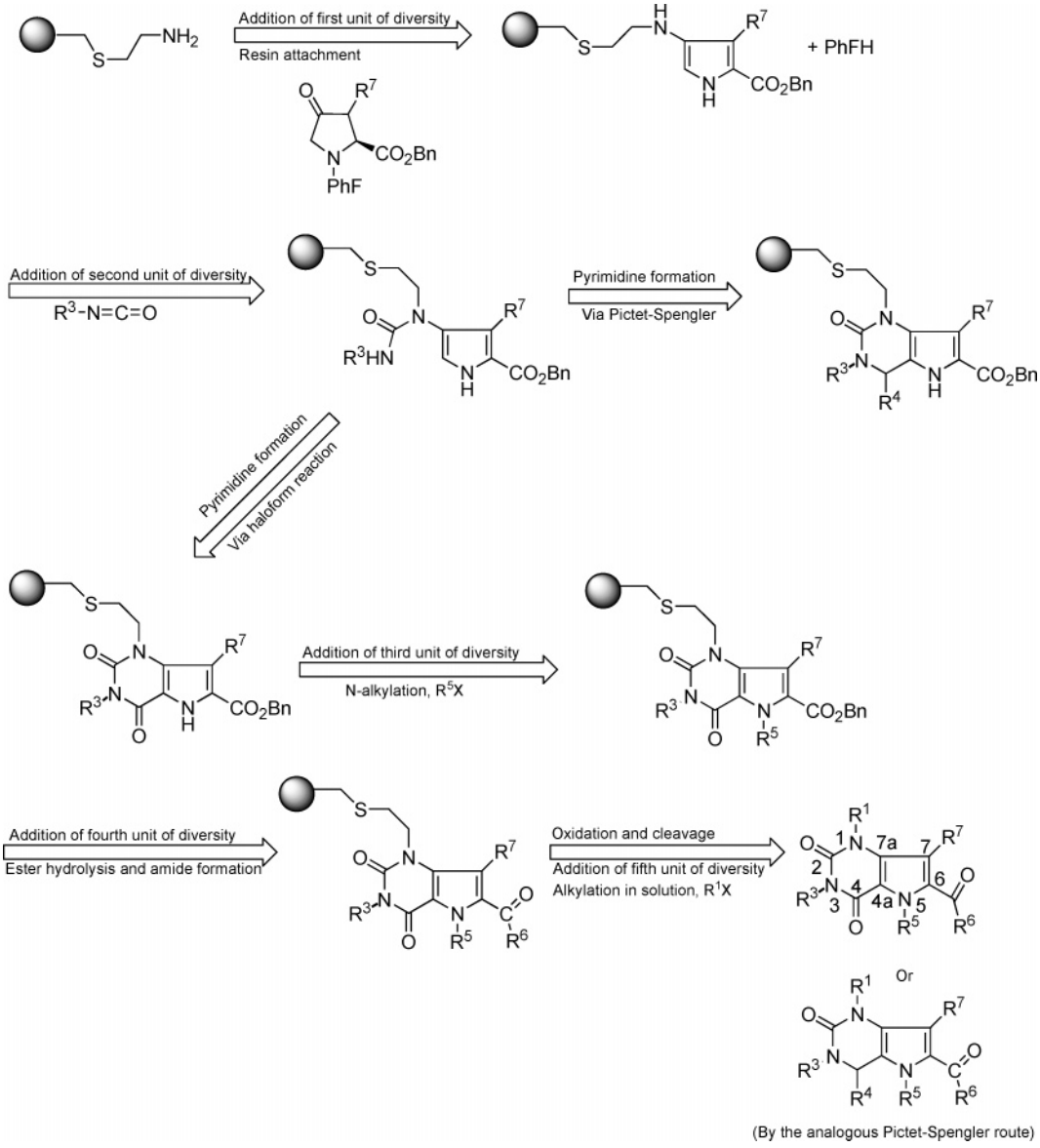
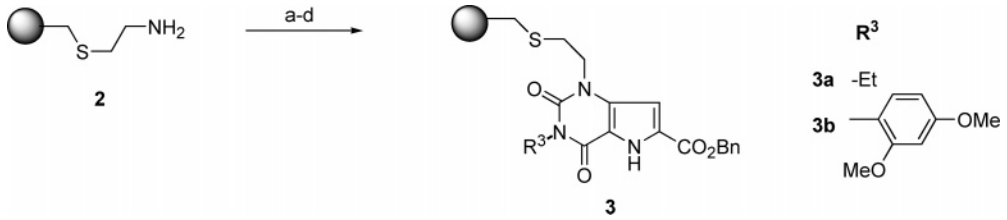
Scheme 1. General Strategy for the Solid-Phase Synthesis of Multisubstituted Pyrrolo[3,2-*d*]pyrimidines



Scheme 2. Preparation of Resin-Bound N3-Modified Pyrrolo[3,2-*d*]pyrimidines[a]



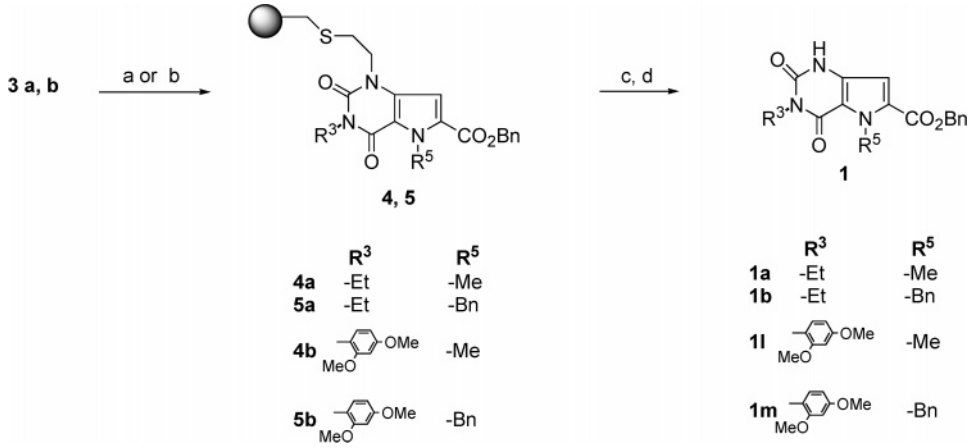
[a] (a) 200 mol % 4-oxo-*N*-(PhF)proline benzyl ester, 680 mol % Et_3N, 20 mol % $Et_3N{\cdot}HBr$, 50 °C, THF/CH_3CN (50:50), 24 h. (b) 400 mol % R^3NCO, CH_2Cl_2, rt, overnight. (c) 1000 mol % Cl_3CCOCl, dioxane, 70 °C, 4 h. (d) 1000 mol % Cs_2CO_3, DMF, rt, overnight.

proline benzyl ester to furnish resin-bound amino pyrrole, which was converted to resin-bound pyrrolo[3,2-*d*]pyrimidines **3** on treatment with ethyl and 2,4-dimethoxyphenyl isocyanates followed by acylation using trichloroacetyl chloride in dioxane and cyclization via a haloform reaction on treatment with Cs_2CO_3 in DMF (Scheme 2).

The success of the on-resin reactions was monitored by the ninhydrin test[13] and FT-IR spectral analysis of the dry resins in KBr pellets. In some cases, conversions were ascertained by cleaving samples and examination of the crude products by ^1H NMR spectroscopy and LC/MS analysis. Resin cleavage was performed in a two-step procedure in accordance with the safety-catch approach.[6−8] The linker sulfur was first oxidized to a sulfone using 500 mol % of *m*-CPBA in DCM, and the products were then liberated from the resin by subsequent β-elimination in the presence of 1000 mol % of *t*-BuONa in THF.[9,14,15]

Pyrrolopyrimidines **3a** and **3b** were employed to examine the influence of alkyl and aryl N3 substituents on subsequent chemistry on the solid support. Diversity was added at the

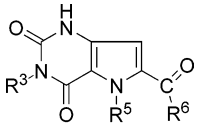
Scheme 3. N5 Position Modification by N-Alkylation[a]



[a] (a) 300 mol % methyl iodide, 300 mol % of Cs_2CO_3, DMF, overnight, rt. (b) 300 mol % benzyl bromide, 300 mol % Cs_2CO_3, DMF, 3 h, 60 °C. (c) 500 mol % *m*-CPBA, CH_2Cl_2, 1 h, rt. (d) 1000 mol % *t*-BuONa, THF, 1 h, 0 °C.

N5 and C6 positions after division of the N3-modified pyrrolo[3,2-*d*]pyrimidine resins **3** into separate batches. Diversification at N5 was accomplished by resin N-alkylations using methyl iodide and benzyl bromide to provide methyl and benzyl substituents as alkyl and aryl representatives, respectively (Scheme 3). The resins were treated with either 300 mol % of methyl iodide or 300 mol % of benzyl bromide in the presence of 150−300 mol % of Cs_2CO_3 as base and DMF as solvent overnight at room temperature or for 3 h at 60 °C, respectively. Because of the similarities of the FT-IR spectra of the resin-bound products before and after N5-alkylation (resins **3**, **4**, and **5**), conversion was ascertained from the ^{1}H NMR spectra and LC/MS analysis of crude compounds **1a**, **1b**, **1l**, and **1m** that were obtained from cleavage of portions of resins **4** and **5** after the alkylation reactions. The extent of alkylation at N5 was inferred on the basis of the disappearance of the N5 pyrrole hydrogen peak at ∼13 ppm and appearance of new peaks corresponding to the methyl and benzyl substituents at 4.1 and 6.0 ppm, respectively. The N5 crude benzylated products **1b** and **1m** were obtained in reasonable purities of 61 and 80%, respectively, as determined by analytical HPLC. The presence of signals for contaminants in the aromatic and aliphatic regions was observed in the ^{1}H NMR spectra of these products; however, LC/MS analysis of the crude products suggested total conversion to the alkylated products, and no ion for the nonalkylated material was observed. The methylated crude products **1a** and **1l** were obtained in lower purities of 30 and 21%, respectively, as determined by analytical HPLC. The ^{1}H NMR spectra and LC/MS and TLC analysis (50/50 hexanes/EtOAc) of crude **1a** and **1l** suggested the presence of side products due in part to undesired benzyl ester hydrolysis in the presence of Cs_2CO_3 and methylation of the free carboxylic acid. By TLC analysis (50/50 hexanes/EtOAc), crude products **1a**, **1b**, **1l**, and **1m** showed a baseline bromocresol green positive spot, indicative of the presence of carboxylic acid. The higher purities of the benzylated products **1b** and **1m** may be explained by benzylation with benzyl bromide of product from benzyl ester hydrolysis, leading indirectly to the desired target. Noteworthy, carboxylic acids and amides **1c**, **1f**, **1i**, **1n**, **1q**, and **1t** were later isolated in relatively higher purities (65−90%) and yields (21−65%) from resins **4a** and **4b** (Table 1), because the subsequent step, involving ester hydrolysis with LiOH, removed the methyl ester impurity. N5-Alkylated C6-benzyl esters **1a**, **1b**, **1l**, and **1m** could be purified effectively by silica gel chromatography.

Table 1. Pyrrolo[3,2-*d*]pyrimidine Yields and Purities[a]

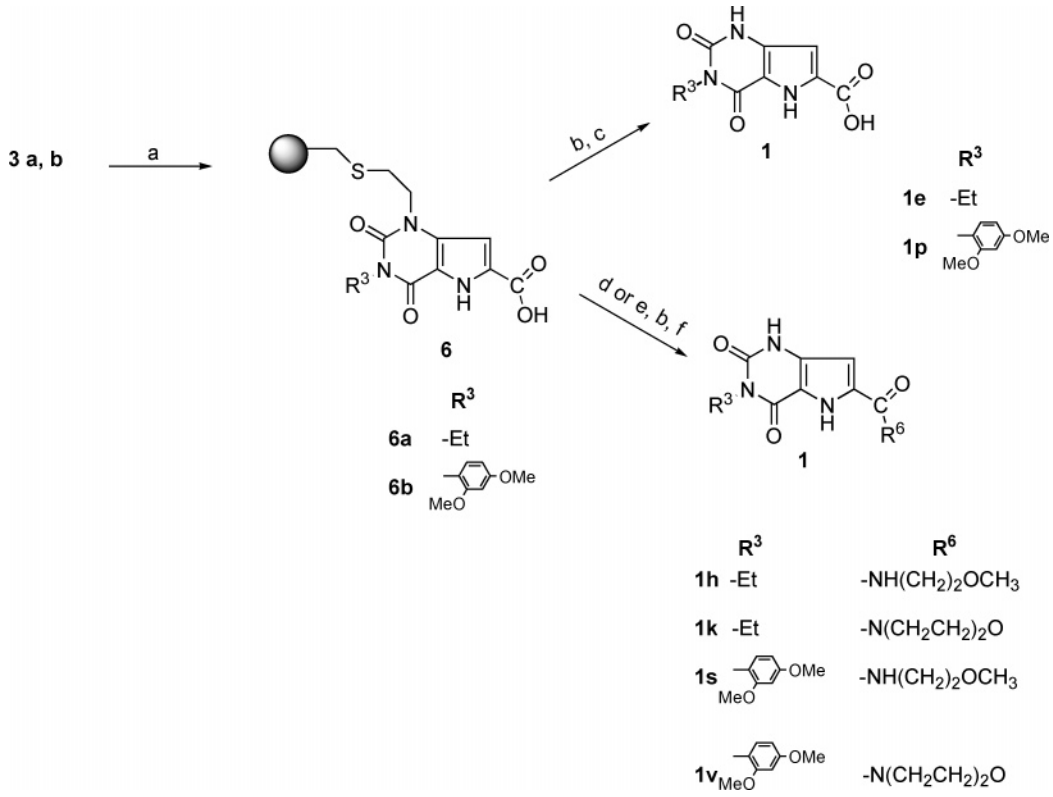


1

				crude		purified	
compd	R^3	R^5	R^6	yield %	purity %	yield %	purity %
1a	Et	Me	OBn	46	30[b]	8[d]	85
1b	Et	Bn	OBn	77	61	4[d]	81
1c	Et	Me	OH	52	85	23[e]	87
1d	Et	Bn	OH	79	83	15[e]	91
1e	Et	H	OH	81	89	18[e]	99
1f	Et	Me	$-NH(CH_2)_2OCH_3$	65	90	12[f]	97
1g	Et	Bn	$-NH(CH_2)_2OCH_3$	38	98	15[g]	99
1h	Et	H	$-NH(CH_2)_2OCH_3$	83	71	45[g]	99
1i	Et	Me	$-N(CH_2CH_2)_2O$	50	83	30[g]	99
1j	Et	Bn	$-N(CH_2CH_2)_2O$	60	61	33[g]	99
1k	Et	H	$-N(CH_2CH_2)_2O$	43	96	17[g]	99
1l	DMP	Me	OBn	58	21[b]	13[d]	88
1m	DMP	Bn	OBn	34	80	10[d]	96
1n	DMP	Me	OH	32	65	9[h]	92
1o	DMP	Bn	OH	46	88	17[h]	89
1p	DMP	H	OH	49	75	np[c]	np[c]
1q	DMP	Me	$-NH(CH_2)_2OCH_3$	35	89	np[c]	np[c]
1r	DMP	Bn	$-NH(CH_2)_2OCH_3$	28	78	15[f]	85
1s	DMP	H	$-NH(CH_2)_2OCH_3$	23	83	12[h]	87
1t	DMP	Me	$-N(CH_2CH_2)_2O$	21	86	8[g]	99
1u	DMP	Bn	$-N(CH_2CH_2)_2O$	24	90	17[f]	91
1v	DMP	H	$-N(CH_2CH_2)_2O$	24	89	np[c]	np[c]

[a] DMP: 2,4-dimethoxyphenyl. Yields are calculated on the basis of the weight of the products and the loadings of amino pyrrole resins. Purities were determined by analytical HPLC examination. [b] % Purity refers to the desired component in a mixture with methyl ester product; see text. [c] Compounds were not purified. [d] Purification by chromatography on silica gel. [e] Purification by aqueous extractions. [f] Purification by sodium bicarbonate wash. [g] Purification by RP-HPLC. [h] Purification by trituration with petroleum ether.

Scheme 4. Hydrolysis and C6 Modification[a]

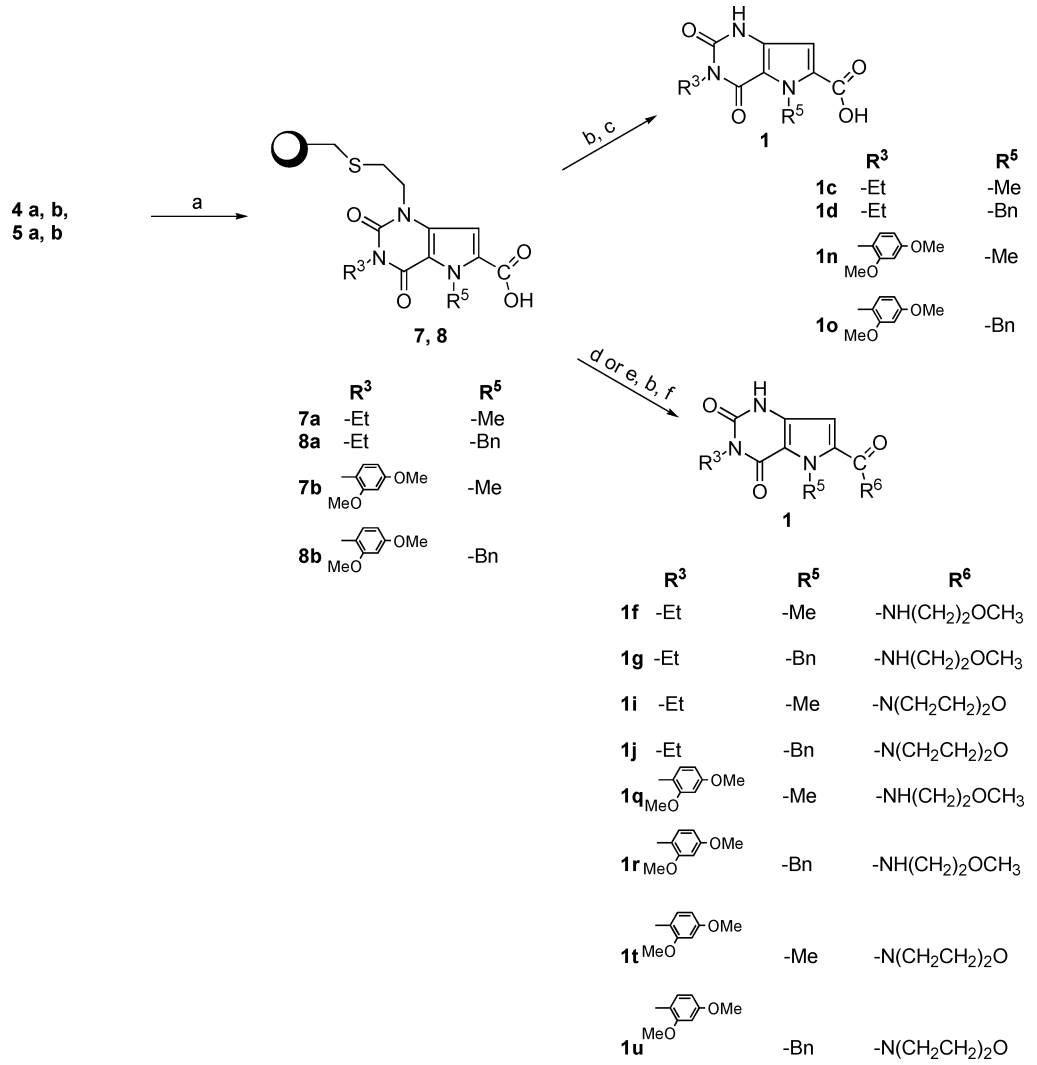


[a] (a) 1000 mol % LiOH, THF/H_2O/MeOH 3:1.5:1 (v/v), overnight, 70 °C. (b) 500 mol % *m*-CPBA, CH_2Cl_2, 1 h, rt. (c) 1100 mol % *t*-BuONa, THF, 1 h, 0 °C. (d) 33 mol % triphosgene (BTC), 400 mol % methoxyethylamine, 900 mol % collidine, 2 h, rt, twice. (e) 33 mol % triphosgene (BTC), 400 mol % morpholine, 900 mol % collidine, 2 h, rt, twice. (f) 1000 mol % *t*-BuONa, THF, 1 h, 0 °C.

The C6 position was next modified by hydrolysis of the benzyl ester on treatment of resins **3**−**5** with LiOH (1000 mol %) in a mixture of THF/H_2O/MeOH 3:1.5:1 (v/v) overnight at 70 °C (Schemes 4 and 5). Once again, because spectral differences in the FT-IR spectra were insufficient for judging conversion in the hydrolysis reaction, conversion to carboxylic acid products **1c**−**e** and **1n**−**p** was evaluated by cleavage of portions of resins **6**−**8** and ^{1}H NMR spectroscopy of the crude products. Quantitative hydrolysis was assessed by the disappearance of the aromatic and the benzyl peaks at ∼7.4 and ∼6.0 ppm, respectively. Furthermore, ions corresponding to the benzyl ester derivatives were not observed in the LC/MS analysis of the crude products. The purity of the crude acids after cleavage from the solid support was determined by HPLC to be between 65 and 89%. Compounds of higher purity were effectively obtained by partitioning the crude acids between sodium bicarbonate and diethyl ether, acidification of the aqueous phase with 1 N HCl, and extraction of the product with ethyl acetate. In the case of **1n** and **1o**, compounds of higher purity were obtained by trituration with petroleum ether.

Resin-bound pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acids **6**−**8** were converted to pyrrolo[3,2-*d*]pyrimidine-6-carboxamides by treating preactivated resins with methoxyethylamine and morpholine as primary and secondary amine representatives. Activation of resin-bound carboxylic acids **6**−**8** was performed by in situ conversion to their acid chlorides using 33 mol % of triphosgene (BTC) in the presence of 900 mol % of collidine as base for 2 min at room temperature.[16] Coupling was then performed by the addition of 400 mol % of methoxyethylamine or 400 mol % of morpholine for 2 h at room temperature (Schemes 4 and 5). High coupling yields were ensured by repeating the coupling procedure once more after resin washings, utilizing the same conditions. This coupling protocol proved to be efficient because most couplings were found to be quantitative, as indicated by the ^{1}H NMR spectra of crude products **1f**, **1h**, **1i**, **1k**, **1q**, **1s**, **1t**, and **1v**. Couplings to the resin-bound N5-benzyl derivatives succeeded; however, only in 65−80% conversion. The ^{1}H NMR spectra of crude products **1g**, **1j**, **1r**, and **1u** exhibited two peaks at slightly different chemical shifts for both the N1 and the C7 protons, originating from uncoupled pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acids and the desired amide products. Analysis of crude products **1g**, **1j**, **1r**, and **1u** by LC/MS supported these findings. Peaks corresponding to the ions of coupled and uncoupled pyrrolo-[3,2-*d*]pyrimidine-6-carboxylates were observed. Partial coupling to the N5-benzyl derivatives probably stems from the steric hindrance imposed by the benzyl substituent, which reduces the coupling efficiency to the proximal carboxylic acid. The pyrrolo[3,2-*d*]pyrimidine-6-carboxamides were obtained in reasonably high purity of 65−98% after cleavage from the solid support without any further treatment. Removal of unreacted pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acids by partitioning the crude products between sodium bicarbonate and ethyl acetate gave purer samples of amide, as indicated by TLC analysis (90/10 DCM/methanol), which demonstrated that the baseline bromocresol green-positive spot for the acid derivative had disappeared. In the cases of **1g**−**k** and **1t**, the ^{1}H NMR spectra indicated signals for

Scheme 5. Hydrolysis and C6 Modification of N5-Modified Derivatives



(a) 1000 mol % LiOH, THF/H_2O/MeOH 3:1.5:1 (v/v), overnight, 70 °C. (b) 500 mol % *m*-CPBA, CH_2Cl_2, 1 h, rt. (c) 1100 mol % *t*-BuONa, THF, 1 h, 0 °C. (d) 33 mol % triphosgene (BTC), 400 mol % methoxyethylamine, 900 mol % collidine, 2 h, rt, twice. (e) 33 mol % triphosgene (BTC), 400 mol % morpholine, 900 mol % collidine, 2 h, rt, twice. (f) 1000 mol % *t*-BuONa, THF, 1 h, 0 °C.

contaminants in the aliphatic region and additional purification by HPLC was performed to provide analytically pure samples.

Conclusions

A library composed of 22 N3,N5,C6-trisubstituted pyrrolo-[3,2-*d*]pyrimidines was synthesized on Merrifield resin bearing a cysteamine traceless safety-catch linker in overall yields of 21−83% and purities of 61−98% after cleavage from the solid support (Table 1). The combinatorial synthesis of these derivatives was performed by modification of resin-bound N3-alkyl- and arylpyrrolo[3,2-*d*]pyrimidine-6-carboxylates at the N5 pyrrole nitrogen using N-alkylations and at the C6 position by ester hydrolysis and subsequent amide formations. Further expansion of this methodology to afford libraries of pyrrolo[3,2-*d*]pyrimidines having up to six diversity elements appears feasible by further extensions of this approach and is now being pursued.

Experimental Section

General. Anhydrous solvents (THF, CH_3CN, CH_2Cl_2, and DMF) were obtained by passage through solvent filtration systems (GlassContour, Irvine, CA). Reactions performed at room temperature were shaken using a reciprocating shaker (SK-300, Jeio Tech). Reactions performed at 50−70 °C were performed in an oil bath with occasional manual shaking. ^{1}H NMR spectra were measured in DMSO-d_6 on either a Bruker AV 400-MHz or AV 300-MHz spectrometer and referenced to residual CHD_2SOCD_3 (2.50 ppm). ^{13}C NMR spectra were measured in DMSO-d_6 on 100/75-MHz spectrometers and referenced to DMSO-d_6 (39.5 ppm). In the case of morpholinamides **1i**−**k** and **1t**−**v**, signals for the methylene carbons α to the nitrogen were not detected. Chromatography was performed using 230−400 mesh silica gel. Mass spectral analyses and HPLC purifications were performed by the Université de Montréal Mass Spectroscopy Facility. Analytical HPLC analyses as well as LC/MS determinations were performed using a Thermo Finnigen LCQ ion trap mass spectrometer equipped with a Gilson analytical HPLC on a YMC C18 analytical column (5 μm, 50 × 4.6 mm) using a binary mobile phase system formed from 0.05% TFA in water (solution A) and 0.05% TFA in CH_3CN (solution B). One of two gradient methods was used: (A1) 20−80% solution B in solution A over 4 min,

80−90% solution B in solution A over 1 min, and 90% solution B in solution A for 6 min with a flow rate of 0.5 mL/min and monitoring at 214 nm or (A2) 5−40% solution B in solution A over 4 min, 40−90% solution B in solution A over 1 min, and 90% solution B in solution A for 6 min with a flow rate of 0.5 mL/min and monitoring at 214 nm. Analytical reversed-phase HPLC was performed also on a Merck-Hitachi L-7100 Lachrom liquid chromatograph pump on a Higgins C18 reversed-phase analytical column (5 μ Targa 250 × 4.6 mm; Part No. TS-2546-C185) using a binary mobile phase system formed from 0.1% TFA in water (solution A) and 0.1% TFA in CH_3CN (solution B). One of two gradient methods was used: (A3) 20−80% solution B in solution A over 20 min and 80−90% solution B in solution A over 5 with a flow rate of 1 mL/min, monitoring at 214 nm, or (A4) 10−70% solution B in solution A over 20 min and 70−90% solution B in solution A over 5 min with a flow rate of 1 mL/min, monitoring at 214 nm. Retention times (t_R) are reported as t_R, min (method of elution). Purifications were performed using a Thermo Finnigen LCQ single quadropole mass spectrometer equipped with a Gilson liquid handler semipreparative HPLC on a Prevail C18 column (5 μm, 250 × 22 mm) using a binary mobile phase system formed from 0.05% TFA in water (solution A) and 0.05% TFA in CH_3CN (solution B) and a gradient of 20−80% solution B in solution A over 30 min with a flow rate of 15 mL/min and monitoring at 214 nm. Accurate mass measurements (HRMS) were performed on a LC/MSD-TOF instrument (Agilent Technologies) using positive electrospray. Protonated molecular ions (MH^+) were used for empirical formula confirmation. FT-IR spectra were taken using a Perkin-Elmer Spectrum One apparatus.

Cysteamino Merrifield Resin (2). The resin was prepared according to the procedure previously described[9] on two separate batches of 5 g of Merrifield resin (1.27 mmol/g, 2% DVB 200−400 mesh) using 19 mmol (300 mol %) of cysteamine hydrochloride (dried under vacuum in a desiccator over P_2O_5) and 64 mmol (1000 mol %) of NaH (60% in mineral oil) in dry DMF for 48 h at room temperature. The loading of the dried resins was determined by the picric acid test[17] to be 0.52 and 0.71 mmol/g.

Aminopyrrole Resin. The resin was prepared from cysteamino Merrifield resin **2** according to the procedure previously described[9] on two separate batches employing 4.5 g of resin (loading of 0.52 mmol/g) and 4.1 g of resin (loading of 0.72 mmol/g), 200 mol % of 4-oxo-*N*-(PhF)-proline benzyl ester (PhF = 9-(9-phenylfluorenyl)), 680 mol % of Et_3N, and 20 mol % of Et_3N·HBr in 12 mL of THF/CH_3CN (50:50) for 24 h at 50 °C. Unreacted 4-oxo-*N*-(PhF)-proline benzyl ester was recovered, and PhFH was isolated as described, furnishing 2.73 mmol (0.66 g) and 2.97 mmol (0.72 g) of PhFH (mp 153.2 °C, lit. mp 147−148 °C),[18] indicating aminopyrrole resin loadings of 0.62 and 0.65 mmol/g for the two batches, respectively.

Ureidopyrrole Resins. The aminopyrrole resin (4 g) was suspended in 20 mL of dry DCM and treated as previously described[9] with either 400 mol % of ethyl isocyanate or 400 mol % of 2,4-dimethoxyphenyl isocyanate for 24 h at room temperature. The resins were then filtered and washed with 20-mL volumes of CH_2Cl_2 (2×), EtOH (2×), CH_2Cl_2 (2×), EtOH (2×), CH_2Cl_2 (3×), before drying in vacuo.

Pyrrolopyrimidine Resins (3a, **3b).** Ureidopyrrole resins obtained from the above-mentioned procedure were kept in the same tubes; suspended in 20 mL of dry dioxane; and treated, as described,[9] with 1000 mol % of trichloroacetyl chloride for 4 h at 70 °C; washed with dioxane; swollen in dry DMF; suspended in 20 mL of dry DMF; and treated with 1000 mol % of powdered and flame-dried Cs_2CO_3 at room temperature overnight. The resins were washed with 20-mL volumes of H_2O (2×), EtOH (2×), CH_2Cl_2, EtOH, saturated NH_4Cl, H_2O (2×), EtOH (2×), and CH_2Cl_2 (3×) and lyophilized to remove any residual solvent.

N5-Alkylated Resins (4a, 4b, 5a, and 5b). Pyrrolopyrimidine resins **3a** (0.8 g × 2) and **3b** (1.0 g × 2) were placed in four separate 12-mL polypropylene tubes equipped with polyethylene frits and stopcocks. The resins were swollen in dry DMF; washed with DMF; suspended in 8 mL of dry DMF; and treated with either 300 mol % of methyl iodide or 300 mol % of benzyl bromide in the presence of 300 mol % of flame-dried Cs_2CO_3, overnight at room temperature, or 3 h at 60 °C (oil bath), respectively (150 mol % of Cs_2CO_3 was employed to methylate resin **3b**). The resins were then filtered and washed with 8-mL volumes of DMF (4×), H_2O (2×), EtOH (2×), CH_2Cl_2, EtOH, saturated NH_4Cl, H_2O (2×), EtOH (2×), and CH_2Cl_2 (3×) and lyophilized to remove any residual solvent.

N5-Alkylated Pyrrolo[3,2-*d*]pyrimidine-6-carboxylates (1a, 1b, 1l and 1m). Portions of resins **4a**, **4b**, **5a**, and **5b** (0.15−0.20 g) were transferred to four separate 12-mL polypropylene tubes equipped with polyethylene frits and stopcocks; suspended in 3 mL of dry DCM; and treated, as described,[9] with 500 mol % of *m*-CPBA for 1 h at room temperature. The resins were filtered, washed with 7-mL volumes of CH_2Cl_2 (2×), EtOH (2×), CH_2Cl_2 (2×), EtOH (2×), and CH_2Cl_2 (3×) and lyophilized to remove any residual solvent. The sulfone resins were carefully weighed; suspended in 3 mL of dry THF; and treated, as described,[9] with 1000 mol % of *t*-BuONa for 1 h at 0 °C. The filtrates were collected in ice-cooled saturated NH_4Cl solutions (10 mL/sample). The resins were washed with 7-mL volumes of dry DMF; saturated NH_4Cl (2×); water (2×); DMF (2×); EtOH; DMF (3×); and finally, EtOAc (3×). Another 20 mL of EtOAc and 20 mL of brine were then added to the filtrates to obtain a good separation between the organic and aqueous phases, and the organic layer was separated. The aqueous phase was subsequently extracted twice with CH_2Cl_2 and twice with EtOAc. The organic layers were combined, dried on Na_2SO_4, filtered, and concentrated in a vacuum to furnish crude pyrrolo[3,2-*d*]pyrimidines **1a**, **1b**, **1l**, and **1m** in yields of 34−77% from the amino pyrrole resins and purities of 21−80%. Purification of the crude products on a short silica column using a gradient of 30−50% EtOAc/hexanes as an eluent gave analytically pure products.

Benzyl 2,4-Dioxo-3-ethyl-5-methylpyrrolo[3,2-*d*]pyrimidine-6-carboxylate (1a). Prepared from 180 mg of the sulfone resin to yield crude product (15.0 mg, 30% pure; t_R: 17.97; method A3), from which a portion (14 mg) was chromatographed (gradient of 30−50% EtOAc/hexanes).

Evaporation of the collected fractions gave the title compound (2.5 mg, 8%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.20 (s, 1H), 7.46−7.36 (m, 5H), 6.43 (s, 1H), 5.31 (s, 2H), 4.20 (s, 3H), 3.87 (q, J = 6.9 Hz, 2H), 1.11 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7, 156.0, 150.2, 135.8, 131.0, 128.6, 128.3, 128.1, 128.1, 114.1, 100.0, 66.2, 34.9, 33.7, 13.2. HRMS (*m*/*z*): calcd for $C_{17}H_{18}N_3O_4$ (MH^+), 328.1292; found, 328.1289. R_f: 0.53 (50/50 hexanes/EtOAc). t_R: 6.46 (method A1).

Benzyl 2,4-Dioxo-3-ethyl-5-benzylpyrrolo[3,2-*d*]pyrimidine-6-carboxylate (1b). Prepared from 200 mg of the sulfone resin to yield crude product (34.0 mg, 61% pure; t_R: 20.30, method A3) which was chromatographed (gradient of 30−50% EtOAc/hexanes). Evaporation of the collected fractions gave the title compound (1.6 mg, 4%) as a beige oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.32 (s, 1H), 7.34 (s, 5H), 7.27−7.17 (m, 3H), 6.99 (d, J = 7.6 Hz, 2H), 6.52 (s, 1H), 5.99 (s, 2H), 5.25 (s, 2H), 3.85 (q, J = 6.7 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.5, 155.8, 150.2, 138.4, 135.6, 128.5, 128.5, 128.3, 128.0, 127.7, 127.1, 126.2, 121.5, 113.9, 101.3, 66.2, 48.4, 35.0, 13.1. HRMS (*m*/*z*): calcd for $C_{23}H_{22}N_3O_4$ (MH^+), 404.1605; found, 404.1603. R_f: 0.28 (70/30 hexanes/EtOAc). t_R: 7.29 (method A1).

Benzyl 2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-methylpyrrolo[3,2-*d*]pyrimidine-6-carboxylate (1l). Prepared from 135 mg of the sulfone resin to yield crude product (22.1 mg, 21% pure; t_R: 18.64, method A3), from which a portion (8.0 mg) was chromatographed (70/30 hexanes/EtOAc). Evaporation of the collected fractions gave the title compound (1.8 mg, 13%) as a beige oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.25 (s, 1H), 7.43−7.38 (m, 5H), 7.06 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 6.55 (d, J = 7.7 Hz, 1H), 6.46 (s, 1H), 5.32 (s, 2H), 4.17 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 159.7, 156.1, 155.9, 150.3, 135.8, 131.6, 130.8, 128.6, 128.4, 128.3, 128.1, 117.0, 114.1, 104.8, 100.2, 99.0, 66.2, 55.6, 55.5, 33.7. HRMS (*m*/*z*): calcd for $C_{23}H_{22}N_3O_6$ (MH^+), 436.1503; found, 436.1497. R_f: 0.67 (100% EtOAc). t_R: 6.65 (method A1).

Benzyl 2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-benzylpyrrolo[3,2-*d*]pyrimidine-6-carboxylate (1m). Prepared from 190 mg of the sulfone resin to yield crude product (21.7 mg, 80% pure, t_R: 23.63, method A3), from which a portion (13.4 mg) was chromatographed (gradient of 30−50% EtOAc/hexanes). Evaporation of the collected fractions gave the title compound (3.9 mg, 10%) as a beige oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 7.39 (s, 5H), 7.30−7.20 (m, 3H), 7.15−7.00 (m, 3H), 6.65 (d, J = 2.5 Hz, 1H), 6.65−6.50 (m, 2H), 5.96 (s, 2H), 5.29 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 159.5, 155.9, 155.8, 150.3, 138.2, 135.6, 132.1, 130.8, 128.5, 128.4, 128.2, 128.0, 127.1, 126.4, 117.0, 113.9, 104.9, 101.5, 99.1, 66.3, 55.7, 55.4, 48.4. HRMS (*m*/*z*): calcd for $C_{29}H_{26}N_3O_6$ (MH^+), 512.1816; found, 512.1813. R_f: 0.57 (80/20 hexanes/EtOAc). t_R: 7.35 (method A1).

Pyrrolo[3,2-*d*]pyrimidine-6-carboxylic Acid Resins (6a, 6b, 7a, 7b, 8a, and 8b). N5-Alkylated resins **4a**, **4b**, **5a**, **5b** and pyrrolopyrimidine resins **3a** and **3b** (0.6−1.0 g each resin batch) were transferred to six separate 12-mL polypropylene tubes equipped with polyethylene frits and stopcocks and were swollen in 7 mL of THF for 2 h. The resins were then filtered, washed with THF, suspended in 7 mL of a mixture of THF/H_2O/MeOH (3:1.5:1 v/v), and treated with 1000 mol % of powder LiOH overnight at 70 °C (oil bath). The resins were cooled; filtered; and washed with 7-mL volumes of DMF, saturated NH_4Cl (2×), H_2O (2×), DMF (2×), EtOH, DMF, DCM (2×); and lyophilized to remove any residual solvent.

Pyrrolo[3,2-*d*]pyrimidine-6-carboxylic Acids (1c, 1d, 1e, 1n, 1o, and 1p). Portions of resins **6a**, **6b**, **7a**, **7b**, **8a**, and **8b** (0.20−0.25 g each resin batch) were transferred to six separate 12-mL polypropylene tubes equipped with polyethylene frits and stopcocks and were subjected to sulfur oxidation with *m*-CPBA as described above and subsequent cleavage with 1100 mol % *t*-BuONa for 1 h at 0 °C. The resins were filtered and washed as described above, and the filtrates were acidified with 10 mL of 1 N HCl to pH 0. Ethyl acetate (20 mL) and brine (20 mL) were then added to the filtrates to obtain a good separation between the organic and aqueous phases, and the organic layer was separated. The aqueous phase was subsequently extracted twice with CH_2Cl_2 and twice with EtOAc. The organic layers were combined; dried with Na_2SO_4; filtered; and concentrated in a vacuum to furnish crude pyrrolo[3,2-*d*]pyrimidines **1c**, **1d**, **1e**, **1n**, **1o**, and **1p** in yields of 32−81% from the amino pyrrole resins and purities of 65−89%. Compounds of higher purity were effectively obtained by partitioning the product between sodium bicarbonate and diethyl ether and acidification of the aqueous layer with 1 N HCl and extraction with ethyl acetate. In the case of **1n** and **1o**, compounds of higher purity were obtained by trituration with petroleum ether.

2,4-Dioxo-3-ethyl-5-methylpyrrolo[3,2-*d*]pyrimidine-6-carboxylic Acid (1c). Prepared from 150 mg of the sulfone resin to yield crude product (10.2 mg, 85% pure; t_R: 10.03, method A4) which was purified by aqueous extraction as described above to give the title compound (4.6 mg, 23%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.30 (br s, 1H), 11.20 (s, 1H), 6.36 (s, 1H), 4.16 (s, 3H), 3.87 (q, J = 7.0 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.6, 156.0, 150.3, 131.0, 129.5, 113.6, 99.9, 34.8, 33.6, 13.2. HRMS (*m*/*z*): calcd for $C_{10}H_{12}N_3O_4$ (MH^+), 238.0822; found, 238.0819. t_R: 6.54 (method A2).

2,4-Dioxo-3-ethyl-5-benzylpyrrolo[3,2-*d*]pyrimidine-6-carboxylic Acid (1d). Prepared from 200 mg of the sulfone resin to yield crude product (27.1 mg, 83% pure; t_R: 13.49, method A3), which was purified by aqueous extraction as described above to give the title compound (5.0 mg, 15%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.36 (br s, 1H), 11.28 (s, 1H), 7.36−7.15 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 6.47 (s, 1H), 6.00 (s, 2H), 3.85 (q, J = 6.9 Hz, 2H), 1.07 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.4, 155.8, 150.2, 138.8, 131.6, 129.3, 128.5, 127.0, 126.2, 113.3, 101.1, 48.1, 34.9, 13.2. HRMS (*m*/*z*): calcd for $C_{16}H_{16}N_3O_4$ (MH^+), 314.1135; found, 314.1139. t_R: 5.38 (method A1).

2,4-Dioxo-3-ethyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylic Acid (1e). Prepared from 120 mg of the sulfone resin

to yield crude product (12.0 mg, 89% pure; t_R: 6.80, method A4), which was purified by aqueous extraction as described above to give the title compound (2.6 mg, 18%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.24 (br s, 1H), 12.67 (s, 1H), 11.12 (s, 1H), 6.32 (s, 1H), 3.87 (q, J = 6.9 Hz, 2H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 155.2, 150.6, 131.7, 129.5, 113.3, 98.9, 34.9, 13.3. HRMS (*m*/*z*): calcd for $C_9H_{10}N_3O_4$ (MH^+), 224.0666; found, 224.0658. t_R: 5.46 (method A2).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-methylpyrrolo-[3,2-*d*]pyrimidine-6-carboxylic Acid (1n). Prepared from 230 mg of the sulfone resin to yield crude product (16.6 mg, 65% pure; t_R: 11.87, method A4) which was triturated with petroleum ether to give the title compound (4.9 mg, 9%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.21 (s, 1H), 7.05 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.55 (dd, J = 2.5 Hz, 8.6 Hz, 1H), 6.40 (s, 1H), 4.13 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.6, 160.4, 156.2, 155.9, 150.3, 131.6, 130.9, 130.3, 117.2, 113.5, 104.8, 99.9, 99.0, 55.6, 55.5, 33.6. HRMS (*m*/*z*): calcd for $C_{16}H_{16}N_3O_6$ (MH^+), 346.1034; found, 346.1038. t_R: 4.44 (method A1).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-benzylpyrrolo-[3,2-*d*]pyrimidine-6-carboxylic Acid (1o). Prepared from 240 mg of the sulfone resin to yield crude product (30.2 mg, 88% pure; t_R: 12.53, method A3), which was triturated with petroleum ether to give the title compound (11.2 mg, 17%) as a beige powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.60−13.10 (br s, 1H), 11.35 (s, 1H), 7.40−7.20 (m, 3H), 7.09−7.04 (m, 3H), 6.67 (d, J = 2.6 Hz, 1H), 6.55 (dd, J = 2.6 Hz, 8.6 Hz, 1H), 6.54 (s, 1H), 5.98 (s, 2H), 3.80 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.4, 160.5, 156.0, 155.8, 150.4, 138.7, 132.2, 130.9, 129.5, 128.4, 127.1, 126.4, 117.1, 113.4, 104.9, 101.3, 99.1, 55.7, 55.5, 48.2. HRMS (*m*/*z*): calcd for $C_{22}H_{20}N_3O_6$ (MH^+), 422.1347; found, 422.1345. t_R: 5.59 (method A1).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine-6-carboxylic Acid (1p). Prepared from 270 mg of the sulfone resin to yield the title compound (28.6 mg, 49%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.81 (s, 1H), 11.23 (s, 1H), 7.06 (d, J = 8.6, 1H), 6.65 (d, J = 2.5, 1H), 6.55 (dd, J = 2.5 Hz, 8.5 Hz, 1H), 6.38 (s, 1H), 3.79 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 160.4, 156.0, 155.4, 150.8, 132.4, 130.9, 130.7, 129.9, 117.4, 113.4, 104.8, 99.1, 55.7, 55.5. HRMS (*m*/*z*): calcd for $C_{15}H_{14}N_3O_6$ (MH^+), 332.0877; found, 332.0880. t_R: 9.04 (method A4).

Pyrrolo[3,2-*d*]pyrimidine-6-carboxamides (1f−k, q−v). Portions of resins **6**−**8** (0.14−0.30 g each resin batch) were transferred to 12 separate 12-mL polypropylene tubes equipped with polyethylene frits and stopcocks, swollen in 7 mL of dry THF for 2 h, washed with THF, suspended in 2−4 mL of dry THF, and treated with 33 mol % of triphosgene (BTC) and 900 mol % of colidine for 2 min at room temperature with shaking.[16] The resins were then treated with either 400 mol % of methoxyethylamine or 400 mol % of morpholine for 2 h at room temperature with shaking. The resins were then filtered and washed with 7 mL volumes of dry DCM (4×) and dry THF (2×), and the coupling was repeated using the same conditions. The resins were then filtered, washed with 7-mL volumes of DCM (5×), and lyophilized to remove any residual solvent. The resins were carefully weighed, transferred back to the same tubes equipped with polyethylene frits and stopcocks, and subjected to sulfur oxidation with *m*-CPBA and subsequent cleavage with *t*-BuONa as described above to give crude pyrrolo[3,2-*d*]pyrimidines **1f**−**k** and **1q**−**v** in yields of 21−83% from the aminopyrrole resins and purities of 71−98%. Removal of unreacted pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acids by partitioning the crude product between sodium bicarbonate and ethyl acetate provided amide of higher purity. In addition, analytically pure amides **1g**−**k** and **1t** were isolated by HPLC.

2,4-Dioxo-3-ethyl-5-methylpyrrolo[3,2-*d*]pyrimidine-6-methoxyethylcarboxamide (1f). Prepared from 120 mg of the sulfone resin to yield crude product (12.6 mg, 90% pure; t_R: 9.60, method A4), from which a portion (6.4 mg) was washed with sodium bicarbonate as described above to give the title compound (1.2 mg, 12%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.41−11.14 (br s, 1H), 8.57 (t, J = 5.4 Hz, 1H), 6.46 (s, 1H), 4.11 (s, 3H), 3.85 (q, J = 6.9 Hz, 2H), 3.40 (m, 4H), 3.24 (s, 3H), 1.08 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3, 155.9, 150.5, 131.3, 118.3, 96.2, 70.3, 57.9, 38.5, 34.7, 33.6, 13.2. HRMS (*m*/*z*): calcd for $C_{13}H_{19}N_4O_4$ (MH^+), 295.1401; found, 295.1397. t_R: 6.32 (method A2).

2,4-Dioxo-3-ethyl-5-benzylpyrrolo[3,2-*d*]pyrimidine-6-methoxyethylcarboxamide (1g). Prepared from 120 mg of the sulfone resin to yield crude product (9.3 mg, 98% pure; t_R: 13.49, method A3), from which a portion (5.2 mg) was purified by HPLC to give the title compound (2.1 mg, 15%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.59 (t, 1H), 7.26−7.15 (m, 3H), 7.05−7.00 (m, 2H), 6.48 (s, 1H), 6.00 (s, 2H), 3.85 (q, J = 6.9 Hz, 2H), 3.40 (m, 4H), 3.20 (s, 3H), 1.07 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3, 155.7, 150.4, 139.0, 132.8, 131.9, 128.3, 127.0, 126.7, 111.6, 97.4, 70.2, 57.9, 47.8, 38.6, 34.8, 13.2. HRMS (*m*/*z*): calcd for $C_{19}H_{23}N_4O_4$ (MH^+), 371.1714; found, 371.1708. t_R: 5.38 (method A1).

2,4-Dioxo-3-ethyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-methoxyethylcarboxamide (1h). Prepared from 130 mg of the sulfone resin to yield crude product (16.7 mg, 71% pure, t_R: 7.71, method A4), from which a portion (2.2 mg) was purified by HPLC to give the title compound (1.2 mg, 45%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.59 (t, 1H), 6.47 (s, 1H), 3.85 (q, J = 6.9 Hz, 2H), 3.40 (m, 4H), 3.21 (s, 3H), 1.06 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.3, 155.2, 150.8, 132.8, 131.9, 111.9, 96.3, 70.4, 58.0, 38.7, 34.8, 13.3. HRMS (*m*/*z*): calcd for $C_{12}H_{17}N_4O_4$ (MH^+), 281.1244; found, 281.1249. t_R: 5.60 (method A2).

2,4-Dioxo-3-ethyl-5-methylpyrrolo[3,2-*d*]pyrimidine-6-morpholincarboxamide (1i). Prepared from 130 mg of the sulfone resin to yield crude product (11.0 mg, 83% pure; t_R: 8.96, method A4), from which a portion (2.7 mg) was purified by HPLC to give the title compound (1.6 mg, 30%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.26−10.89 (br s, 1H), 5.95 (s, 1H), 3.87 (q, J = 6.8 Hz,

2H), 3.84 (s, 3H), 3.58−3.54 (m, 8H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 155.6, 150.5, 133.8, 131.9, 110.7, 94.6, 66.1, 34.6, 32.9, 13.3. HRMS (*m*/*z*): calcd for $C_{14}H_{19}N_4O_4$ (MH^+), 307.1401; found, 307.1401. t_R: 6.04 (method A2).

2,4-Dioxo-3-ethyl-5-benzylpyrrolo[3,2-*d*]pyrimidine-6-morpholincarboxamide (1j). Prepared from 150 mg of the sulfone resin to yield crude product (19.0 mg, 61% pure; t_R: 10.45, method A3), from which a portion (3.8 mg) was purified by HPLC to give the title compound (2.1 mg, 33%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.23 (s, 1H), 7.32−7.22 (m, 3H), 7.08−7.05 (m, 2H), 6.02 (s, 1H), 5.65 (s, 2H), 3.87 (q, J = 6.7 Hz, 2H), 3.50 (m, 8H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 155.6, 150.4, 138.1, 133.2, 132.0, 128.6, 127.5, 127.2, 96.0, 65.6, 47.6, 34.7, 13.2. HRMS (*m*/*z*): calcd for $C_{20}H_{23}N_4O_4$ (MH^+), 383.1714; found, 383.1710. t_R: 5.16 (method A1).

2,4-Dioxo-3-ethyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-morpholincarboxamide (1k). Prepared from 145 mg of the sulfone resin to yield crude product (10.0 mg, 96% pure; t_R: 7.12, method A4), from which a portion (3.1 mg) was purified by HPLC to give the title compound (1.2 mg, 17%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.23−10.83 (br s, 1H), 6.03 (s, 1H), 3.87 (q, J = 7.0 Hz, 2H), 3.65−3.50 (m, 8H), 1.09 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 155.1, 150.8, 131.9, 131.8, 111.2, 96.1, 66.1, 34.7, 13.3. HRMS (*m*/*z*): calcd for $C_{13}H_{17}N_4O_4$ (MH^+), 293.1244; found, 293.1246. t_R: 5.43 (method A2).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-methylpyrrolo-[3,2-*d*]pyrimidine-6-methoxyethylcarboxamide (1q). Prepared from 170 mg of the sulfone resin to yield the title compound (15.5 mg, 35%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.22 (s, 1H), 8.61 (t, J = 5.3 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.55 (dd, J = 2.6 Hz, 8.5 Hz, 1H), 6.49 (s, 1H), 4.07 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.48−3.40 (m, 4H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 160.3, 156.1, 156.0, 150.6, 133.1, 132.0, 130.9, 117.3, 112.2, 104.8, 99.0, 96.4, 70.3, 58.0, 55.6, 55.5, 38.6, 33.6. HRMS (*m*/*z*): calcd for $C_{19}H_{23}N_4O_6$ (MH^+), 403.1612; found, 403.1615. t_R: 11.52 (method A4).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-benzylpyrrolo-[3,2-*d*]pyrimidine-6-methoxyethylcarboxamide (1r). Prepared from 190 mg of the sulfone resin to yield crude product (16.7 mg, 78% pure; t_R: 13.17, method A3), which was washed with sodium bicarbonate as described above to give the title compound (9.0 mg, 15%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (t, J = 5.2 Hz, 1H), 7.26−7.18 (m, 3H), 7.07 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 8.7 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 2.4 Hz, 1H), 6.52 (s, 1H), 5.94 (s, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 3.45−3.30 (m, 4H), 3.22 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.5, 160.2, 156.1, 155.9, 139.1, 132.9, 130.9, 128.3, 127.1, 126.9, 117.8, 112.0, 104.8, 99.1, 98.1, 70.2, 57.9, 55.6, 55.5, 47.8, 38.6. HRMS (*m*/*z*): calcd for $C_{25}H_{27}N_4O_6$ (MH^+), 479.1925; found, 479.1919. t_R: 5.62 (method A1).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine-6-methoxyethylcarboxamide (1s). Prepared from 265 mg of the sulfone resin to yield crude product (15.5 mg, 83% pure; t_R: 9.81, method A4) which was triturated with petroleum ether to give the title compound (7.8 mg, 12%) as a brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.35 (s, 1H), 11.30 (s, 1H), 8.50 (t, J = 4.9 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 2.4 Hz, 8.6 Hz, 1H), 6.52 (s, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.45−3.35 (m, 4H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 159.3, 156.0, 155.5, 150.9, 133.0, 132.5, 130.9, 117.5, 112.0, 104.8, 99.1, 96.5, 70.4, 58.0, 55.6, 55.5, 38.7. HRMS (*m*/*z*): calcd for $C_{18}H_{21}N_4O_6$ (MH^+), 389.1456; found, 389.1457. t_R: 6.36 (method A2).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-methylpyrrolo-[3,2-*d*]pyrimidine-6-morpholincarboxamide (1t). Prepared from 170 mg of the sulfone resin to yield crude product (9.7 mg, 86% pure; t_R: 11.01, method A4), from which a portion (3.3 mg) was purified by HPLC to give the title compound (1.3 mg, 8%) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.23 (s, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 6.55 (dd, J = 2.5 Hz, 8.7 Hz, 1H), 6.00 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.60−3.48 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 156.0, 155.8, 150.6, 134.1, 132.5, 130.9, 117.3, 110.8, 110.8, 104.8, 99.0, 94.9, 66.1, 55.7, 55.5, 38.8, 33.0. HRMS (*m*/*z*): calcd for $C_{20}H_{23}N_4O_6$ (MH^+), 415.1612; found, 415.1611. t_R: 4.14 (method A1).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5-benzylpyrrolo-[3,2-*d*]pyrimidine-6-morpholincarboxamide (1u). Prepared from 190 mg of the sulfone resin to yield crude product (14.7 mg, 90% pure; t_R: 12.75, method A3), which was washed with sodium bicarbonate as described above to give the title compound (10.3 mg, 17%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33−7.24 (m, 3H), 7.07 (d, J = 8.4 Hz, 3H), 6.67 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 2.5 Hz, 8.6 Hz, 1H), 6.08 (s, 1H), 5.65 (d, J = 15.2 Hz, 1H), 5.57 (d, J = 15.2 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.64−3.08 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 160.4, 155.9, 155.8, 150.6, 138.1, 133.4, 132.8, 131.0, 128.7, 127.6, 127.4, 117.3, 110.6, 104.8, 99.1, 96.3, 65.6, 55.7, 55.5, 47.6. HRMS (*m*/*z*): calcd for $C_{26}H_{27}N_4O_6$ (MH^+), 491.1925; found, 491.1919. t_R: 5.56 (method A1).

2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine-6-morpholincarboxamide (1v). Prepared from 270 mg of the sulfone resin to yield the title compound (17.3 mg, 24%) as a beige powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.60 (s, 1H), 11.24 (s, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 2.6 Hz, 1H), 6.55 (dd, J = 2.6 Hz, 8.6 Hz, 1H), 6.09 (s, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.64−3.54 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9, 160.4, 156.0, 155.3, 150.9, 132.4, 132.1, 130.9, 117.5, 111.2, 104.8, 99.1, 96.4, 66.1, 55.6, 55.5. HRMS (*m*/*z*): calcd for $C_{19}H_{21}N_4O_6$ (MH^+), 401.1456; found, 401.1454. t_R: 9.44 (method A4).

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Supporting Information Available. ^{1}H NMR, ^{13}C NMR, and HPLC spectra of products **1a**−**v**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Grahner, B.; Winiwarter, S.; Lanzner, W.; Muller, C. E. *J. Med. Chem.* **1994**, *37*, 1526−1534.
(2) Romeo, G.; Russo, F.; De Blasi, A. *J. Heterocycl. Chem.* **2001**, *38*, 391−395.
(3) (a) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Hanson, J. C.; Kicska, G. A.; Sauve, A. A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *46*, 155−160. (b) Bantia, S.; Miller, P. J.; Parker, C. D.; Ananth, S. L.; Horn, L. L.; Kilpatrick, J. M.; Morris, P. E.; Hutchison, T. L.; Montgomery, J. A.; Sandhu, J. S. *Int. J. Immunol. Pharmacol.* **2001**, *1*, 1199−1210. (c) Pathak, V. P. *Org. Process Res. Dev.* **2000**, *4*, 129−130.
(4) Stamford, A. W. *Ann. Rep. Med. Chem.* **2002**, *37*, 53.
(5) Heinicke, J.; Klausmeier, U. Eur. Pat. Appl., EP 1357114 A1, 2003.
(6) Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867−868.
(7) Marshall, G. R.; Flanigan, E. *Tetrahedron Lett.* **1970**, *27*, 2403−2406.
(8) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun*. **1971**, 636−637.
(9) Rombouts, F. J. R.; Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 589−598.
(10) Marcotte, F.-A.; Lubell, W. D. *Org. Lett.* **2002**, *4*, 2601−2603.
(11) Blankenship, J. W.; Lubell, W. D. Synthesis of Pyrrolo[3,2-*d*]pyrimidines for Application as Beta-Sheet Mimics. In *Peptides 2004: Proceedings of the Third International and Twenty-Eight European Peptide Symposium*, Prague, Czech Republic; Flegel, M., Fridkin, M., Gilon, C., Slaninova, J., Eds.; Kenes International: Israel, 2005; pp 746−747.
(12) Bullington, J. L.; Wolff, R. R.; Jackson, P. F. *J. Org. Chem.* **2002**, *67*, 9439−9442.
(13) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, 34, 595−598.
(14) García-Echeverría, C. *Tetrahedron Lett*. **1997**, *38*, 8933−8934.
(15) Miranda, L. P.; Lubell, W. D.; Halkes, K. M.; Groth, T.; Grøtli, M.; Rademann, J.; Gotfredsen, C. H.; Meldal, M. *J. Comb. Chem*. **2002**, *4*, 523−529.
(16) Falb, E.; Yechezkel, T.; Salitra, Y.; Gilon, C. *J. Pept. Res*. **1999**, *53*, 507−517.
(17) Gisin, B. F. *Anal. Chim. Acta* **1972**, 248−249.
(18) In *CRC Handbook of Chemistry and Physics*, 48th ed.; Weast, R. C., Ed.; The Chemical Rubber Co.: Cleveland, 1967; p C-325.

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