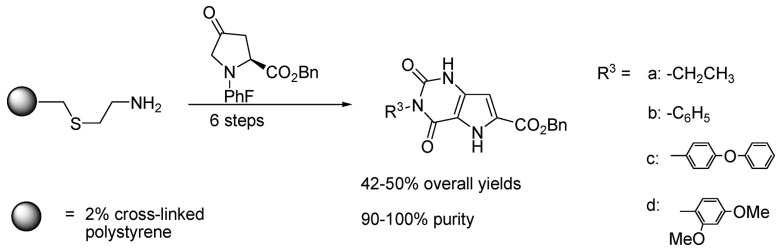
JOURNAL OF combinatorial CHEMISTRY

Article

Deazapurine Solid-Phase Synthesis: Construction of 3-Substituted Pyrrolo[3,2-*d*]pyrimidine-6-carboxylates on Cross-Linked Polystyrene Bearing a Cysteamine Linker

Frederik J. R. Rombouts, Gil Fridkin, and William D. Lubell

J. Comb. Chem., **2005**, 7 (4), 589-598• DOI: 10.1021/cc050002l • Publication Date (Web): 01 June 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Deazapurine Solid-Phase Synthesis: Construction of 3-Substituted Pyrrolo[3,2-*d*]pyrimidine-6-carboxylates on Cross-Linked Polystyrene Bearing a Cysteamine Linker

Frederik J. R. Rombouts, Gil Fridkin, and William D. Lubell*

Département de chimie, Université de Montréal, C.P. 6128, Succursale Centre Ville, Montréal, Québec, Canada H3C 3J7

Received January 6, 2005

The first solid-phase methodology for the preparation of pyrrolo[3,2-*d*]pyrimidines is presented. Merrifield resin bearing a cysteamine "traceless" linker was treated with 4-oxo-*N*-(PhF)proline benzyl ester (**10**; PhF = 9-(9-phenylfluorenyl)) to provide resin-bound aminopyrrole **20**, which was treated with ethyl, phenyl, 4-phenoxyphenyl, and 2,4-dimethoxyphenyl isocyanates to furnish resin-bound ureidopyrroles **21a**−**d**. Resin-bound pyrrolo[3,2-*d*]pyrimidines **22a**−**d** were then obtained by acylation of **21** using trichloroacetyl chloride in dioxane followed by treatment with Cs_2CO_3 in DMF. Cleavage of pyrrolo[3,2-*d*]pyrimidines **22a**−**d** from the resin was achieved in two steps, by oxidation of the sulfur to the sulfone followed by β-elimination in the presence of *t*-BuONa. Four pyrrolo[3,2-*d*]pyrimidines, **24a**−**d**, with different alkyl and aryl substituents at the N3 pyrimidine nitrogen, were thus obtained in overall yields of 42−50% and purities of 90−100%.

Introduction

The key roles purines and pyrimidines play in cellular processes have made them valuable leads for drug discovery. Pyrrolo[3,2-*d*]pyrimidines, a class of deazapurine analogues, exhibit for instance interesting biological activity in part due to their resemblance to pyrimidines and purines. For example, phenyl-substituted deazaxanthines **1** (R^1, R^3 = alkyl, R^6 = Ph, Figure 1) exhibit antagonistic activity and moderate selectivity for the A_1- and A_2-adenosine receptors.[1,2] Deazapurine-based C-nucleosides, such as immucilin-H (**2**) and the (pyridinylmethyl)deazapurine peldesine (**3**), are potent purine nucleoside phosphorylase inhibitors that exhibit potential for the treatment of T-cell-dependent diseases, such as T-cell leukemia.[3] Several pyrimido[5,4-*b*]indole-2,4-diones **4** have shown antagonist activity at the α_1-adrenoceptors, some exhibiting selectivity for the α_{1D} subtype.[4] 6-Piperidyl-8-phenyl-9-deazapurine **5** was identified from a high-throughput screen as a potent neuropeptide Y5 receptor antagonist and lead compound for the development of novel antiobesity drugs.[5] Pyrrolopyrimidinone **6** inhibited phosphodiesterase with subnanomolar activity.[6] Pyrrolotriazolopyrimidines of type **7**, which were prepared from the corresponding pyrrolo[3,2-*d*]pyrimidines, were also recently claimed as phosphodiesterase 5 inhibitors.[7] 3-(2,3-Dimercaptopropyl)-substituted pyrrolo[3,2-*d*]pyrimidines **8** have been claimed as matrix metalloproteinase inhibitors.[8] Finally, 4-(pyrrolopyrimidin-6-yl)benzenesulfonamide derivatives **9** have been claimed as novel selective A_{2A}/A_{2B} antagonists.[9]

Their potential medicinal applications have inspired many solution-phase approaches for making specific examples and libraries of pyrrolopyrimidines. No solid-phase methodology exists, however, for the synthesis of pyrrolo[3,2-*d*]pyrimidine derivatives which could allow for the generation of large libraries of diverse analogues for screening against various biological targets.

Purine scaffolds have been modified on a solid support. For example, four 2,6,9-trisubstituted purine derivatives were synthesized on an amine resin by attachment of 2-fluoro-6-chloropurine, subsequent alkylation at C9, displacement of the fluoride by various amines, and cleavage using TFA (Figure 2A).[10] Resin-bound amine capture of N9-alkylated 2-fluoro-6-(phenylsulfenyl)purines, which were obtained from crude N9 alkylation reactions, gave C2-resin-bound N9-alkylated 6-(phenylsulfenyl)purines. After oxidation of the thioether to a sulfone, the purines were substituted by different amines at the C6 position and cleaved with TFA to prepare a library of 1000 trisubstituted analogues in a 96-well format (Figure 2B).[11] 2,6,9-Trisubstituted purines were synthesized by a resin capture and release strategy featuring the capture of 2-fluoro-6-chloro-9-alkylpurines with a (mercaptomethyl)polystyrene resin, fluoride displacement with primary and secondary amines, thioether oxidation, and release from the resin by C6 substitution with amines and anilines (Figure 2C).[12] In addition, a set of 10 purines substituted at the 8- and 9-positions were made from attachment of 4,6-dichloro-5-nitropyrimidine to Rink amide resin, chloride displacement, and nitro group reduction to furnish diaminopyrimidines that were converted to purines by three different routes, prior to resin cleavage using TFA.[13]

Solid-phase methodology has also been reported for preparing libraries of pyrimidine derivatives. For example, 2,4,6-trisubstituted pyrimidines were synthesized by condensation of a resin-bound thiouronium salt with acetylenic ketones to form pyrimidinecarboxylates that were cleaved

* To whom correspondence should be addressed. Phone: (514) 934-1459. Fax: (514) 343-7586. E-mail: lubell@chimie.umontreal.ca.

10.1021/cc050002l CCC: $30.25
Published on Web 06/01/2005

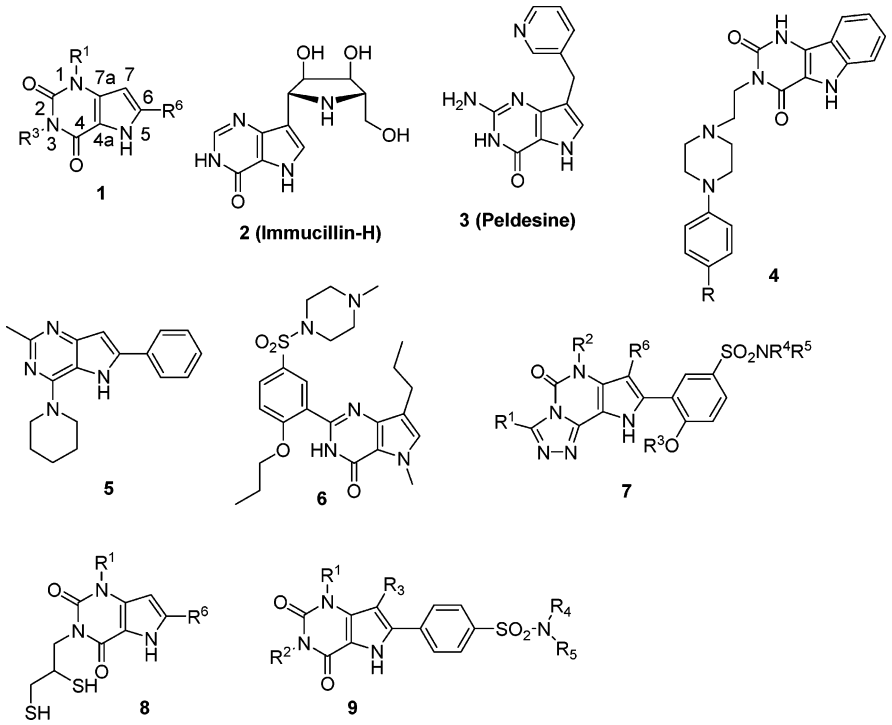


Figure 1. Representative examples of biologically active pyrrolo[3,2-*d*]pyrimidines.

from the resin by oxidation of the sulfur to the corresponding sulfone followed by displacement with amines. Resin-bound pyrimidinecarboxylates were later subjected to a Ugi four-component condensation to produce pyrimidinecarboxamides, which were similarly cleaved by oxidation to the sulfone and nucleophilic displacement (Figure 2D).[14] Libraries of furo[3,4-*d*]pyrimidines, pyrrolo[3,4-*d*]pyrimidines, and pyrimido[4,5-*d*]pyridazines have also been synthesized by a microwave-promoted Biginelli-type condensation employing urea, aromatic aldehydes, and 4-[(chloroacetoacetoxy)-methyl]polystyrene resin, followed by three different cyclative cleavage strategies with microwave heating, to produce the desired heterocyclic products (Figure 2E).[15]

In contrast to the abundant solid-phase methodologies for the preparation of purines and pyrimidines, the solid-phase synthesis of pyrrolo[3,2-*d*]pyrimidine libraries has not been explored, to the best of our knowledge. In light of their biological activity, and that of related purine and pyrimidine hetrocycles, solid-phase methodology for the preparation of pyrrolo[3,2-*d*]pyrimidines merited study.

Pyrrolo[3,2-*d*]pyrimidine solid-phase synthesis was expected to proceed as in our solution-phase strategy, in which the pyrimidine ring was constructed onto a 4-aminopyrrole-2-carboxylate prepared from hydroxyproline (Scheme 1).[16] An effective linking strategy was necessary for attaching the 4-aminopyrrole-2-carboxylate to the resin prior to an acylation step using different isocyanates to introduce diversity at the N3 pyrimidine nitrogen. A cysteamine linking strategy has now been developed to adapt our solution-phase protocol to the solid phase. Potential for further diversity to be introduced by alkylation and modification of the pyrrole nitrogen and carboxylate was expected to enlarge the library of pyrrolopyrimidines that could be made by this process. In this paper, we demonstrate the first solid-phase synthesis of pyrrolo[3,2-*d*]pyrimidine by the synthesis of four analogues. In a following paper, the expansion of the pyrrolo-[3,2-*d*]pyrimidine library to include N5- and C6-modified analogues will be presented.

Results and Discussion

Solid-phase synthesis of pyrrolo[3,2-*d*]pyrimidines was demonstrated by the preparation of four examples with different substituents at the N3 position on Merrifield resin modified with a cysteamine linker. As in our four-step solution-phase pyrrolo[3,2-*d*]pyrimidine synthesis protocol, 4-oxo-*N*-(PhF)proline benzyl ester (**10**; PhF = 9-(9-phenylfluorenyl)) was treated with a primary amine to obtain a 4-aminopyrrole-2-carboxylate, which was acylated with various isocyanates to produce 4-ureidopyrroles. The pyrrolo-[3,2-*d*]pyrimidine products were obtained by a haloform reaction sequence featuring acylation with trichloroacetyl chloride and cyclization in the presence of Cs_2CO_3.[16] Considering various strategies for adapting the solution-phase method to a solid-phase approach, we found that an amino resin would react with 4-oxo-*N*-(PhF)prolinate **10** to provide resin-bound 4-aminopyrrole-2-carboxylate **20**. Merrifield resin bearing a cysteamine "traceless" linker was selected because similar sulfur-containing linkers have been proven effective in solid-phase organic[17,18] and peptide[19,20] synthesis. Oxidation of the sulfur to the sulfone followed by β-elimination was predicted to liberate pyrrolo[3,2-*d*]pyrimidine product from the resin.

The feasibility of the synthesis and cleavage of pyrrolo-[3,2-*d*]pyrimidine from the cysteamine linker was first tested in solution. 4-Oxo-*N*-(PhF)prolinate **10** was treated with 400 mol % *S*-benzylcysteamine hydrochloride in the presence of 400 mol % DIEA in THF or MeCN as solvent to yield pyrrole **11** in 72% and 95% yields, respectively (Scheme 1). 4-{[(Benzylthio)ethyl]amino}pyrrole **11** was acylated with phenyl and ethyl isocyanate to provide ureas **12** and **13** in

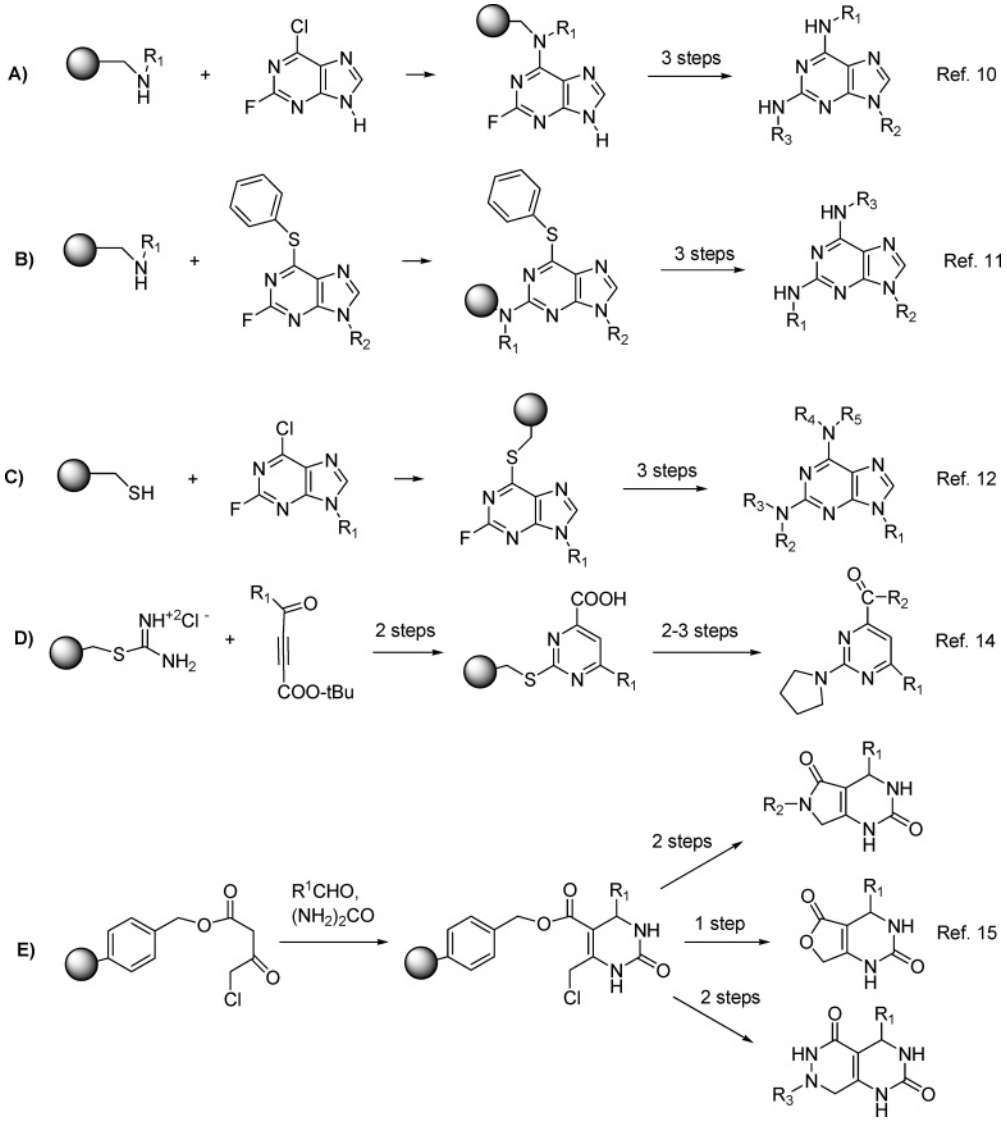
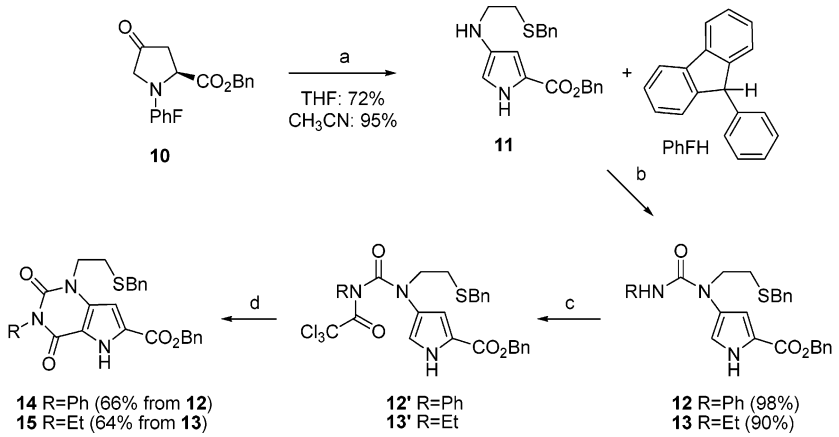


Figure 2. Representative solid-phase syntheses of substituted purine and pyrimidine derivatives.

Scheme 1. Solution-Phase Synthesis of *N*-[(Benzylthio)ethyl]pyrrolopyrimidines **14** and **15**[a]

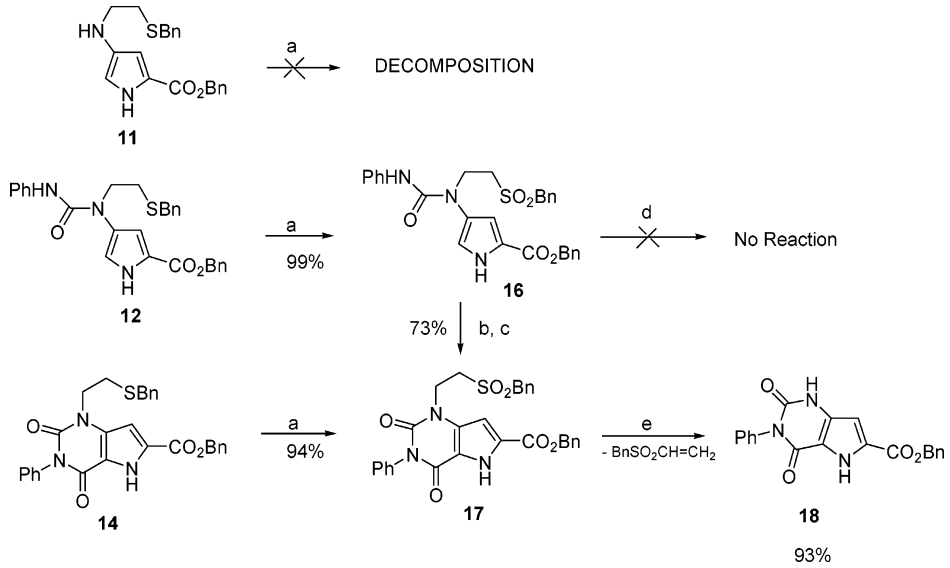


[a] Conditions and reagents: (a) 400 mol % $BnSCH_2CH_2NH_3Cl$, 400 mol % DIEA, THF or MeCN, 50 °C, 4 h; (b) 105 mol % isocyanate, CH_2Cl_2, room temperature, 1−2 h; (c) 1000 mol % Cl_3CCOCl, MeCN, reflux, 3 h; (d) 1000 mol % Cs_2CO_3, MeCN, 1 h (**14**) to overnight (**15**).

98% and 90% respective yields after chromatography. Conversion of ureidopyrroles **12** and **13** to the corresponding pyrrolo[3,2-*d*]pyrimidines **14** and **15** was subsequently effected by acylation with trichloroacetyl chloride and cyclization in the presence of cesium carbonate.

Sulfur oxidation to sulfone and elimination of benzyl vinyl sulfone were examined using aminopyrrole **11**, ureidopyrrole **12**, and pyrrolopyrimidine **14** to assess the ease of releasing pyrrole products at different stages of the solid-phase reaction pathway (Scheme 2). As inferred from TLC monitoring,

Scheme 2. Oxidation of Thioethers and β-Elimination of Sulfones[a]



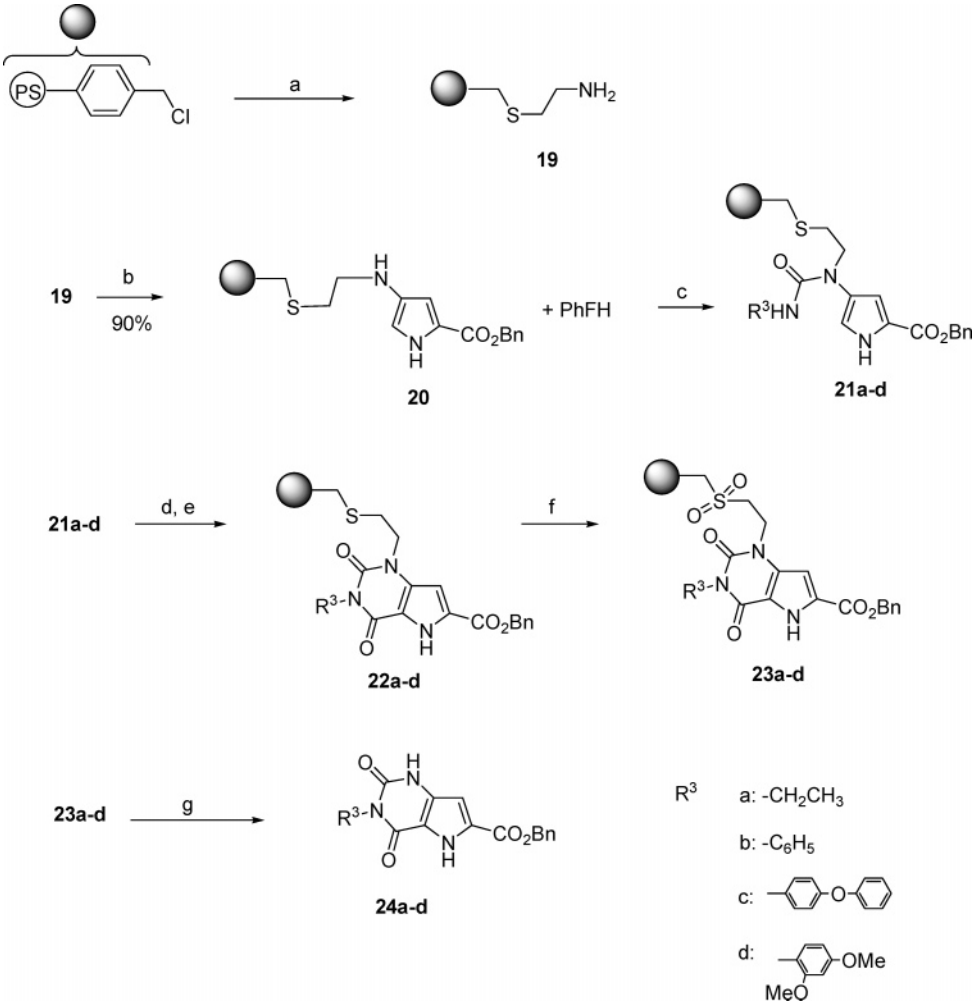
[a] Conditions and reagents: (a) 250 mol % *m*-CPBA, CH_2Cl_2, 0 °C to room temperature, 30 min; (b) 1000 mol % Cl_3CCOCl, MeCN, reflux, 3 h; (c) 1000 mol % Cs_2CO_3, MeCN, 1 h; (d) 1000 mol % *t*-BuONa, THF, 0 °C, 75 min; (e) 500 mol % *t*-BuONa, THF, 0 °C, 15 min.

pyrrole **11** decomposed completely when treated with 250 mol % *m*-CPBA at 0 °C, indicating that pyrrole liberation could not be performed at this stage. On the other hand, ureidopyrrole **12** and pyrrolo[3,2-*d*]pyrimidine **14**, which have pyrrole substituents possessing decreased electron-donating capacity, were quantitatively oxidized to the corresponding sulfones **16** and **17** under the same conditions. Furthermore, oxidized urea **16** was also converted efficiently to pyrrolopyrimidine **17** using trichloroacetyl chloride and Cs_2CO_3 (Scheme 2). Elimination of benzyl vinyl sulfone ($pK_{a(DMSO)}(Et_2SO_2) = 32.8$)[21] from ureidopyrole **16** and pyrrolopyrimidine **17** was conducted employing sodium *tert*-butoxide ($pK_{a(DMSO)}$(*t*-BuOH) = 32.2)[22] as a nonnucleophilic base, to avoid reactions on sensitive functions, such as hydrolysis of the benzyl ester. The more hygroscopic potassium *tert*-butoxide caused partial ester hydrolysis. Although urea **16** was treated with up to 1000 mol % sodium *tert*-butoxide in THF at 0 °C, after 1.25 h, ^{1}H NMR spectroscopy and MS analysis showed that the starting material was recovered unchanged. Apparently, deprotonation of trisubstituted urea **16** may render the dianion as a poor leaving group for β-elimination of the vinyl sulfone. This result indicated that, like the 4-aminopyrrole, the 4-ureidopyrrole could not be liberated from the resin. On the contrary, when sulfone **17** was treated with 500 mol % *tert*-butoxide in THF at 0 °C, the reaction was complete after 15 min and pyrrolo[3,2-*d*]pyrimidine **18** was obtained in 93% yield after isolation and crystallization from chloroform (Scheme 2). Earlier attempts to use only 200 mol % *tert*-butoxide gave no reaction. Apparently, prior to elimination 1 equiv of base was consumed by pyrrole deprotonation and another by deprotonation of the more acidic methylene protons between the phenyl and sulfone groups ($pK_{a(DMSO)}$-($MeSO_2CH_2Ph$) = 25.4).[23] The feasibility of the linker strategy was thus demonstrated in solution.

Cysteaminopolystyrene resin was prepared by treating Merrifield resin ((chloromethyl)polystyrene, 1−1.5 mequiv/g, 2% DVB) with 2-aminoethanethiolate in DMF for 2 days at room temperature (Scheme 3). Substitution was monitored qualitatively by the ninhydrin test (instant positive) and quantitatively by the picric acid test, which gave an amine loading of 0.99 mmol/g. In addition, the FT-IR spectrum of resin **19** (KBr pellets) showed no band at 2600−2550 cm^{-1} for free thiol, suggesting that only thiolate displacement of the chloride occurred and all amines were primary (Figure 3a).

Pyrrolo[3,2-*d*]pyrimidine synthesis on resin commenced by preparation of resin-bound 4-aminopyrrole-2-carboxylate **20** by treating cysteamine resin **19** with 4-oxo-*N*-(PhF)-prolinate **10**, Et_3N, and Et_3N·HBr in a 1:1 mixture of THF/MeCN for 24 h at 50 °C (Scheme 3). On the solid phase, less 4-oxo-*N*-(PhF)prolinate (200 mol %) was employed relative to that employed in solution and 1:1 THF/MeCN was used as a solvent, instead of MeCN, to improve resin swelling. Qualitative monitoring of the solid-phase chemistry was performed using FT-IR spectroscopy of the resin in KBr pellets. The FT-IR spectrum of aminopyrrole resin **20** exhibited a large ester carbonyl peak around 1700 cm^{-1}, which correlated well with the spectrum of pyrrole **11**, which was made in solution (Figure 3). Measuring the amount of recovered 9-phenylfluorene (PhFH) after evaporation of the resin filtrate and chromatography suggested 90% conversion of the amine to pyrrole **20**. On the basis of recovered PhFH, the resin loading was calculated to be 0.76 mmol/g. Unreacted 4-oxo-*N*-(PhF)prolinate **10** was also recovered after column chromatography of the resin filtrate and could be recycled. Ureidopyrroles **21a**−**d** were prepared using different isocyanates after pyrrole resin **20** was split into four vessels (Scheme 3). Ethyl, phenyl, 4-phenoxyphenyl, and 2,4-dimethoxyphenyl isocyanates were obtained from commercial sources and used in excess (400 mol %) to demonstrate the effectiveness of our method to produce pyrrolopyrimidines with alkyl and aryl N3 substituents. Qualitative assessment of the acylation reaction and urea formation was judged by a negative ninhydrin test and the appearance of a second carbonyl peak in the FT-IR spectra

Scheme 3. Solid-Phase Synthesis of Pyrrolopyrimidines[a]



[a] Conditions and reagents: (a) 300 mol % 2-aminoethanethiol hydrochloride, 1000 mol % NaH, DMF, 48 h at room temperature; **(**b) 200 mol % **10**, 680 mol % Et_3N, 20 mol % Et_3N·HBr, 50 °C, THF/MeCN (50:50), 24 h; (c) 400 mol % R^3NCO, CH_2Cl_2, rt, overnight; (d) 1000 mol % Cl_3CCOCl, dioxane, 70°, 4 h; (e) 1000 mol % Cs_2CO_3, DMF, overnight; (f) 500 mol % *m*-CPBA, CH_2Cl_2, room temperature, 1 h; (g) 1000 mol % *t*-BuONa, THF, 0 °C, 1 h.

of the four resins. This new peak correlated with the urea carbonyl absorption that was previously observed in the FT-IR spectrum of ureidopyrrole **12**, which was made in solution (Figure 4). Resin-bound pyrrolo[3,2-*d*]pyrimidines **22a**−**d** were synthesized from ureas **21a**−**d** by a two-step process adapted from the solution-phase protocol (Scheme 3). To improve swelling, acetonitrile was replaced by dioxane in the trichloroacetylation step and by DMF in the Cs_2CO_3 cyclization. After reaction of ureas **21a**−**d** with 1000 mol % trichloroacetyl chloride in dioxane at 70 °C for 4 h, the resin was washed with dioxane and DMF, and subsequently stirred overnight in the presence of 1000 mol % powdered and dried Cs_2CO_3 in DMF. A third carbonyl peak was observed in the FT-IR spectra of the dried resins, which were similar to the spectrum of pyrrolopyrimidine **14** (Figure 5).

Pyrrolopyrimidines **22a**−**d** were cleaved from the resin in two steps, as in solution. Sulfur oxidation was performed using *m*-CPBA in DCM (Scheme 3). The resins' appearance turned from brown and lumpy to yellow and granular. The FT-IR spectra (not shown) of resins **23a**−**d** from oxidation were, however, similar to those of resins **22a**−**d** and to that of sulfone **17**, which was made in solution. The FT-IR spectra of **23a**−**d** indicated the presence of an appreciable amount of OH stretch at 3415 cm^{-1}, originating likely from water present in the *m*-CPBA or the ethanol which was used for washing. Accordingly, the resins were lyophilized before the cleavage step to ensure accurate weighing and to avoid hydrolysis or trans esterification. Pyrrolo[3,2-*d*]pyrimidines **23a**−**d** were cleaved from the resin using 1000 mol % sodium *tert*-butoxide in THF for 1 h at 0 °C. The resin was then filtered and washed, and the filtrate and washings were added to a saturated aqueous ammonium chloride solution and extracted with DCM and EtOAc. Final evaporation and crystallization from ethanol yielded pure (>90%) pyrrolo-[3,2-*d*]pyrimidines **24a**−**d** in 42−50% yields.

Conclusion

The first synthesis of pyrrolo[3,2-*d*]pyrimidines on a solid phase has been accomplished using Merrifield resin bearing a traceless cysteamine linker and 4-oxo-*N*-(PhF)proline **10** as 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%. Chemical modification of resin-bound pyrrolo[3,2-*d*]pyrimidines **22a**−**d** at the pyrrole nitrogen and carboxylate should allow greater diversity to be added onto the parent heterocycle for the synthesis of diverse libraries of pyrrolo-[3,2-*d*]pyrimidines with different substituents at positions 3,

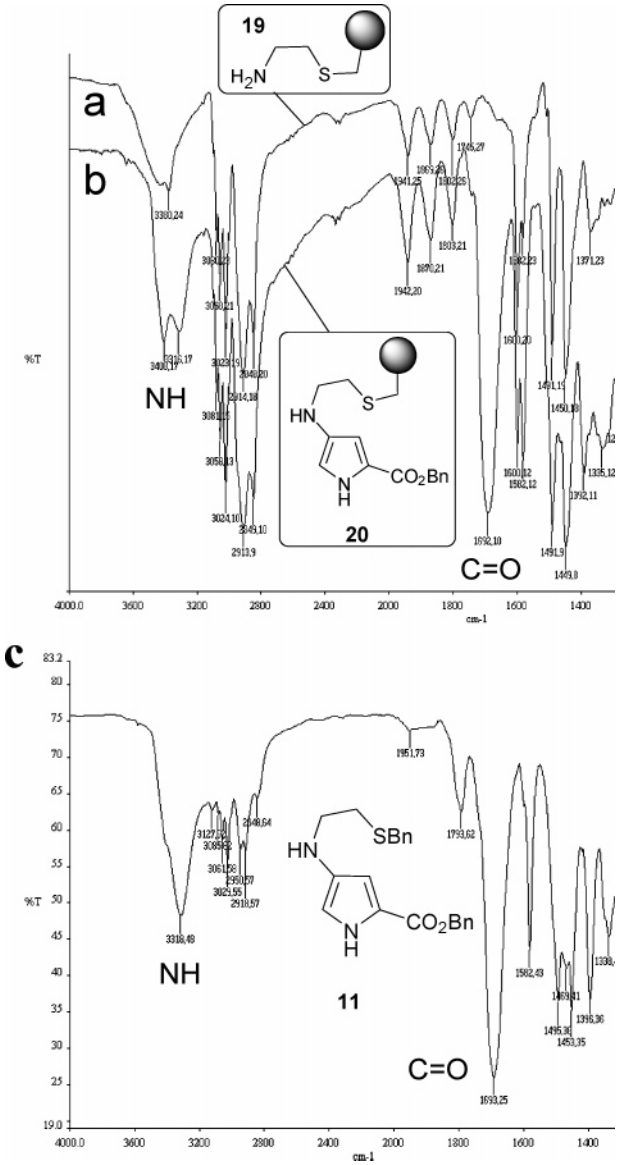


Figure 3. FT-IR spectra of cysteamine polystyrene resin **19** before (a) and after (b) reaction with **10** and that of (c) pyrrole **11**.

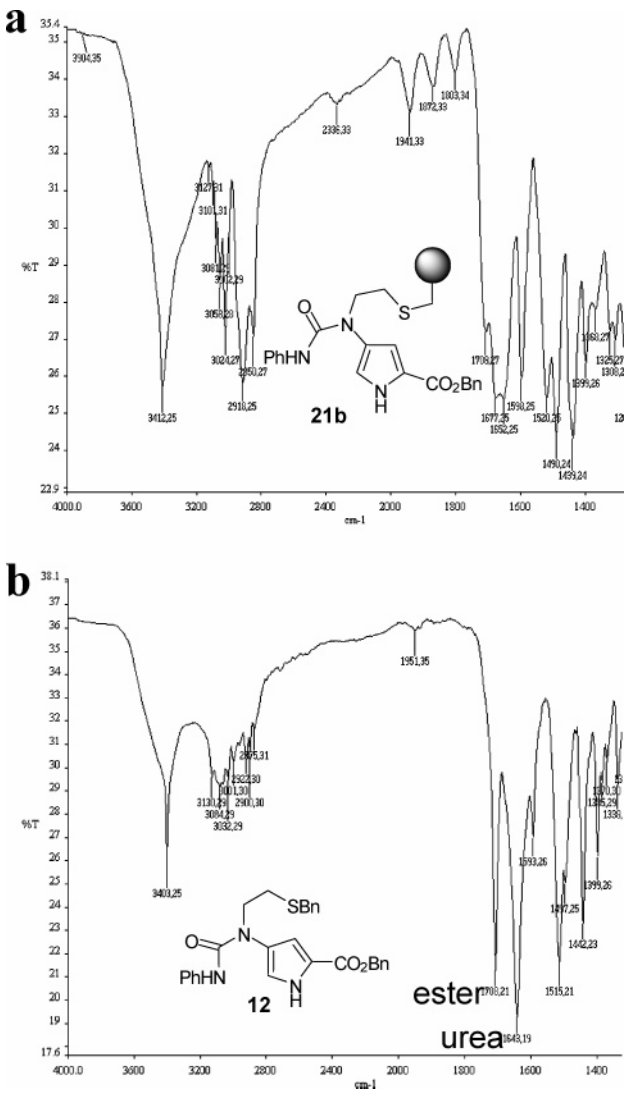


Figure 4. FT-IR spectra of (a) resin-bound urea **21b** and (b) urea **12**.

5, and 6. In light of the importance of purine and pyrimidine analogues in biological systems, this solid-phase synthesis of pyrrolopyrimidines offers significant potential for delivering libraries of active compounds.

Experimental Section

General Procedures. Anhydrous solvents (THF, CH_3CN, CH_2Cl_2, and DMF) were obtained by passage through solvent filtration systems (GlassContour, Irvine, CA). Trichloroacetyl chloride was distilled from quinoline. Solution-phase chemistry was performed under Ar. 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 $CDCl_3$, DMSO-d_6, or CD_3OD at 400/300 MHz and referenced to the peak for internal tetramethylsilane (0.00 ppm) except those for **18**, **24a**, and **24b**, which were referenced to the peak for residual CHD_2SOCD_3 (2.50 ppm). ^{13}C NMR spectra were measured in $CDCl_3$, 100/75 MHz, and referenced to $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm), or CD_3OD (48.0 ppm). Chromatography was performed using 230−400 mesh silica gel. Infrared spectra were taken on a PerkinElmer Spectrum One apparatus. Mass spectral data were obtained by the Université de Montréal mass spectrometry facility. Accurate mass measurements (HRMS) were performed either by the FAB technique with benzyl alcohol as internal reference or on an LC-MSD-Tof instrument (Agilent Technologies) using positive electrospray. Either protonated molecular ions (MH^+) or sodium adducts (MNa^+) were used for empirical formula confirmation.

Benzyl 4-{[2-(Benzylsulfanyl)ethyl]amino}-1*H*-pyrrole-2-carboxylate (11). A stirred solution of 4-oxo-*N*-PhF-prolinate **10** (300 mg, 0.653 mmol, prepared according to ref 24) in 30 mL of THF was treated with 400 mol % *S*-benzylcysteamine hydrochloride followed by 400 mol % DIEA, heated to 50 °C, stirred for 4 h, and treated with a solution of saturated aqueous NH_4Cl, followed by 30 mL of EtOAc. The layers were separated, and the aqueous layer was subsequently extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to a residue that was purified by column chromatography (silica gel, gradient of 20−40%

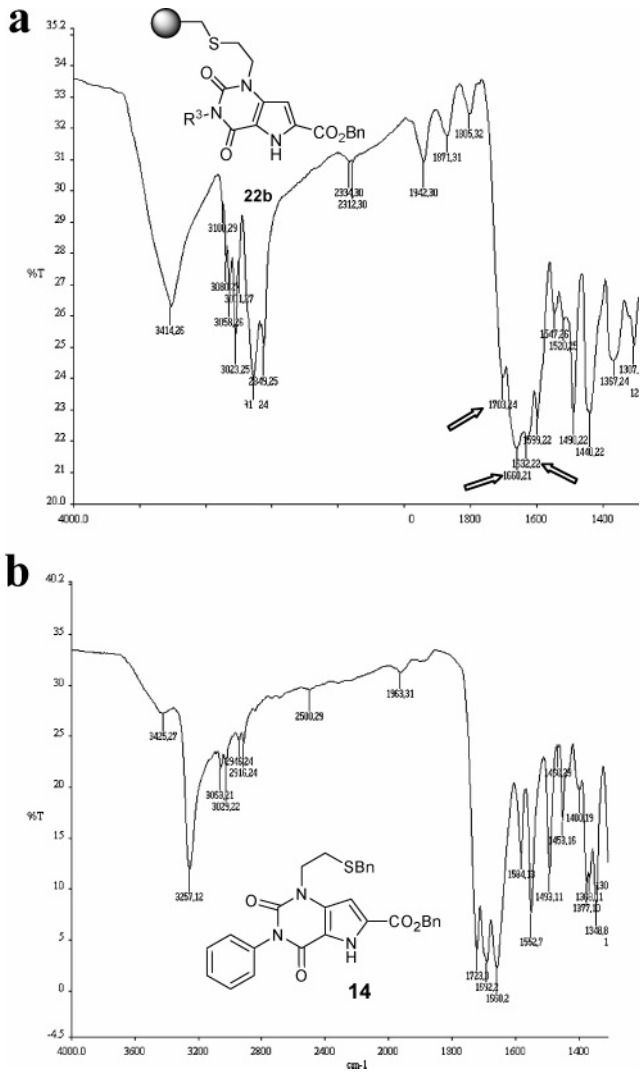


Figure 5. FT-IR spectra of (a) resin-bound pyrrolo[3,2-*d*]pyrimidine **22b** and (b) pyrrolopyrimidine **14**.

EtOAc/hexanes). Evaporation of the collected fractions yielded the pyrrole as a brown oil. Yield: 72%. IR (NaCl, cm^{-1}): 3318 (NH), 1693 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 7.41−7.22 (m, 10H), 6.47 (dd, J = 2.6, 1.9 Hz, 1H), 6.36 (dd, J = 2.8, 1.9 Hz, 1H), 5.27 (s, 2H), 3.70 (s, 2H), 3.10 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 138.2, 136.5, 136.2, 128.8, 128.5, 128.15, 128.11, 127.1, 120.7, 108.5, 104.7, 65.9, 45.7, 35.9, 31.0. HRMS (*m*/*z*): calcd for $C_{21}H_{22}N_2O_2S$ (MH^+), 367.1480; found, 367.1470.

General Procedure A: Preparation of Ureidopyrroles from 4-Aminopyrroles. A solution of aminopyrrole **11** (0.54 mmol) in dry CH_2Cl_2 was treated with 105 mol % isocyanate, stirred for 2 h at room temperature, and evaporated. The residue was purified by column chromatography (silica gel, gradient of EtOAc in hexanes).

i. Benzyl 4-{1-[2-(Benzylsulfanyl)ethyl]-3-phenylureido}-1*H*-pyrrole-2-carboxylate (12). The title compound was prepared from aminopyrrole **11** and phenyl isocyanate using general procedure A. Yield: 98%. White crystals (EtOAc/hexanes). Mp: 101.0−101.4 °C. IR (KBr, cm^{-1}): 3403 (NH), 1708, 1643 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.42−6.85 (m, 14H), 6.98 (t, J = 7.3 Hz, 1H), 6.87 (dd, J = 3.1, 1.7 Hz, 1H), 6.84 (dd, J = 2.6, 1.8 Hz, 1H), 6.52 (s, 1H), 5.33 (s, 2H) 3.78 (t, J = 7.2 Hz, 2H), 3.71 (s, 2H), 2.60 (t, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 154.6, 138.6, 138.2, 135.5, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 126.9, 126.0, 123.0, 122.5, 121.2, 119.5, 113.7, 66.6, 48.4, 35.6, 29.1. HRMS (*m*/*z*): calcd for $C_{28}H_{28}N_3O_3S$ (MH^+), 486.1851; found, 486.1840. Anal. Calcd for $C_{28}H_{27}N_3O_3S$: C, 69.11; H, 5.80; N, 8.64. Found: C, 68.97; H, 5.66; N, 8.59.

ii. Benzyl 4-{1-[2-(Benzylsulfanyl)ethyl]-3-ethylureido}-1*H*-pyrrole-2-carboxylate (13). The title compound was prepared from aminopyrrole **11** and ethyl isocyanate using general procedure A. Yield: 90%. White crystals (Et_2O). Mp: 93.5−93.8 °C. IR (KBr, cm^{-1}): 3401, 3117 (NH), 1716, 1627 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.44−7.15 (m, 10H), 6.86 (dd, J = 3.1, 1.7 Hz, 1H), 6.77 (dd, J = 2.6, 1.7 Hz, 1H), 5.33 (s, 2H), 4.48 (s (br t), 1H), 3.72 (t, J = 7.4 Hz, 2H), 3.72 (s, 2H), 3.19 (m (br dq), 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 157.2, 138.3, 135.6, 128.9, 128.7, 128.5, 128.41, 128.39, 126.9, 126.8, 122.2, 120.8, 113.8, 66.5, 48.3, 35.6, 35.5, 29.3, 15.5. HRMS (*m*/*z*): calcd for $C_{24}H_{28}N_3O_3S$ (MH^+), 438.1851; found, 438.1831.

General Procedure B: Preparation of Pyrrolo[3,2-*d*]-pyrimidines from Ureidopyrroles. A solution of urea (0.20 mmol) in 10 mL of dry acetonitrile was treated with 1000 mol % distilled trichloroacetyl chloride, heated at reflux for 3 h, cooled to room temperature, and quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under vacuum to obtain crude acetylated compounds **12′** and **13′**, which were each redissolved in 10 mL of dry MeCN and stirred in the presence of 1000 mol % Cs_2CO_3 for 1 h or overnight, respectively. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the aqueous phase was extracted with 3 × 20 mL of ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvent yielded the crude pyrrolo[3,2-*d*]-pyrimidine, which was crystallized from toluene. An additional crop may be obtained by adding hexanes.

i. Benzyl 2,4-Dioxo-1-[2-(Benzylsulfanyl)ethyl]-3-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (14). The title compound was prepared from **12** using general procedure B. The (trichloroacetyl)ureidopyrrole was characterized as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.3 (s, 1H), 7.36 (m, 5H), 7.20 (m, 8H), 6.94 (s (br), 2H), 6.64 (s, 1H), 6.44 (s, 1H), 5.29 (s (br), 2H), 3.70 (s (br t), 2H), 3.64 (s, 2H), 2.54 (s (br t), 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 160.9, 154.6, 137.6, 137.3, 135.3, 128.7, 128.5, 128.3, 128.0, 127.2, 126.9, 125.0, 120.8, 113.1, ∼95.0 (CCl_3, br), 92.0, 66.4, 60.7, 50.6, 35.4, 27.5, 21.0, 14.0. Pyrrolopyrimidine **14** was isolated in 66% yield as yellow crystals. Mp: 164.2−166.6 °C. IR (KBr, cm^{-1}): 3257 (NH), 1723, 1692, 1660 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.50−7.23 (m, 15H), 6.54 (d, J = 2.4 Hz, 1H), 5.37 (s, 2H), 4.03 (t, J = 7.2 Hz, 2H), 3.77 (s, 2H), 2.78 (t, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 155.4, 151.1, 137.9, 135.2, 134.9, 134.0, 129.4, 128.9, 128.83, 128.77,

128.7, 128.60, 128.55, 128.2, 127.2, 113.7, 99.5, 67.5, 45.3, 36.4, 28.6. HRMS (*m*/*z*): calcd for $C_{29}H_{26}N_3O_4S$ (MH^+), 512.1644; found, 512.1654.

ii. Benzyl 2,4-Dioxo-1-[2-(Benzylsulfanyl)ethyl]-3-ethyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (15). The title compound was prepared from **13** using general procedure B. The trichloroacetyl ureidopyrrole was characterized as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.41−7.17 (m, 10H), 6.91 (s, 1H), 6.78 (s, 1H), 5.32 (s (br), 2H), 3.79 (s (br), 2H), 3.70 (s, 2H), 3.61 (s (br), 2H), 2.61 (t, J = 7.3 Hz, 2H), 1.15 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 160.6, 154.8, 137.8, 135.5, six phenyl CH groups not distinguishable from impurity, 125.1, 121.3, 112.4, CCl_3 not resolved, 92.1, 66.5, 50.2, 44.1, 35.6, 27.7, 12.6. Pyrrolopyrimidine **15** was isolated in 64% yield as white crystals. Mp: 151.6−152.2 °C. IR (KBr, cm^{-1}): 3196 (NH), 1735, 1698, 1657 (C═O). ^{1}H NMR (400 MHz, $CDCl_3$): 9.97 (s, 1H), 7.46−7.19 (m, 10H), 6.47 (d, J = 2.4 Hz, 1H), 5.37 (s, 2H), 4.09 (q, J = 7.0 Hz, 2H), 4.00 (t, J = 7.2 Hz, 2H), 3.77 (s, 2H), 2.74 (t, J = 7.5 Hz, 2H), 1.25 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.0, 155.3, 150.7, 137.9, 135.0, 133.5, 128.9, 128.80, 128.77, 128.7, 128.6, 127.7, 127.2, 113.7, 99.3, 67.4, 45.2, 36.8, 36.4, 28.5, 13.2. HRMS (*m*/*z*): calcd for $C_{25}H_{26}N_3O_4S$ (MH^+), 464.1644; found, 464.1646.

General Procedure C: Oxidation of the Sulfides to the Corresponding Sulfones. A solution of sulfide (0.45 mmol) in 20 mL of dry CH_2Cl_2 was treated with 250 mol % *m*-CPBA (85%), stirred for 30 min at room temperature, and subsequently quenched with 20 mL of saturated $NaHCO_3$ in water. The aqueous layer was extracted 3-fold with CH_2Cl_2, and the organic layers were combined, washed with brine, and dried over $MgSO_4$. Purification by flash column chromatography (silica gel, EtOAc/hexanes) yielded the pure sulfones.

i. Benzyl 4-{1-[2-(Benzylsulfonyl)ethyl]-3-phenylureido}-1*H*-pyrrole-2-carboxylate (16). The title compound was prepared from **12** using general procedure C and isolated in 99% yield as white crystals (EtOAc/hexanes). Mp: 162.0−163.0 °C. IR (cm^{-1}, KBr): 3412 (NH), 1708, 1643 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H), 7.45−7.37 (m, 10H), 7.28−7.26 (m, 4H), 7.05 (m, 2H), 6.85 (s, 1H), 6.53 (s, 1H), 5.33 (s, 2H), 4.36 (s, 2H), 4.07 (t, J = 7.3 Hz, 2H), 3.21 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 154.5, 138.2, 135.4, 130.8, 129.0, 128.9, 128.7, 128.6, 128.5, 127.6, 125.6, 123.4, 122.9, 121.1, 119.6, 113.3, 66.7, 59.5, 49.3, 43.9. HRMS (*m*/*z*): calcd for $C_{28}H_{28}N_3O_5S$ (MH^+), 518.1750; found, 518.1735.

ii. Benzyl 2,4-Dioxo-1-[2-(Benzylsulfonyl)ethyl]-3-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (17). The title compound was prepared from **14** in 94% yield using general procedure C and from **16** in 73% yield using general procedure B. White crystals (toluene). Mp: 241.0−241.5 °C. IR (KBr, cm^{-1}): 3254 (NH), 1728, 1698, 1669 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.44−7.15 (m, 15H), 6.67 (d, J = 2.4 Hz, 1H), 5.29 (s, 2H), 4.24 (t, J = 6.9 Hz, 2H), 4.23 (s, 2H), 3.26 (t, J = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 155.1, 151.3, 134.9, 134.8, 133.4, 130.7, 129.5, 129.3, 129.2, 129.0, 128.82, 128.78, 128.7, 128.51, 128.47, 127.2, 113.7, 99.5, 67.5, 60.2, 48.2, 39.6. HRMS (*m*/*z*): calcd for $C_{29}H_{26}N_3O_6S$ (MH^+), 544.1542; found, 544.1527. Anal. Calcd for $C_{29}H_{25}N_3O_6S$: C, 64.08; H, 4.64; N, 7.73. Found: C, 63.82; H, 4.56; N, 7.71.

Benzyl 2,4-Dioxo-3-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (18). An ice-cooled solution of **17** (0.15 mmol, 80 mg) in 20 mL of dry THF was treated with 500 mol % *t*-BuONa (0.74 mmol, 71 mg). The resulting solution was stirred for 15 min at 0 °C and quenched with an ice-cooled aqueous solution of saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the volatiles yielded crude **18**, which was crystallized from chloroform and isolated in 93% yield as a white solid. Mp: 324.5−325.0 °C. IR (KBr, cm^{-1}): 3256 (NH), 1739, 1701, 1656 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (s, 1H), 11.36 (s, 1H), 7.48−7.27 (m, 10H), 6.47 (s, 1H), 5.34 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.0, 155.7, 151.0, 136.1, 135.9, 132.3, 129.4, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 114.1, 99.5, 66.1. Anal. Calcd for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.18; N, 11.63. Found: C, 66.13; H, 4.17; N, 11.58.

Cysteamino-Merrifield Resin 19. Merrifield resin (5 g, 1−1.5 mequiv/g, 2% DVB) was swollen in dry DMF for 2 h, filtered, and suspended in 10 mL of dry DMF. In a separate flask, 15 mmol (300 mol %) of cysteamine hydrochloride (dried over P_2O_5) was added to an ice-cooled suspension of 50 mmol (1000 mol %) of NaH (60% in mineral oil) in dry DMF (10 mL). The resulting mixture was stirred at room temperature until the evolvement of hydrogen gas stopped (about 2 h) and then cannulated into the solution containing the Merrifield resin, and the mixture was shaken for 48 h at room temperature. Filtration and washing with 10 mL portions of CH_2Cl_2, EtOH, H_2O, EtOH, CH_2Cl_2, EtOH, H_2O, EtOH (2×), and CH_2Cl_2 (3×) yielded resin **19**, which was dried in vacuo. The loading was determined to be 0.99 mmol/g by the picric acid test.[25]

Aminopyrrole Resin 20. Cysteamino-Merrifield resin **19** (4 g, 0.99 mmol/g) was placed in a 60 mL polypropylene tube equipped with a polyethylene frit and stopcock, swollen in 10 mL of dry THF for 2 h, filtered, washed with 20 mL of dry THF/MeCN (50:50), and finally suspended in 10 mL of THF/MeCN (50:50). The stopcock was changed for a stopper prior to immersion in the oil bath. The suspension was then treated with 7.92 mmol (200 mol %) of 4-oxoprolinate **10**, 26.93 mmol (680 mol %) of Et_3N, and 0.792 mmol (20 mol %) of $Et_3N{\cdot}HBr$, and the mixture was heated to 50 °C for 24 h using an oil bath. The resin was filtered and washed with 10 mL volumes of CH_2Cl_2 (2×), EtOH (2×), CH_2Cl_2 (2×), EtOH (2×), and CH_2Cl_2 (2×) before being dried in vacuo.

Unreacted **10** was recovered, and PhFH was isolated by evaporation of the combined filtrates and purification by column chromatography (silica gel, CH_2Cl_2), which furnished 3.62 mmol (1.66 g) of **10** and 3.57 mmol (0.86 g) of PhFH (mp 153.2 °C, lit.[26] mp 147−148 °C), indicating an aminopyrrole resin loading of 0.76 mmol/g.

Ureidopyrrole Resins 21a−d. Aminopyrrole resin **20** (4 g, 0.76 mmol/g) was divided among four 12 mL

polypropylene tubes (1 g/tube) each equipped with a polyethylene frit and stopcock. The resins were swollen in 5 mL of dry CH_2Cl_2 for 2 h, filtered, washed twice with 5 mL of dry CH_2Cl_2, suspended in 5 mL of dry CH_2Cl_2, and treated with 3.04 mmol (400 mol %) of the isocyanate. The resulting mixture was then shaken for 24 h at room temperature. The resins were then filtered and washed with 5-mL volumes of CH_2Cl_2 (2×), EtOH (2×), CH_2Cl_2 (2×), EtOH (2×), and CH_2Cl_2 (3×) before being dried in vacuo.

Pyrrolopyrimidine Resins 22a−d. Ureidopyrrole resins **21a−d** obtained from the above-mentioned procedure were kept in the same tubes and swollen in 5 mL of dry dioxane for 2 h, filtered, and washed twice with 5 mL of dry dioxane. The stopcocks were changed for stoppers. The resins were each suspended in 5 mL of dry dioxane, treated with trichloroacetyl chloride (7.6 mmol, 1000 mol %, 0.84 mL), placed under an Ar atmosphere, and heated to 70 °C for 4 h using an oil bath. The resins were cooled. The stoppers were changed for stopcocks, and the resins were each filtered, washed 3-fold with 5 mL of dry dioxane, and dried with a nitrogen flow. The resins were swollen in 5 mL of dry DMF, filtered, washed twice with dry DMF, suspended in 5 mL of dry DMF, treated with 7.6 mmol (1000 mmol %) of powdered and flame-dried Cs_2CO_3, shaken overnight at room temperature, filtered, washed with 5 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.

Sulfone Resins 23a−d. Pyrrolopyrimidine resins **22a−d** were loaded (150 mg/tube) into four 12 mL polypropylene tubes equipped with polyethylene frits and stopcocks. The resins were swollen in 5 mL of CH_2Cl_2, filtered, washed twice with 5 mL of CH_2Cl_2, suspended in 2 mL of CH_2Cl_2, treated with 500 mol % *m*-CPBA, shaken for 1 h at room temperature, filtered, washed with 5 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.

Pyrrolopyrimidines 24a−d. Sulfone resins **23a−d** obtained from the above-mentioned procedure were removed from the tubes, carefully weighed, and loaded again into 12 mL polypropylene tubes equipped with polyethylene frits and stopcocks. The resins were swollen in 5 mL of dry THF, filtered, and washed twice with 5 mL of dry THF. The stopcocks were exchanged for stoppers. The resins were each suspended in 2 mL of dry THF, cooled in an ice bath, treated with 1000 mol % of *t*-BuONa, and agitated for 1 h at 0 °C. The stoppers were removed, and the filtrates were collected in ice-cooled saturated NH_4Cl solutions (10 mL/sample). The resins were washed with 5 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. Pure pyrrolo[3,2-*d*]pyrimidines **24a−d** were obtained by drying the combined organic layers on Na_2SO_4, filtering, evaporation of the volatiles, and crystallization of the residue from EtOH.

i. Benzyl 2,4-Dioxo-3-ethyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (24a) was isolated in 49% overall yield from aminopyrrole resin **20** as a beige solid. Mp: 321.9−322.9 °C. IR (KBr, cm^{-1}): 3258 (NH), 1725, 1698, 1649 (C═O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.02 (s, 1H), 11.19 (s, 1H), 7.49−7.32 (s, 5H), 6.40 (s, 1H), 5.31 (s, 2H), 3.88 (q, J = 6.8 Hz, 2H), 1.11 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.6, 155.2, 150.6, 135.9, 131.6, 128.5, 128.2, 128.0, 127.9 (C4a not resolved), 99.3, 66.1, 34.9, 13.2. HRMS (*m*/*z*): calcd for $C_{16}H_{16}N_3O_4$ (MH^+), 314.1135; found, 314.1132.

ii. Benzyl 2,4-Dioxo-3-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (18, 24b) was isolated in 50% overall yield from aminopyrrole resin **20** as a white solid. Mp: 325.1−325.4 °C. IR (KBr, cm^{-1}): 3254 (NH), 1739, 1701, 1656 (C═O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.12 (s, 1H), 11.38 (s, 1H), 7.50−7.25 (m, 10H), 6.47 (s, 1H), 5.33 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 155.6, 150.9, 136.1, 135.9, 132.3, 129.3, 128.8, 128.5, 128.21, 128.18, 128.0, 127.9, 114.1, 99.5, 66.1. HRMS (*m*/*z*): calcd for $C_{20}H_{16}N_3O_4$ (MH^+), 362.1135; found, 362.1125.

iii. Benzyl 2,4-Dioxo-3-(4-phenoxyphenyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidine-6-carboxylate (24c) was isolated in 44% overall yield from aminopyrrole resin **20** as a beige solid. Mp: 313.4 °C. IR (KBr, cm^{-1}): 3254 (NH), 1740, 1699, 1655 (C═O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.13 (s, 1H), 11.36 (s, 1H), 7.47−7.03 (m, 14H), 6.46 (s, 1H), 5.33 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.6, 156.4, 156.2, 155.7, 151.0, 135.9, 132.2, 130.9, 130.2, 128.5, 128.23, 128.18, 128.0, 124.0, 119.2, 118.2, 114.1, 99.5, 66.1. HRMS (*m*/*z*): calcd for $C_{26}H_{20}N_3O_5$ (MH^+), 454.1397; found, 454.1383.

iv. Benzyl 2,4-Dioxo-3-(2,4-dimethoxyphenyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylate (24d) was isolated in 42% overall yield from aminopyrrole resin **20** as a beige solid. Mp: 257.0−259.0 °C. IR (KBr, cm^{-1}): 3218 (NH), 1727, 1707, 1656 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.04 (s, 1H), 11.25 (s, 1H), 7.50−7.30 (m, 5H), 7.09 (d, J = 8.5 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 8.6, 2.5 Hz, 1H), 6.47 (s, 1H), 5.33 (s, 2H), 3.77 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 159.7, 155.9, 155.5, 150.7, 135.9, 132.3, 130.9, 128.5, 128.2, 128.0, 117.3, 114.0, 104.9, 99.5, 99.1, 66.1, 55.7, 55.5. HRMS (*m*/*z*): calcd for $C_{22}H_{19}N_3O_6Na$ (MNa^+), 444.1166; found, 444.1163.

Acknowledgment. This research was supported in part by the Natural Sciences and Engineering Research Council of Canada (NSERC), Fonds Québecois de la recherche sur la nature et les technologies (FQRNT), Valorisation-Recherche Québec (VRQ), the Chemical Society of Canada (CSC), Merck Frosst, AstraZeneca, Boehringer Ingelheim, and Shire Biochem. We thank Dr. Alexandra Fürtös and Mr. Dalbir S. Sekhon of the Université de Montréal mass spectrometry facility for mass spectral analyses.

Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra of products **11−17** and **24a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) For a review on purine/pyrimidine receptors see: Ralevic, V.; Burnstock, G. *Pharmacol. Rev.* **1998**, *50*, 413−492. (b) For a review on adenosine receptors see: Fredholm, B. B.; Zerman, A. P.; Jacobson, K. A.; Koltz, K.-N.; Luiden, J. *Pharmacol. Rev.* **2001**, *53*, 527−552.

(2) Grahner, B.; Winiwarter, S.; Lanzner, W.; Muller, C. E. *J. Med. Chem.* **1994**, *37*, 1526−1534.

(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) Romeo, G.; Russo, F.; De Blasi, A. *J. Heterocycl. Chem.* **2001**, *38*, 391−395.

(5) Norman, M. H.; Chen, N.; Chen, Z. D.; Fotsch, C.; Hale, C.; Han, N. H.; Hurt, R.; Jenkins, T.; Kincaid, J.; Liu, L. B.; Lu, Y. L.; Moreno, O.; Santora, V. J.; Sonnenberg, J. D.; Karbon, W. *J. Med. Chem.* **2000**, *43*, 4288−4312 and refs 16−19 therein.

(6) Stamford, A. W. *Annu. Rep. Med. Chem.* **2002**, *37*, 53.

(7) Vidal, J. B.; Esteve, T. C.; Gracia, F. J.; Prieto, S.; Jose, M. PCT Int. Appl. WO 2002012246 A1, 2002.

(8) Heinicke, J.; Klausmeier, U. Eur. Pat. Appl. EP 1357114 A1, 2003.

(9) Vidal, J. B.; Esteve, T. C. PCT Int. Appl. WO 2003082873 A1, 2003.

(10) Dorff, P. H.; Garigipati, R. S. *Tetrahedron Lett.* **2001**, *42*, 2771−2773.

(11) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *J. Org. Chem.* **2001**, *66*, 8273−8276.

(12) Ding, S.; Gray, N. S.; Ding, Q.; Wu, X.; Schultz, P. G. *J. Comb. Chem.* **2002**, *4*, 183−186.

(13) Lucrezia, R. D.; Gilbert, I. H.; Floyd, C. D. *J. Comb. Chem.* **2000**, *2*, 249−253.

(14) Obrecht, D.; Abrecht, C.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65−72.

(15) Pérez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501−510.

(16) Marcotte, F.-M.; Rombouts, F. J. R.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6984−6987.

(17) García-Echeverría, C. *Tetrahedron Lett*. **1997**, *38*, 8933−8934.

(18) 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.

(19) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun*. **1971**, 636−637.

(20) Katti, S. B.; Misra, P. K.; Haq, W.; Mathur, K. B. *J. Chem. Soc., Chem. Commun*. **1992**, 843−844.

(21) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006−7014.

(22) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295−3299.

(23) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305−3313.

(24) Sharma, R.; Lubell, W. D. *J. Org. Chem*. **1996**, *61*, 202−209.

(25) Gisin, B. F. *Anal. Chim. Acta* **1972**, 248−249.

(26) *CRC Handbook of Chemistry and Physics*, 48th ed.; Weast, R. C., Ed.; The Chemical Rubber Co.: Cleveland, 1967; p C-325.

CC050002L