Structure−Activity Relationships of a Series of Pyrrolo[3,2-*d*]pyrimidine Derivatives and Related Compounds as Neuropeptide Y5 Receptor Antagonists

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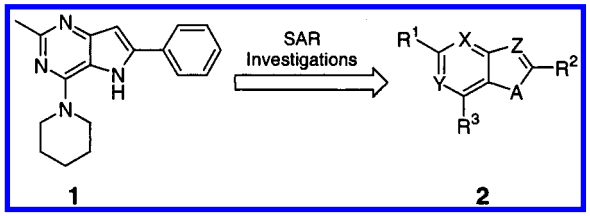
Neuropeptide Y (NPY) has been shown to play an important role in the regulation of food intake and energy balance. Pharmacological data suggests that the Y5 receptor subtype contributes to the effects of NPY on appetite, and therefore a Y5 antagonist might be a useful therapeutic agent for the treatment of obesity. In attempts to identify potential Y5 antagonists, a series of pyrrolo[3,2-*d*]pyrimidine derivatives was prepared and evaluated for their ability to bind to Y5 receptors in vitro. We report here the synthesis and initial structure−activity relationship investigations for this class of compounds. The target compounds were prepared by a variety of synthetic routes designed to modify both the substitution and the heterocyclic core of the pyrrolo[3,2-*d*]pyrimidine lead **1**. In addition to identifying several potent Y5 antagonists for evaluation as potential antiobesity agents, a pharmacophore model for the human Y5 receptor is presented.

Introduction

Obesity is the most common metabolic disorder in the western world and affects more than 30% of the adult population in the United States.[1] Furthermore, obesity has now been directly implicated as one of the major risk factors in the development of several potentially life-threatening disorders including heart disease, high blood pressure, stroke, late-onset diabetes, and certain forms of cancer.[2] A series of pharmacologic approaches are currently being investigated within the pharmaceutical industry to help manage this disease which is a major cause of morbidity and mortality.[3−7] The approach that we have investigated is to develop a neuropeptide Y (NPY) antagonist which may reduce food intake in humans. In the early 1980s NPY was shown to potently stimulate appetite and increase food intake. It was not until recently, however, that investigators have cloned and characterized an NPY receptor that is thought to mediate NPY's orexigenic effects.[8−15] Antagonism of this NPY feeding receptor, which has been designated as the Y5 subtype, might attenuate NPY signaling in the hypothalamus and provide a mechanism for treating obesity.[16−19] The identification of the Y5 receptor as a potential feeding receptor subtype has stimulated a number of investigations in this area. For example, Novartis[20−23] and Synaptic[24] were the first to report a series of 2,4-diaminoquinazolines and arylsulfonamides as potent Y5 receptor antagonists. Subsequently, a number of patents have also claimed a variety of compound classes that act at the Y5 receptor.[25−31] Recently, Youngman and co-workers have described the results of their structure−activity investigations of a series of *β*-aminotetralins targeted to the Y5 receptor.[32]

High-throughput screening against the Y5 receptor led to the identification of several potential leads possessing high affinity to this receptor. Pyrrolo[3,2-*d*]-pyrimidine **1** was one of these hits and will be the focus of the following discussion.



In this structure−activity relationship (SAR) investigation, we prepared analogues of **1** with specific changes to the parent structure to better understand the structural features required for binding to the Y5 receptor (general structure **2**). Through the iterative process of synthesis and biological evaluation, we have gained insight into the pharmacophores important for binding within this class of compounds. In addition, we have prepared several derivatives with very high affinities for the Y5 receptor. The preliminary results of these investigations are reported, and a pharmacophore model is proposed.

Chemistry

A variety of synthetic routes were required to prepare derivatives of pyrrolopyrimidine **1**. Although some of the methods could be generalized, the synthetic routes employed were mainly dictated by which heterocyclic core was being prepared (variables X, Y, Z, and A in compound **2**) and which R group was being modified (R^1, R^2, and R^3 substituents in compound **2**). In this article we will restrict our discussion to compounds with single changes to pyrrolopyrimidine **1**. For clarity, the discus-

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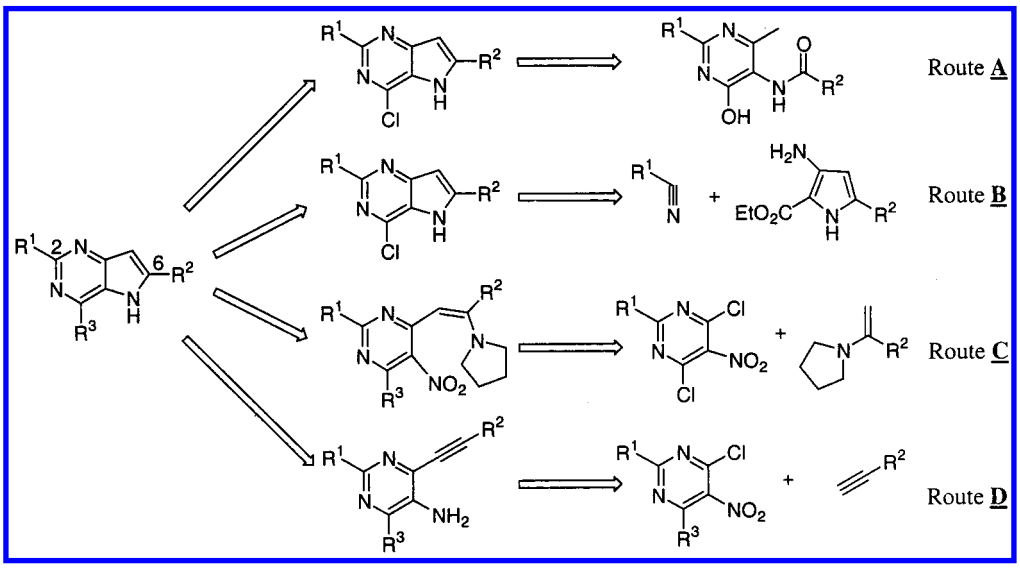
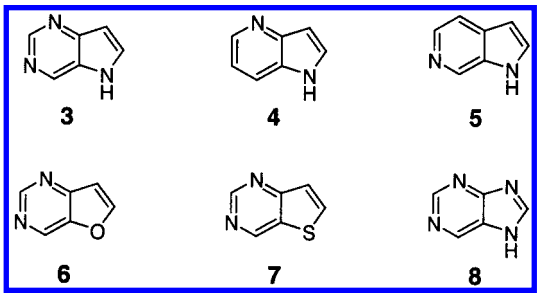
Scheme 1



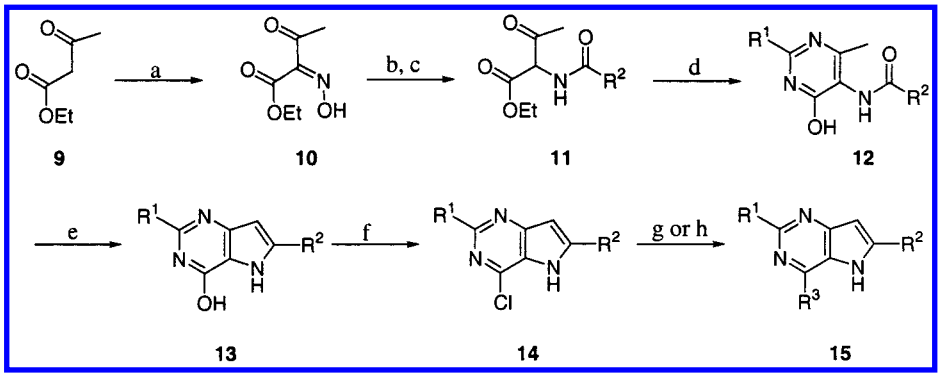
sion of the synthetic methods is organized based on the heterocyclic core prepared (i.e., pyrrolo[3,2-*d*]pyrimidine **3**, pyrrolo[3,2-*d*]pyridine **4**, pyrrolo[3,4-*d*]pyridine **5**, furano[3,2-*d*] pyrimidine **6**, thiopheno[3,2-*d*]pyrimidine **7**, and purine **8**).



The majority of the derivatives prepared in this study are representatives of the pyrrolo[3,2-*d*]pyrimidine class of compounds (**3**). Surprisingly, there are very few literature examples of the synthesis of pyrrolo[3,2-*d*]-pyrimidines. Among these reports Sokolova and co-workers published a series of papers describing the synthesis of pyrrolo[3,2-*d*]pyrimidines by employing the Madelung cyclization as a key step in the synthesis.[33,34] Although this method was useful for the preparation of several analogues, poor yields were obtained and modifying the R^1 and the R^2 substituents on the pyrrolopyrimidine core was difficult. Therefore, we found it preferable to develop alternative routes to this class of compounds. The key steps of the four general synthetic routes employed to prepare pyrrolo[3,2-*d*]pyrimidines are outlined in Scheme 1. Route A employs the Madelung cyclization of an amide to the *o*-methyl group of the pyrimidine. Route B forms the substituted pyrrole initially followed by the subsequent formation of the pyrimidine ring. Route C employs an enamine addition to a dichloronitropyrimidine compound followed by an intramolecular cyclization to form the pyrrole ring. Route D involves the addition of an acetylene followed by a copper(I)-mediated cyclization of the acyetylene amine intermediate. Each of these methods proved to be useful in providing access to the appropriately substituted pyrrolo[3,2-*d*]pyrimidines.

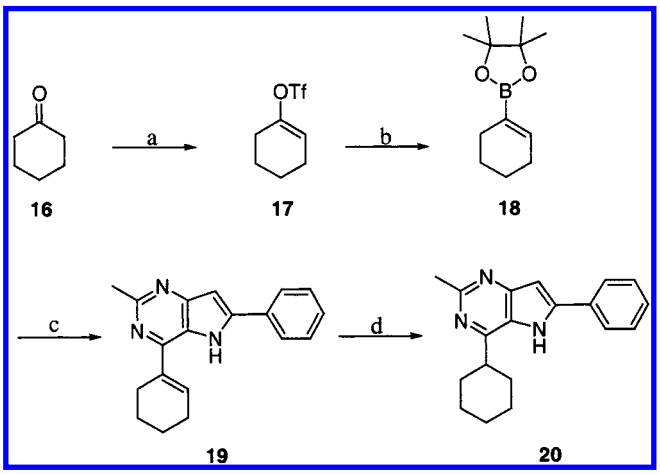
The first method that was employed (route A) was analogous to that reported by Sokolva et al.[33] and is outlined in Scheme 2. Treatment of ethyl acetoacetate (**9**) with sodium nitrite and acetic acid provided ethyl 2-hydroxyimino-3-butyrate (**10**).[35,36] This material was reduced with zinc and sulfuric acid to give the corresponding 2-aminoacetoacetic acid ethyl ester.[37] This amine was isolated and acylated with an appropriate acid chloride to give **11**;[38] however, higher yields were

Scheme 2[a]



[a] (a) $NaNO_2$, AcOH, H_2O; (b) Zn, H_2SO_4, H_2O; (c) $R_2(C{=}O)Cl$, NaOAc; (d) $R^1(C{=}NH)NH_2{\cdot}HCl$, NaOEt, EtOH; (e) NaOEt, 360 °C; (f) $POCl_3$, 1,2-dichloroethane, reflux; (g) 1° or 2° amines ($R^3 = NR_2$), K_2CO_3, H_2O; (h) $R^3B(OR)_2$, $Pd_2(dba)_3$, 1 M Na_2CO_3, toluene, EtOH, reflux.

Scheme 3[a]



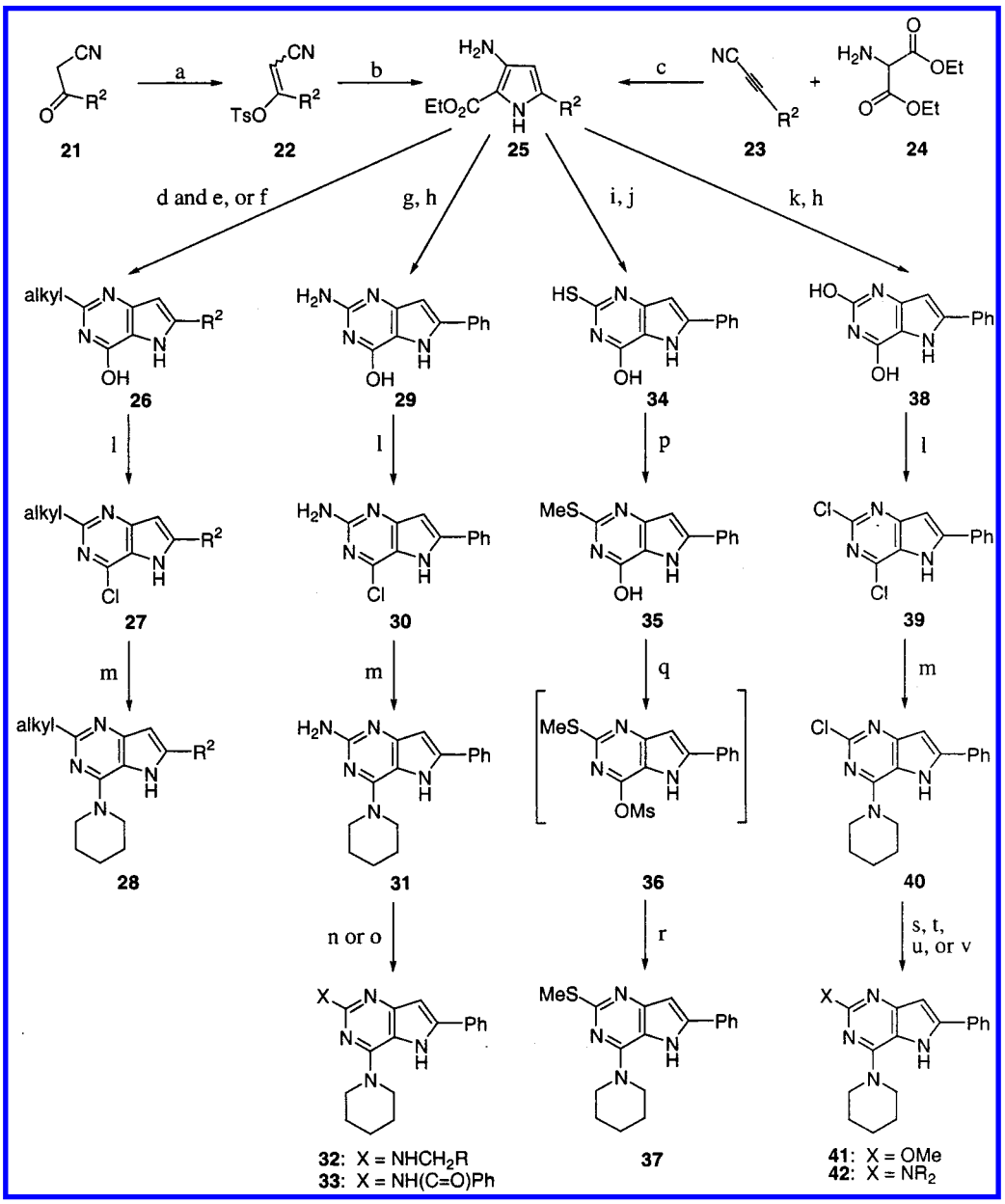
[a] (a) $Tf_2(O)$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2; (b) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, DMSO, 70 °C; (c) **14** (where R^1 = Me and R^2 = Ph), Ph_3P, $Pd_2(dba)_3$, 1 M Na_2CO_3, toluene, EtOH, reflux; (d) H_2(70 psi), PtO_2, EtOH.

obtained by the in situ acylation of the amine by the method described by Tarzia and co-workers.[39] Condensation of the ethyl *N*-acylated-2-aminoacetoacetates **11** with acetamidine hydrochloride in sodium ethoxide provided acylpyrimidine intermediates **12**. Madelung cyclization of pyrimidines **12** at 360 °C gave the desired 3-hydroxypyrrolo[3,2-*d*]pyrimidines **13**, albeit in poor yields. Pyrrolopyrimidines **13** were converted to their corresponding chlorides **14** by treatment with phosphorus oxychloride in dichloroethane, and these key chloro intermediates were condensed with a variety of amines to give 4-amino-substituted pyrrolopyrimidines. Route A provided easy access to pyrrolopyrimidine derivatives where R^3 was modified; however, modifications at R^1 and R^2 were limited due to the high temperatures required for the Madelung cyclization. Therefore, only a few derivatives with modifications in these positions were prepared (e.g., R^1 was limited to Me, *i*-Pr, and Ph, and R^2 was limited to Ph and Ph(4-Me)). In addition to the preparation of 4-amino-subsituted analogues, the carbon-substituted derivatives were prepared by the Suzuki coupling of chloro intermediates **14** with the appropriate boronic acid derivatives.

Of particular interest to our SAR investigation was the cyclohexyl derivative **20** wherein the piperidine nitrogen of compound **1** was replaced with a carbon atom. The synthesis of this derivative involved the preparation of boronic ester **18** (Scheme 3). The enol triflate **17**, prepared by the reaction of cyclohexanone with triflic anhydride,[40] was treated with bis(pinocolato)diboron to give boronic ester **18**. The boronic ester **18** was condensed with chloro intermediate **14** (where R^1 = Me and R^2 = Ph) to give cyclohexene derivative **19** which was hydrogenated to provide the desired pyrrolo[3,2-*d*]pyrimidine **20**.

The general method involving the use of 3-amino-2-carboxyl-5-substituted pyrroles (route B) proved to be very fruitful and allowed synthetic entries into several pyrrolopyrimidine analogues with varying substitution patterns. The syntheses of derivatives using this general route are outlined in Scheme 4. The key 5-substituted 3-amino-1*H*-pyrrole-2-carboxylate intermediates **25** were prepared by two different methods. Treatment of α-cyano ketones **21** with *p*-toluenesulfonic anhydride in dichloromethane provided the corresponding *p*-toluenesulfonyl enol esters **22**.[41] The crude enol esters were immediately condensed with diethyl aminomalonate to provide pyrrole intermediates **25** in 21−61% yields. Alternatively, the substituted pyrroles **25** were prepared by the reaction of diethyl aminomalonate (**24**) with sodium ethoxide and substituted cyanoacetylenes **23**.[42] With a variety of 5-substituted 3-amino-1*H*-pyrrole-2-carboxylates (**25**) in hand, several analogues with modifications at the R^1 position (see general structure **2**) were prepared. Derivatives wherein R^1 is an alkyl group were prepared by treating pyrroles **25** with an alkyl cyanide in anhydrous hydrochloric acid at room temperature followed by heating with sodium hydroxide to give alcohol intermediates **26**. Attempts to prepare analogous compounds by the condensation of **25** (where R^2 = Ph) with acetamidine hydrochloride were unsuccessful; however, the 2-trifluoromethyl derivative could be obtained by the reaction of pyrrole **25** with trifluoromethylacetamidine in refluxing xylene. Treatment of **26** with refluxing phosphorus oxychloride followed by displacement of the resulting chlorides **27** with primary or secondary amines provided 2-alkyl-substituted pyrrolopyrimidine analogues **28**. To synthesize derivatives with a nitrogen at the R^1 position, the intermediate pyrrole **25** (where R^2 = Ph) was reacted with cyanamide and concentrated hydrochloric acid in refluxing dioxane followed by heating the resulting intermediate with aqueous sodium hydroxide to give **29**. Alcohol **29** was converted to chloride **30** by reaction with phosphorus oxychloride, and the resulting chloride was displaced with piperidine to give **31**. The 2-amino group of compound **31** was then modified by either reductive amination or acylation reactions to give compounds of types **32** and **33**, respectively. Incorporation of a thiomethyl group in the R^1 position of the pyrrolopyrimidine was accomplished as shown in Scheme 4. The reaction of pyrrole **25** (where R^2 = Ph) with ethyl isothiocyanatoformate in refluxing benzene followed by treatment of the resulting intermediate with potassium hydroxide provided thiol **34**.[43] Thiomethyl **35** was obtained by methylation of **34** with methyl iodide in acetone. Attempts to chlorinate **35** resulted in decomposition; however, when compound **35** was treated with methanesulfonyl chloride the mesylate **36** was obtained. This material was reacted with piperidine without isolation to give the thiomethyl-substituted pyrrolopyrimidine **37**. The two final classes of analogues whose syntheses are illustrated in Scheme 4 contain a methoxy or substituted amine group in the R^1 position of the pyrrolopyrimidine ring. These derivatives were prepared by initially treating pyrrole **25** (where R^2 = Ph) with potassium cyanate followed by heating the intermediate in refluxing sodium hydroxide to give diol **38**. The reaction of diol **38** with phosphorus oxychloride gave the corresponding dichloro compound **39**.[44] The 4-chloro group of dichloro intermediate **39** was displaced upon heating with piperidine in aqueous potassium carbonate for 4 h to give compound **40**; however, displacement of the 2-chloro group required more vigorous reaction conditions. Reaction of chloro derivative **40** with either sodium methoxide or primary and secondary amines at elevated temperatures (110−189 °C) and for extended reaction times (44−72 h) resulted in the preparation of

Scheme 4[a]



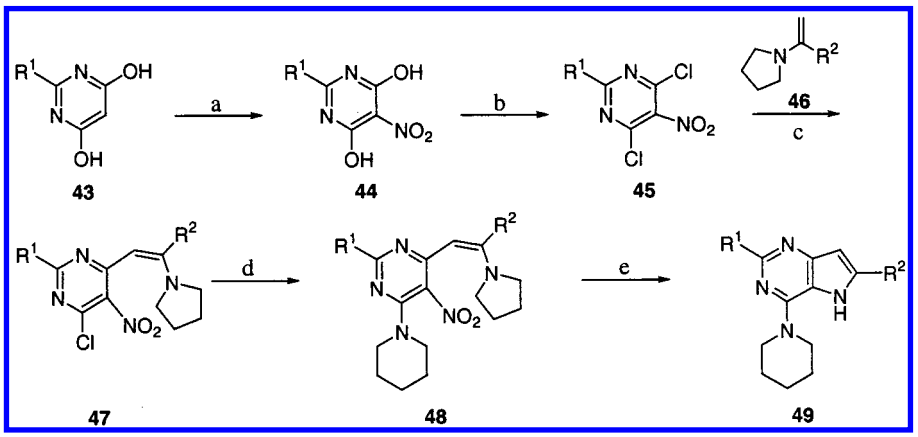
[a] (a) Ts_2O, Et_3N, CH_2Cl_2; (b) diethyl aminomalonate hydrochloride, NaOEt, EtOH; (c) NaOEt, EtOH; (d) alkyl-CN, HCl(g); (e) NaOH, EtOH, reflux; (f) $F_3C(C{=}NH)NH_2$, *o*-xylene, reflux; (g) H_2NCN, HCl(concd), dioxane, reflux; (h) NaOH(aq), reflux; (i) $S{=}C{=}NCO_2Et$, benzene, reflux; (j) KOH(aq), reflux; (k) KNCO, HOAc, H_2O; (l) $POCl_3$, reflux; (m) piperidine, K_2CO_3, H_2O, reflux; (n) RCHO, $NaCNBH_3$, MeOH, reflux; (o) $(PhC{=}O)_2O$, pyridine, reflux; (p) MeI, K_2CO_3, acetone; (q) MsCl, CH_2Cl_2, Et_3N; (r) piperidine; (s) NaOMe, DMSO, reflux, 72 h; (t) $HNMe_2$, or H_2NMe, *n*-BuOH, HCl(concd), reflux (44−72 h); (u) HNR_2, dioxane, reflux; (v) HNR_2, K_2CO_3, H_2O, 72 h.

methoxy and substituted amino derivatives **41** and **42**, respectively.

The third method developed for the preparation of pyrrolopyrimidine derivatives is based on the work of Montgomery et al. (route C), wherein the key step involved the addition of an enamine **46** to a chloropyrimidine intermediate **45**[45] (Scheme 5). This synthetic route proved to be particularly useful for the preparation of pyrrolopyrimidine derivatives with modifications in the R^2 position. Nitration of 2-methyl-4,6-dihydroxypyrimidine (**43**) with nitric acid gave 2-methyl-4,6-dihydroxy-5-nitropyrimidine (**44**, where R^1 = Me).[46,47] The requisite dichloro intermediate **45** required for the enamine reaction was obtained by the treatment of **44** with phosphorus oxychloride. Enamines **46**, prepared by the tin tetrachloride-mediated condensation of methyl ketones with pyrrolidine (see Boger et al.[48]), were immediately reacted with dichloropyrimidines **45** to give enamine intermediates **47**. These intermediates were treated directly with piperidine, to give **48**, and the nitro group was subsequently reduced with tin(II) chloride in dimethylformamide. Upon reduction of the nitro group the compounds rapidly cyclized to give the desired substituted pyrrolopyrimidines **49**.

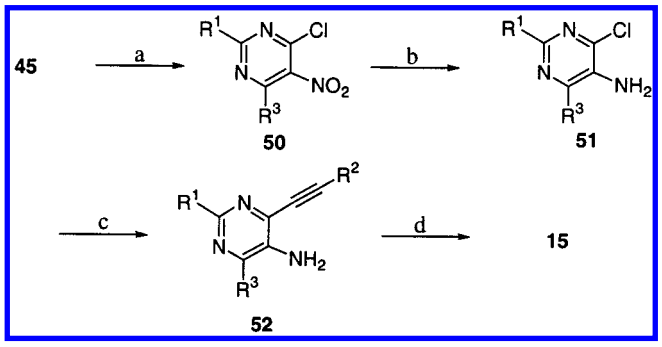
The final synthetic route employed to prepare the pyrrolo[3,2-*d*]pyrimidine ring system is outlined in Scheme 6 (route D). Treatment of dichloropyrimidines **45** with a secondary amine at room temperature provided polysubstituted pyrimidines **50**. The nitro group was reduced with tin(II) chloride, and the resulting amine **51** was converted to compound **52** by the palladium-catalyzed addition of a monosubstituted acety-

Scheme 5[a]



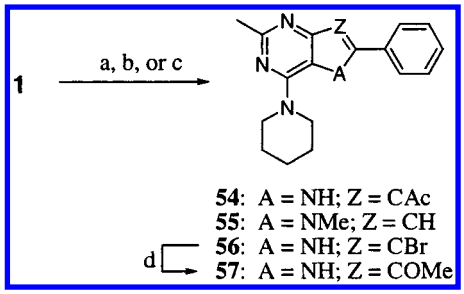
[a] (a) TFA, HNO_3 (90%), 12−21 °C; (b) $POCl_3$, *i*-Pr_2NEt, toluene, reflux; (c) *i*-Pr_2NEt, toluene, rt; (d) piperidine, Et_3N, toluene:dioxane (1:2), 100 °C; (e) $SnCl_2$, DMF, rt−reflux.

Scheme 6[a]



[a] (a) $HN(R)_2$, Et_3N, THF, rt; (b) $SnCl_2 \cdot 2H_2O$, Et_2O, HCl(concd), 0 °C; (c) $HC{\equiv}CR^2$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 70 °C; (d) CuI, DMF, 110 °C.

Scheme 7[a]



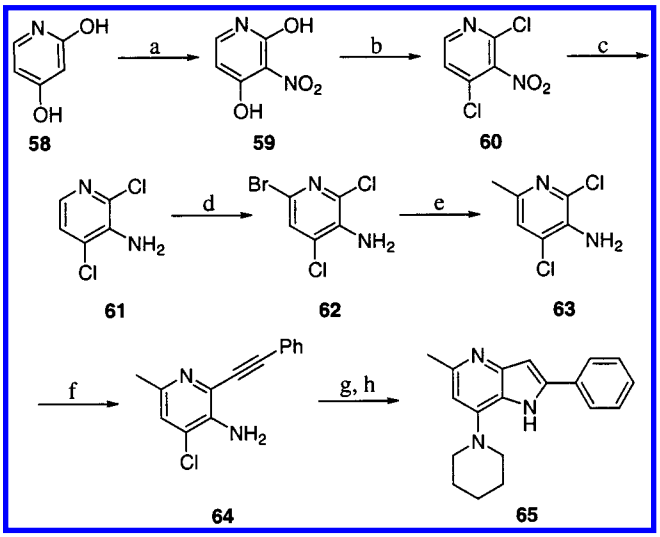
[a] (a) Ac_2O, K_2CO_3, DMAP, DMF, 110 °C; (b) *n*-BuLi, Me_2SO_4, −78 °C; (c) AcOH, Br_2, H_2O, 45 °C; (d) NaOMe, MeOH, reflux.

lene. Cyclization was accomplished by heating acetylenes **52** with copper(I) iodide in dimethylformamide to provide the targeted pyrrolo[3,2-*d*]pyrimidines **15**.[49]

Additional derivatives containing single-point changes were also made directly from the lead pyrrolopyrimidine **1** as shown in Scheme 7. Condensation of **1** with acetic anhydride in dimethylformamide at 110 °C provided the 7-acetyl derivative **54**, and the *N*-methyl analogue **55** was obtained by alkylating the N5 nitrogen of pyrrolopyrimidine **1** with dimethyl sulfate. Treatment of **1** with bromine in acetic acid provided 7-bromo-substituted derivative **56**. Finally, the corresponding 7-methoxy derivative **55** was obtained when bromide **56** was heated with sodium methoxide in refluxing methanol.

The compounds containing the deazapyrrolopyrimidine ring systems (pyrrolo[3,2-*d*]pyridine **4** and pyrrolo[3,4-*d*]pyridine **5**) were prepared by employing a copper-

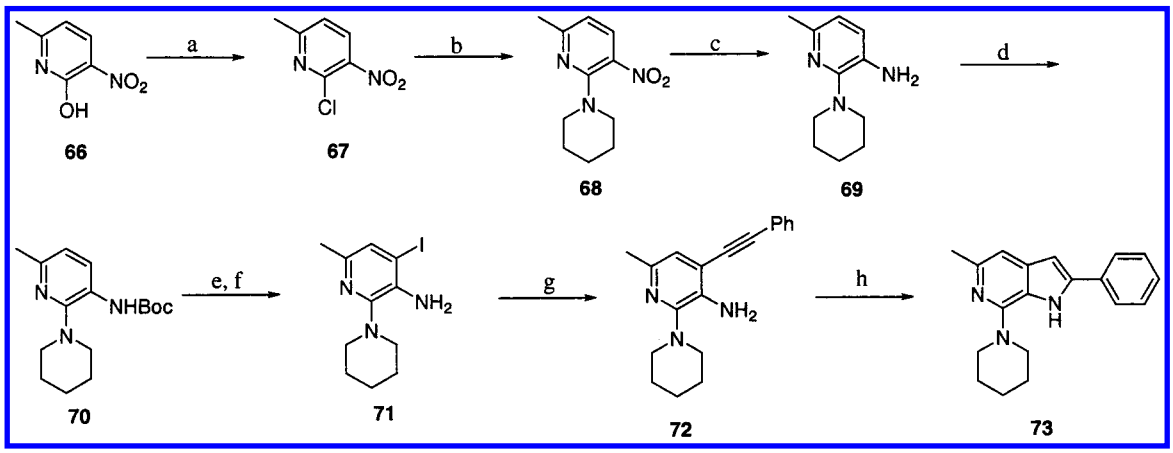
Scheme 8[a]



[a] (a) HNO_3 (fuming), H_2SO_4(concd), 0 °C; (b) $POCl_3$, reflux; (c) $SnCl_2 \cdot 2H_2O$, Et_2O, HCl(concd); (d) *N*-bromosuccinimide, DMF, 0 °C; (e) $MeB(OH)_2$, $Pd(PPh_3)_2Cl_2$, DMF, K_2CO_3, 100 °C; (f) phenylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 80 °C; (g) CuI, DMF, 110 °C; (h) piperidine, *o*-xylene, 140 °C.

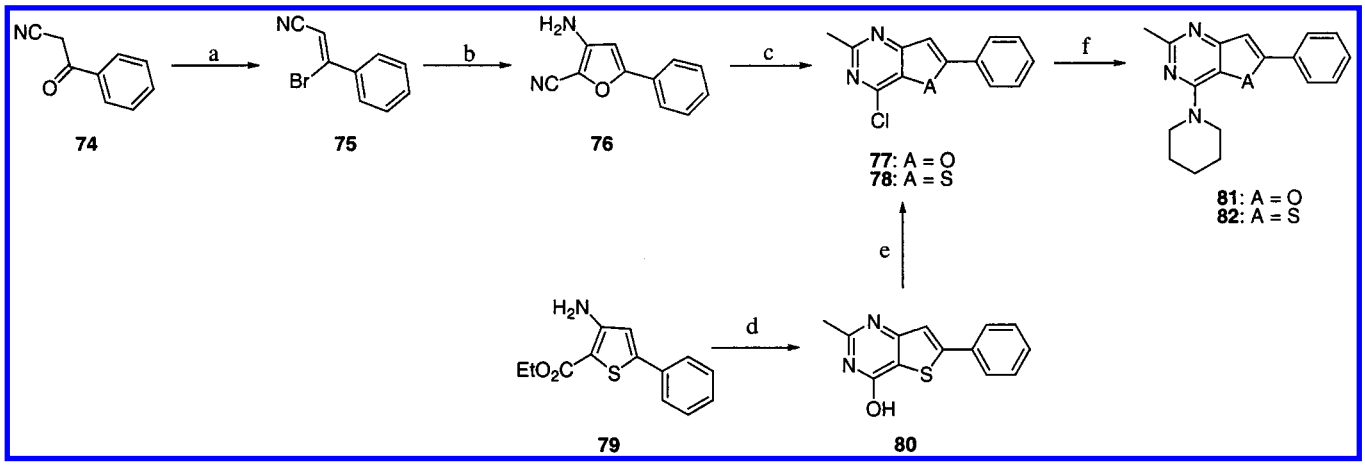
mediated cyclization of an appropriately substituted acetylenic pyridine as the key step to form the pyrrole ring (Schemes 8 and 9). The synthesis of the N3 deaza derivative began with nitration of 2,4-dihydroxypyridine (**58**) with fuming nitric acid to provide nitropyridine **59** in good yield. The aminodichloro intermediate **61** was obtained by treating **59** with phosphorus oxychloride followed by reduction of the nitro group with tin(II) chloride. The methyl substituent was introduced by bromination of the 6-position of the pyridine ring with *N*-bromosuccinimide followed by a Suzuki coupling with methylboronic acid to give compound **63**. The synthesis of pyrrolo[3,2-*d*]pyridine **65** was completed by an analogous sequence as described for the route D pyrrolopyrimidine synthesis. Palladium-catalyzed addition of phenylacetylene proceeded smoothly at the 2-position to provided compound **64** in good yield, and displacement of the 4-chloro substituent was not observed. Treatment of **64** with copper(I) iodide in dimethylformamide at 110 °C, followed by the addition of piperidine, provided the desired pyrrolo[3,2-*d*]pyridine **65**.

Scheme 9[a]



[a] (a) $POCl_3$, *i*-Pr_2NEt, reflux; (b) piperidine, $ZnCl_2$, THF, rt; (c) H_2, Pd/C; (d) NaHMDS, Boc_2O, THF; (e) *t*-BuLi, THF, −78 to −20 °C, then 1-chloro-2-iodoethane, −20 °C to rt; (f) 4 M HCl, EtOAc; (g) phenylacetylene, CuI, Et_3N, $PdCl_2(PPh_3)_2$, reflux; (h) CuI, DMF, reflux.

Scheme 10[a]



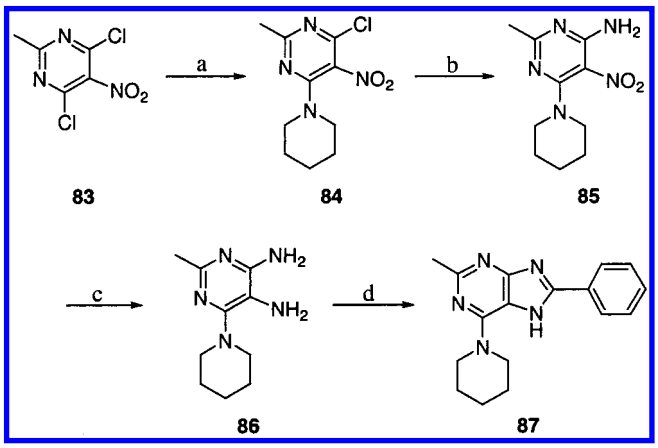
[a] (a) PBr_3, 170 °C; (b) $NCCH_2OH$, NaH, $MgSO_4$, THF, rt; (c) $Me(C{=}O)NMe_2$, $POCl_3$, 160 °C; (d) $Me(C{=}NH)NH_2{\cdot}HCl$, NaOMe, poly(ethylene glycol), 120 °C; (e) $POCl_3$, 100 °C; (f) piperidine (neat or in toluene), 100−160 °C.

The second deaza derivative (pyrrolo[3,4-*d*]pyridine **73**) was prepared starting from 6-methyl-3-nitrohydropyridin-2-one (**66**) (Scheme 9). Compound **66** was chlorinated with phosphorus oxychloride to give compound **67**. The chloride group of **67** was displaced with piperidine, and the nitro group was hydrogenated to give the corresponding aminopyridine **69**. Treatment of aminopyridine **69** with di-*tert*-butyl dicarbonate provided carbamate **70** in good yield. Ortho-directed metalation of **70** with *tert*-butyllithium followed by treatment with 1-chloro-2-iodoethane and hydrolysis of the *tert*-butyl carbamate gave the polysubstituted pyridine **71**. The target compound, pyrrolo[3,4-*d*]pyridine **73**, was obtained by the palladium-catalyzed addition of phenylacetylene and the subsequent cyclization of the resulting acetylene **72** with copper(I) iodide.

The syntheses of both the furan and thiophene derivatives are shown in Scheme 10. Treatment of benzoyl acetonitrile (**74**) with phosphorus tribromide at 170 °C provided vinyl bromide **75** in good yield. The polysubstituted furan intermediate **76** was easily obtained by the condensation of bromonitrile **75** with glycolonitrile in tetrahydrofuran. The chloroimidate of *N*,*N*-dimethylacetamide was freshly prepared in situ and reacted with aminonitrile furan **76** to give the 4-chlorofurano[3,2-*d*]pyrimidine intermediate **77**. This chloride was not isolated but was reacted directly with piperidine to provide the desired furano[3,2-*d*]pyrimidine **81**. The corresponding thiopheno[3,2-*d*]pyrimidine **82** was prepared in three steps starting from 3-amino-5-phenylthiophene-2-carboxylate (**79**). Condensation of **79** with acetamidine hydrochloride provided alcohol **80**, which was converted immediately to the chloride **78** using phosphorus oxychloride. Displacement of the chloride on compound **78** with piperidine gave the desired thiopheno[3,2-*d*]pyrimidine derivative **82**.

The final synthetic sequence employed in this study is shown in Scheme 11 for the preparation of the purine derivative **87**. One of the two chloro groups of dicholopyrimidine **83** was displaced with piperidine at room temperature to give compound **84**. Treatment of **84** with ammonia in a sealed tube at 90 °C provided the tetrasubstituted pyrimidine **85** in good yield, and the reduction of the nitro group of **85** was accomplished by hydrogenation with 10% palladium on carbon. The final target compound, purine **87**, was obtained by the condensation of diamine **86** with benzoic acid in phosphorus oxychloride.[50] In general, the compounds described herein were prepared and purified as their hydrochloride salts.

Scheme 11[a]

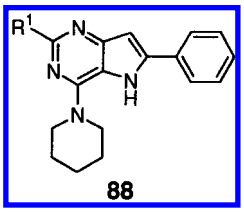


[a] (a) Piperidine, *i*-Pr_2NEt, THF, rt; (b) NH_3, MeOH, 90 °C, sealed tube; (c) H_2, Pd/C, EtOH; (d) benzoic acid, $POCl_3$, 120 °C.

Results and Discussion

The pyrrolopyrimidine derivatives prepared in this study were evaluated in an in vitro radioligand-binding assay to determine their affinity for the human NPY5 receptor.[51] Secondary in vitro functional assays were also conducted to establish that these derivatives were acting as antagonists at the Y5 receptor,[52] and potent compounds were examined in in vivo models to evaluate inhibition of feeding in mice and rats. In this report we will restrict our discussion to the in vitro activity of the compounds at the human Y5 receptor.[53] To establish the SAR of this series of compounds, each variable of general structure **2** was systematically modified, including substituents R^1, R^2, and R^3, as well as the different heterocyclic cores obtained by varying X, Y, Z, and A. The following structure−activity tables examine each of these variables independently and report the in vitro binding affinities of the derivatives at the human Y5 receptor. Data for the lead compound **1** has been included in most tables for ease of comparison. We begin our discussion by examining the effects of the various substituents on the pyrrolo[3,2-*d*]pyrimidine core structure (R^1, R^2, and R^3). Derivatives of the original lead compound **1** with modifications at R^1 are shown in Table 1. The pyrrolopyrimidine without substitution at the 2-position (**88a**, R^1= H) showed weak binding affinity at the Y5 receptor indicating that 2-substitution of the pyrrolopyrimidine core was preferred for good activity. Small electron-donating groups such as alkyl and amino demonstrated the best binding affinities (compounds **1**, **88b**−**d**, **31**, **42a**−**c**) versus the electron-withdrawing trifluoromethyl substituent (compound **88h**). However, the methoxy and thiomethyl derivatives showed lower activity (compounds **41** and **37**, respectively) indicating that the binding affinity did not correlate well with electronegativity of the R^1 substituent. Alkyl substituents in the 2-position of the pyrrolopyrimidine ring exhibited good correlation between binding affinity and steric size (Me > Et ≈ *n*-Pr ≈ *c*-Pr > *i*-Bu > *i*-Pr > Ph; **1**, **88b**−**g**). This sensitivity to steric size was also observed in the amino series: the 2-NH_2-substituted derivative **31** showed potent affinity at the Y5 receptor with an IC_{50} of 2 nM, whereas the affinity diminished up to 3 orders of magnitude as the bulk of the substituent was increased (compounds **42a**−**d**). When the electron-donating ability of the nitrogen was reduced as in the case of benzamide **33**, decreased activity was also observed. The increased steric size of benzamide substituent may also contribute to the lower affinity of this derivative.

Table 1. In Vitro Y5 Receptor Binding Affinities for 2-Substituted Pyrrolo[3,2-*d*]pyrimidines

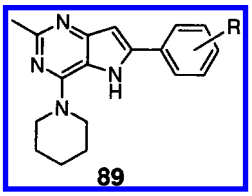


compd no.[a]	R^1	hY5 receptor binding[b] IC_{50} (nM)[c]
88a	H	2300 ± 1500
1	Me	1.1 ± 0.4
88b	Et	20 ± 0.0
88c	*n*-Pr	28 ± 10
88d	*c*-Pr	32 ± 18
88e	*i*-Pr	8300 ± 470
88f	*i*-Bu	460 ± 230
88g	Ph	9300 ± 470
88h	CF_3	590 ± 49
31	NH_2	1.2 ± 0.2
42a	NHMe	29 ± 3.0
42b	NHPr	120 ± 2.5
42c	NMe_2	280 ± 80
42d	1-piperidinyl	4000 ± 1000
41	OMe	540 ± 77
37	SMe	4700 ± 1200
33	NH(C=O)Ph	750 ± 150

[a] Hydrochloride salts with the exception of **88g** and **37**. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound.

Receptor binding data for derivatives with modifications at R^2 have been divided into two categories. The effects of substitution on the 6-phenyl group are summarized in Table 2, while alkyl and heterocyclic derivatives are reported in Table 3. In general, substitution on the phenyl ring is well-tolerated and a number of very potent derivatives were obtained with IC_{50}'s < 1 nM (Table 2). A clear preference for meta and para substitution was observed with the ortho-substituted counterparts possessing significantly lower affinity for the Y5 receptor. This order of activity was consistent across three series of compounds (i.e., Cl-, F_3C-, and F-substituted derivatives **89a**−**c**,**d**−**f**,**g**−**i**, respectively). The series of polyfluorinated derivatives also demonstrated that meta and para substitution enhanced activity over ortho substitution (**89m**,**n** vs **89o**−**q**). These results suggest that the phenyl ring prefers to be in a planar orientation relative to the pyrrolopyrimidine core structure. Molecular mechanics calculations of the chloro series (**89a**−**c**) indicate that there is a significantly larger dihedral angle between the phenyl and the pyrrolopyrimidine rings of the ortho derivative (40.3° for **89a**) as compared to either the meta (**89b**) or para (**89c**) derivatives that have corresponding dihedral angles of 11.3° and 4.6°, respectively.[54] With the exception of the biphenyl derivative (**89l**), good activity was maintained with a variety of substituents in the 4-position of the phenyl ring regardless of their electronic properties (**89c**,**f**,**i**,**j**). The reduced activity of the biphenyl derivative (**89l**) may be due to the increased steric volume of this derivative.

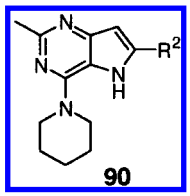
Table 2. In Vitro Y5 Receptor Binding Affinities for Substituted 6-Phenylpyrrolo[3,2-*d*]pyrimidines



compd no.[a]	R	hY5 receptor binding[b] IC_{50} (nM)[c]
1	H	1.1 ± 0.4
89a	2-Cl	660 ± 140
89b	3-Cl	<0.1
89c	4-Cl	<0.1
89d	2-CF_3	2500 ± 790
89e	3-CF_3	<0.1
89f	4-CF_3	0.7 ± 0.6
89g	2-F	44 ± 11
89h	3-F	0.3 ± 0.1
89i	4-F	0.3 ± 0.1
89j	4-Me	0.5 ± 0.3
89k	4-OMe	41 ± 30
89l	4-Ph	1400 ± 270
89m	2,5-diF	79 ± 4.0
89n	2,6-diF	380 ± 100
89o	3,5-diF	0.4 ± 0.3
89p	3,4-diF	<0.1
89q	3,4,5-triF	<0.1

[a] Hydrochloride salts. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound.

Table 3. In Vitro Y5 Receptor Binding Affinities for 6-Substituted Pyrrolo[3,2-*d*]pyrimidines



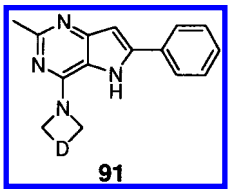
compd no.[a]	R^2	hY5 receptor binding[b] IC_{50} (nM)[c]
90a	Me	160 ± 71
90b	*n*-Pr	66 ± 7.0
90c	*n*-Bu	10 ± 3.0
90d	*n*-pentyl	0.2 ± 0.1
90e	*c*-Hex	11 ± 7.0
90f	CH_2(*c*-Hex)	8.5 ± 1.5
90g	1-adamantyl	45 ± 19
90h	CH_2[(3-CF_3)Ph]	170 ± 78
90i	CH_2[(4-OMe)Ph]	2400 ± 600
90j	CH_2[(4-F)Ph]	860 ± 110
90k	CH_2CH_2Ph	5.3 ± 1.8
90l	CH_2CH_2[(4-OMe)Ph]	150 ± 3.0
90m	CH_2OPh	18 ± 9.5
90n	CH_2S[(4-Cl)Ph]	670 ± 32
90o	CH_2SO_2[(4-Cl)Ph]	8500 ± 1500
90p	2-thienyl	100 ± 74
90q	2-furanyl	1100 ± 800
90r	2-(5-Me)furanyl	0.5 ± 0.4
90s	2-benzofuranyl	0.3 ± 0.2
90t	2-benzothienyl	140 ± 61
90u	2-pyridyl	150 ± 100
90v	2-pyrazinyl	1400 ± 150

[a] Hydrochloride salts. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound.

Derivatives containing alternative replacements for the 6-phenyl group of the lead pyrrolopyrimidine are illustrated in Table 3. The straight chain alkyl derivatives **90a**−**d** show an excellent correlation between Y5 binding affinity and the length of the alkyl group (*n*-pentyl > *n*-Bu > *n*-Pr > Me). These results suggest that these alkyl groups are reaching out to fill a hydrophobic pocket on the human Y5 receptor, and significant binding energy is gained at a distance of 4−5 atoms out from the pyrrolopyrimidine ring. This hydrophobic pocket was able to accommodate medium alkyl and alkylaryl groups such as cyclohexyl, methylenecyclohexyl, and phenethylene derivatives (**90e**,**f**,**k**, respectively), as well as bulky groups such as adamantyl (**90g**). Insertion of a methylene spacer between the pyrrolopyrimidine ring and the cyclohexyl group was beneficial for activity (**90f** vs **90e**); however, insertion of a methylene spacer in the phenyl series reduced binding affinity (**89e** vs **90h**, **89k** vs **90i**, and **89i** vs **90j**). A series of derivatives containing two-atom spacers between the pyrrolopyrimidine and the phenyl group were also prepared. Compounds containing the ethylene and ether spacers retained good affinity (**90k**−**m**), while sulfide and sulfone derivatives were less active (**90n**,**o**). The poor activity of sulfone **90o** supports the hypothesis that hydrophobic groups are preferred in this area of the receptor. The final class of derivatives in this position consisted of compounds wherein the phenyl ring of **1** was replaced with a heterocyclic group (**90p**−**v**). Both the thiophene **90p** and furan **90q** showed decreased affinity as compared to compound **1**. However the effect of adding a methyl group to the 4-position of the furan analogue was striking. As this alkyl group reached out into the hydrophobic pocket of the receptor, the affinity increased 4 orders of magnitude (**90q** vs **90r**). The subnanomolar binding affinity was maintained as the hydrophobic region was expanded further by the addition of a fused phenyl ring (i.e., benzofuran **90s**). Interestingly, a similar increase in potency was not observed in the corresponding thiophene (**90p**) and benzthiophene (**90t**) series. The nitrogen heterocyles, pyridine **90u** and pyrimidine **90v**, did not improve binding interactions in the hydrophobic pocket of the receptor.

The SARs resulting from modifying the R^3 position of the pyrrolopyrimidine ring system are summarized in Tables 4−6 below. Initially the effects of various ring modifications were investigated (Table 4), and series of derivatives with increasing ring size were prepared. The smallest ring (azetidine **91a**) showed a slight reduction in activity; however, derivatives with five-, six-, and seven-membered rings (**91b**, **1**, and **91c**) in the 4-position of the pyrrolopyrimidine all demonstrated potent affinities for the human Y5 receptor. Unsaturation in these rings had no significant effect on the activity of these potent compounds (**91d**,**e**); however, when a heteroatom was introduced into the ring, as in the case of morpholine **91f** and piperizine **91g**, activity was reduced. In addition, removal of the basic nitrogen of **91g** by acylation or sulfonylation of the piperizine nitrogen did not improve activity (compounds **91h**,**i**, respectively). Therefore, as was observed in the R^2 position, these results show that hydrophobic groups in the R^3 position are preferred. More support for this conclusion was also obtained for the series of substituted piperidine derivatives shown in Table 5. Piperidine analogues with hydrophobic substituents (**92a**−**d**) pos-

Table 4. In Vitro Y5 Receptor Binding Affinities for 4-Substituted Pyrrolo[3,2-*d*]pyrimidines

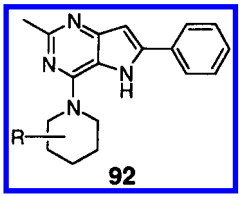


91

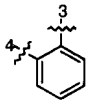
compd no.[a]	D	hY5 receptor binding[b] IC_{50} (nM)[c]
91a	CH_2	57 ± 2.0
91b	CH_2CH_2	0.7 ± 0.2
1	$CH_2CH_2CH_2$	1.1 ± 0.4
91c	$CH_2CH_2CH_2CH_2$	1.8 ± 0.3
91d	CH=CH	2.2 ± 1.7[d]
91e	CH_2CH=CH	0.4 ± 0.1
91f	CH_2OCH_2	100 ± 36
91g	CH_2NHCH_2	7200 ± 3600
91h	$CH_2N(Ac)CH_2$	6000 ± 1000
91i	$CH_2N(SO_2Me)CH_2$	7500 ± 500

[a] Hydrochloride salts with the exception of **91g**. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound. [d] 2.2 ± 1.7 (mean ± standard deviation, n = 77).

Table 5. In Vitro Y5 Receptor Binding Affinities for 4-Piperidino-Substituted Pyrrolo[3,2-*d*]pyrimidines



92

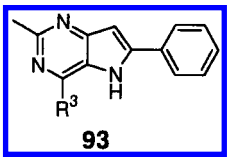
compd no.[a]	R	hY5 receptor binding[b] IC_{50} (nM)[c]
1	H	1.1 ± 0.4
92a	2-Me	3.0 ± 1.5
92b	2,6-*cis*-diMe	17 ± 9.0
92c	2-Et	74 ± 25[d]
92d	3,5-diMe	190 ± 120
92e	$2\text{-}CH_2CH_2OH$	730 ± 310
92f	$2\text{-}CH_2NMe_2$	5200 ± 2700
92g	4-OH	250 ± 17
92h	$4\text{-}NMe_2$	>10000
92i		220 ± 330

[a] Hydrochloride salts with the exception of **92d**,**h**. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound. [d] 74 ± 25 (mean ± standard deviation, n = 87).

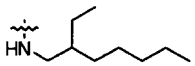
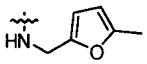
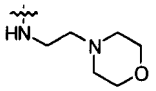
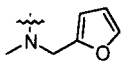
sessed higher affinities than those substituted with hydrophilic groups (**92e**−**h**). The decrease in activity was particularly dramatic when a basic amine is incorporated in this portion of the molecule (**91g** and **92f**,**h**). Isoquinoline **92i** was prepared to further expand the hydrophobic space around the piperizine ring. Although this compound showed lower affinity than compound **1**, its activity was comparable to the 3,5-dimethyl analogue **92d**. The results of **92d**,**i** suggest that some steric bulk can be tolerated in the 3-, 4-, and 5-positions of the piperidine ring without a drastic reduction in activity.

The effects of acyclic amines as well as heterocyclic and carbocyclic substituents at R^3 on the Y5 receptor

Table 6. In Vitro Y5 Receptor Binding Affinities for 4-Substituted Pyrrolo[3,2-*d*]pyrimidines



93

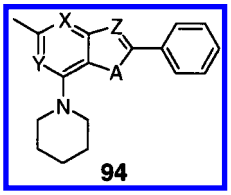
compd no.[a]	R^3	hY5 receptor binding[b] IC_{50} (nM)[c]
93a	NH_2	3100 ± 260
93b	NHPh	540 ± 170[d]
93c	$NHCH_2Ph$	1500 ± 370
93d	$NHCH_2CF_3$	>10000
93e	$NHCH_2CH_2CH_2OEt$	730 ± 330
93f		7800 ± 3900
93g		2600 ± 1400
93h		4000 ± 2300
93i	NEt_2	36 ± 6.0
93j		52 ± 9.0
20	*c*-Hex	8200 ± 2600
93k	3-thienyl	560 ± 100
93l	3-pyridyl	8500 ± 1500

[a] Hydrochloride salts with the exception of **93a**,**c**−**h**,**k**,**l**. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound. [d] 540 ± 170 (mean ± standard deviation, n = 85).

binding affinity of the pyrrolopyrimidine derivatives are shown in Table 6. When the piperidine ring of compound **1** was removed completely, to give the unsubstituted amine (**93a**), lower activity was observed. Secondary amines **93b**−**h** also had lower activity regardless of how much hydrophobic bulk was incorporated on the amine substituent. However, tertiary amines (e.g., **93i**,**j**) had higher affinity. This result supports the previous observation that hydrophobic groups are preferred at R^3. However, further exploration revealed that solely having a hydrophobic group at this position was not sufficient for activity. For example, the lower activity of the cyclohexyl derivative **20** clearly demonstrated that the nitrogen atom at R^3 was preferred. Similarly, other heterocyclic groups connected directly to the pyrrolopyrimidine core through a carbon−carbon bond were also less active (e.g., thiophene **93k** and pyridine **93l**).

The final SARs examined in this investigation resulted from modifications of the lead heterocyclic core obtained by varying X, Y, Z, and A (Table 7). Replacement of the N1 nitrogen of the pyrrolo[3,2-*d*]pyrimidine core system with a carbon gave pyrrolo[3,4-*d*]pyridine **73**. This small modification resulted in a dramatic 1000-fold reduction in activity, indicating that the N1 nitrogen plays a critical role in binding to the human Y5 receptor in this series of compounds. In sharp contrast, elimination of the N3 nitrogen of the pyrrolo[3,2-*d*]-pyrimidine had no effect on activity with the resulting pyrrolo[3,2-*d*]pyridine **65** having an IC_{50} of 1.7 nM. The next position examined was the 7-position of the pyrrolopyrimidine (Z; compound **94**). Any substitution at this position proved to reduce activity (**94a**−**d**, **54**, **56**, and **57**) with the methyl substituent being the best-

Table 7. In Vitro Y5 Receptor Binding Affinities for Furano[3,2-*d*]pyrimidine, Pyrrolo[3,4-*d*]pyridine, Pyrrolo[3,2-*d*]pyridine, Thiopheno[3,2-*d*]pyrimidine, Pyrimidine, and 5-Substituted Pyrrolo[3,2-*d*]pyrimidine Derivatives



94

compd no.[a]	X	Y	Z	A	hY5 receptor binding[b] IC_{50} (nM)[c]
1	N	N	CH	NH	1.1 ± 0.4
73	**CH**	N	CH	NH	1200 ± 520
65	N	**CH**	CH	NH	1.7 ± 0.3
94a	N	N	**CMe**	NH	53 ± 38
94b	N	N	**CEt**	NH	330 ± 94
94c	N	N	**CPh**	NH	420 ± 80
94d	N	N	**CF**	NH	1600 ± 810
54	N	N	**CAc**	NH	5100 ± 2900
56	N	N	**CBr**	NH	580 ± 300
57	N	N	**COMe**	NH	910 ± 250
87	N	N	**N**	NH	470 ± 100
55	N	N	CH	**NMe**	1300 ± 190
81	N	N	CH	**O**	30 ± 0.0
82	N	N	CH	**S**	220 ± 330

[a] Hydrochloride salts with the exception of **54**−**57**. [b] [^{125}I]PYY binding. [c] IC_{50} values reported represent an average of at least two 6-point determinations for each compound.

tolerated (compound **94a**). These results support the hypothesis that planarity between the aromatic ring relative to the pyrrolopyrimidine core is important to binding since substitution at the 7-position perturbs the conformation of the phenyl group. Analogues containing larger alkyl, aryl, or various electron-withdrawing or -donating groups at this position all showed reduced activity. The lower activities of the fluoro derivative **94d** and the purine derivative **87** indicate that not only steric considerations are important at this position but that the electronics of this system may also play a role. Finally, modification of the N5 nitrogen of the pyrrolopyrimidine was examined (Table 7). Alkylation of the N5 nitrogen reduced Y5 binding affinity (compound **55**); however, replacing the nitrogen with other heteroatoms was better tolerated as was seen with furano[3,2-*d*]pyrimidine **81** and thiopheno[3,2-*d*]pyrimidine **82**. Perhaps alkylation of the N5 nitrogen affects an important hydrogen-bonding interaction at the receptor as well as altering the conformation of the phenyl ring relative to the pyrrolopyrimidine ring.

From the SARs discussed, we have generated a pharmacophore model for the interactions of this pyrrolopyrimidine series with the human Y5 receptor. The results and key features of the model are summarized in Figure 1. In general, small electron-donating groups were preferred in the 2-position of the pyrrolopyrimidine ring, and branching was not preferred. One of the key interactions seems to be a hydrogen bond involving the N1 nitrogen. Due to the dramatic effects observed in altering the electronics of the pyrrolopyrimidine ring system, we postulate that the N1 nitrogen may be protonated at the receptor and acting as a hydrogen bond donor in this system. On the other hand, the N3 nitrogen did not play a critical role in binding to the Y5 receptor. Substitution at the 4-position indicated that the receptor had a medium hydrophobic pocket at this position. In general, cyclic hydrophobic amines worked best followed by tertiary amines, while secondary amines and the carbon analogues were less active. The results obtained from alkylation of the N5 nitrogen suggest a possible hydrogen-bonding interaction at this position. The SAR results indicated that a large hydrophobic pocket was likely at the 6-position. Aromatic substitution in the meta and para positions of the 6-phenyl ring enhanced Y5 activity and provided a number of subnanomolar antagonists. Finally, substitution at the 7-position of the pyrrolopyrimidine, or the ortho position of the phenyl ring, was not preferred.

Conclusions

In summary, synthetic entries into a large series of novel pyrrolopyrimidines were developed to explore the SARs of these potential Y5 antagonists. This investigation concentrated on single-point changes to the lead pyrrolopyrimidine **1** to better understand the structural features required for binding to the Y5 receptor. These new deazapurine derivatives were evaluated in an in vitro binding assay to assess how the particular structural modification affected potency. Through the iterative process of synthesis and biological evaluation, we have gained insight into the pharmacophores important to binding to the Y5 receptor within this class of compounds. This study resulted in the development of a working hypothetical model of the human Y5 receptor binding site that we are currently using to aid the development of other novel series of Y5 antagonists. Results of additional studies with other series will be reported in due course. In addition to gaining a better understanding of the receptor interactions, we have prepared several derivatives with very high affinity for the Y5 receptor.[55] These potent Y5 antagonists are currently being examined in more detail using secondary in vitro, in vivo, ADME, and toxicological assays.

Experimental Section

Pharmacology. Membrane Preparation. Human embryonic kidney cells (HEK 293) expressing the human Y5 receptor were harvested from 150-mm culture dishes using PBS. Cells were pelleted by centrifugation at 1500 rpm for 2 min. The resulting pellet was homogenized in 15 mL of ice-cold sucrose buffer (25 mM HEPES, 0.3 M sucrose, pH 7.4) with a motorized, glass-fitted, Teflon homogenizer. The homogenate was centrifuged at 48000*g* at 4 °C for 10 min, resuspended in 15 mL of assay buffer (minimum essential medium with Earle's salts containing 25 mM HEPES, 0.1% BSA, 0.1 mg/mL STI, 0.1 mg/mL Pefabloc, pH 7.4) using a Tissue-Tearor (Biospec Products), and recentrifuged at 48000*g* for 10 min. The pellet was homogenized a third time in 15 mL of assay buffer and the resulting homogenate was centrifuged at 48000*g* for 10 min. The final pellet was resuspended in assay buffer to a wet weight concentration of 10−20 mg/mL.

Radioligand Binding Assay. Binding assays were performed in 96-well U-bottom plates. Membranes (200 μg of tissue) were incubated at 30 °C for 2 h in assay buffer with various drugs in the presence of 0.15 nM [^{125}I]PYY in a total volume of 100 μL. Nonspecific binding was assessed in the presence of 1 μM PYY. The binding reaction was terminated by rapid filtration through Unfilter-96 GF/C glass fiber filter plates, followed by three washes with 300 μL of ice-cold water. Bound radioactivity was determined using a TopCount microplate scintillation and luminescence counter. Nonlinear regression analysis of concentration−response curves to determine IC_{50} values was performed using GraphPad Prism.

Chemistry. General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without

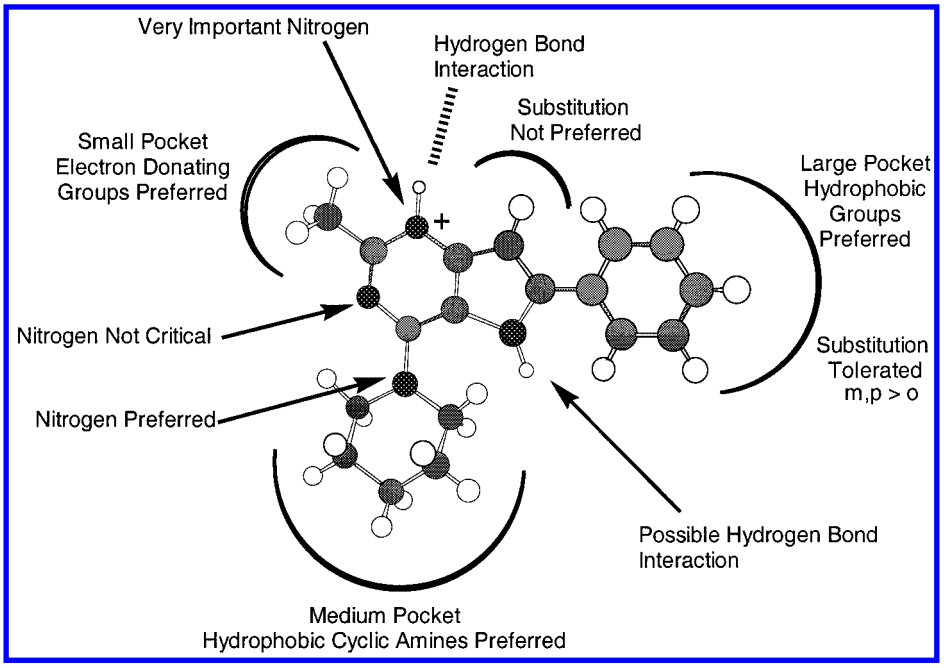


Figure 1. Summary of the preferred features of the pyrrolopyrimidine Y5 receptor antagonists and how they interact with a hypothetical model of the Y5 receptor.

further purification. Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene, and dioxane were obtained from Aldrich Chemical Co. in Sure/Seal bottles. All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atmosphere. Flash chromatography was performed using ICN Biomedicals silica gel (SiliTech 32-63D 60A). Thin-layer chromatography (TLC) was performed with Analtech or Whatman silica gel TLC plates (250 μm). Preparatory TLC was performed with Whatman silica gel TLC plates (2000 μm). ^{1}H NMR spectra were determined with superconducting FT NMR spectrometers operating at 400 and 500 MHz. Chemical shifts are expressed in ppm (δ) downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; quin, quintet), number of protons, and coupling constants in hertz (Hz). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a Buchi 535 capillary melting point apparatus and are uncorrected. Low-resolution mass spectra (MS) were determined on a Perkin-Elmer-SCIEX API 165 mass spectrometer using APCI or ES ionization modes (positive or negative). High-resolution mass spectra (HRMS) were performed on a PerSeptive Biosystems Mariner TOF or by Mass Consortium, San Diego, CA, using FAB ionization.

Four general synthetic methods (routes A−D) were employed to prepare the various pyrrolo[3,2-*d*]pyrimidine analogues examined in this study (vide supra). A representative experimental procedure for each type of synthetic route employed is described below. The general methods used to prepare specific pyrrolo[3,2-*d*]pyrimidine derivatives are indicated, and the supporting characterization data are provided.

Route A. (a) Ethyl 3-Oxo-2-(phenylcarbonylamino)-butanoate (11; R^2 = Ph).[38] To a 1-L, round-bottomed flask were added ethyl 2-(hydroxyimino)-3-oxybutyrate (**10**)[35,36] (25.0 g, 0.157 mol), H_2SO_4 (30% w/v) (230 mL) and crushed ice (250 g). This solution was cooled in an ice−saltwater bath and the internal temperature was monitored with an alcohol thermometer. Powdered zinc (100 mesh) (30.0 g, 0.459 mol) was added to this cooled solution portionwise via a powder addition funnel. The temperature of the reaction was maintained between 0 and 10 °C. After the addition of the zinc was complete the reaction mixture was allowed to stir at 0 °C for 0.5 h. The solution was filtered through a fritted funnel into a 1-L round-bottomed flask. This clear, colorless solution was cooled in an ice−water bath and sodium acetate trihydrate (162.5 g, 1.19 mol) was added with stirring. Benzoyl chloride (18.3 mL, 22.1 g, 0.157 mol) was slowly added to the resulting cloudy solution via a syringe. After the addition was complete, the cold bath was removed and the solution was allowed to stir at room temperature for 24 h. The yellow reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator to give 30.3 g of a yellow oil. This material was purified by flash chromatography on silica gel with 1:4 EtOAc:hexanes as eluant to give 20.0 g (51%) of the title compound as a viscous pale-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (t, 3, J = 7.1), 2.46 (s, 3), 4.31 (m, 2), 5.43 (d, 1, J = 6.4), 7.28 (br m, 1), 7.46 (t, 2, J = 7.6), 7.54 (m, 1), 7.85 (d, 2, J = 7.2). MS *m*/*z*: 250 (M + H), 178 (base).

(b) 2,6-Dimethyl-4-hydroxy-5-benzamidopyrimidine (12; R^1 = Me, R^2 = Ph). Absolute EtOH (150 mL) was added to an oven-dried round-bottomed flask, and small pieces of sodium (4.95 g, 0.215 mol) were added portionwise. A reflux condenser was attached to the flask and the solution was allowed to stir at room temperature until all of the sodium was consumed. Acetamidine hydrochloride (9.95 g, 0.105 mol) was added in one portion, and the resulting creamy white suspension was allowed to stir at room temperature for 0.5 h. In a separate flask ethyl 3-oxo-2-(phenylcarbonylamino)-butanoate (23.8 g, 0.956 mol) was dissolved in absolute EtOH (30 mL). The acetamidine solution was filtered through a plug of Celite into the ketoester solution. As this solution was added, the reaction mixture turned from an orange to a dark-brown color. The mixture was placed under a N_2 atmosphere and allowed to stir at room temperature overnight. As the reaction proceeded solids precipitated out of solution to give a thick brown-orange mixture. The reaction mixture was filtered through a fritted funnel and the solids were washed with EtOH. The solids were dissolved in distilled H_2O, and HCl (concentrated) was added to acidify the solution to a pH of 4−5 (pH paper). Upon acidification solids precipitated out of solution. The solution was cooled in an ice−water bath, the solids were filtered, washed with cold water and dried in a vacuum oven to give 7.59 g (33%) of the title compound as a white powder. The EtOH filtrate was concentrated with a rotary evaporator to give 13 g of a sticky orange oil. This material was purified by flash chromatography on silica gel with 95:5 CH_2Cl_2:MeOH as eluant to give an additional 2.61 g (11%) of the title compound as fluffy pale-yellow flakes (total yield 10.2 g (44%)). Mp: 279−281 °C (lit.[56] mp = 282 °C). ^{1}H

NMR (DMSO-d_6, 500 MHz): δ 2.09 (s, 3), 2.28 (s, 3), 7.51 (t, 2, J = 7.1), 7.58 (t, 1, J = 7.2), 7.96 (d, 2, J = 7.4), 9.51 (s, 1), 12.51 (br s, 1). MS m/z: 244 (M + H). Anal. ($C_{13}H_{13}N_3O_2$) C, H, N.

(c) 2-Methyl-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (13; R^1 = Me, R^2 = Ph). To an oven-dried, 250-mL, round-bottomed flask was added absolute EtOH (45 mL). Small pieces of sodium metal (2.87 g, 0.125 mol) were added portionwise. After all of the sodium was consumed, 2,6-dimethyl-4-hydroxy-5-benzamidopyrimidine (10.1 g, 41.7 mol) was added in one portion via a powder addition funnel. An additional portion of EtOH (20 mL) was added to rinse the last portion of the amide from the funnel. The reaction mixture was heated at reflux for 0.25 h until all of the solids dissolved to give an orange solution. The condenser was replaced with a short-path distillation head and the EtOH was distilled off under a N_2 atmosphere. The resulting solids were scraped off the sides of the flask with a spatula and heated with a heating mantle at 360 °C for 20 min. The residue was allowed to cool to room temperature, dissolved in distilled H_2O (35 mL), and HCl (concentrated) was added portionwise to adjust the pH of the solution to 4−5 (pH paper). The resulting precipitate was filtered and dried in a vacuum oven to give 6.38 g of a tan solid. This material was dissolved in 3 N NaOH (∼30 mL), and the resulting dark-brown solution was filtered through a fritted funnel. Acetic acid was added to the filtrate with stirring. The resulting solids were filtered, washed with distilled H_2O, recrystallized from EtOH and dried in a vacuum oven to give 1.45 g (15%) of the title compound as a tan powder. Mp: >280 °C (lit.[57] mp = 322 dec). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.31 (s, 3), 6.77 (d, 1, J = 2.2), 7.36 (tm, 1, J = 6.5), 7.43 (t, 2, J = 7.6), 7.93 (dd, 2, J = 1.4, 7.2), 11.80 (s, 1), 12.28 (s, 1). MS m/z: 226 (M + H). Anal. ($C_{13}H_{11}N_3O$) C, H, N.

(d) 4-Chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (14; R^1 = Me, R^2 = Ph). Phosphorus oxychloride (2.46 mL, 4.05 g, 26.4 mmol), *N*,*N*-diethylaniline (1.2 mL, 1.12 g, 7.5 mmol), 1,2-dichloroethane (4 mL) and 2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (0.50 g, 2.22 mmol) were added to a 50-mL, oven-dried, round-bottomed flask. The resulting dark-red solution was placed under N_2 and heated at reflux for 3 h. The solution was concentrated with a rotary evaporator to give a dark-red oil. This material was cooled in an ice−water bath and distilled H_2O was added. The solution was filtered through a fritted funnel, and the filtrate was concentrated with a rotary evaporator to give a wet solid. This crude material was basified by the addition of NH_4OH and extracted into EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated with a rotary evaporator to give 0.98 g of an orange oil. This material was purified by flash chromatography on silica gel using EtOAc(20−50%):hexanes(80−50%) as eluant to give 0.24 g (44%) of the title compound as a tan solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.76 (s, 3), 6.90 (s, 1), 7.43 (m, 3), 7.80 (dm, 2, J = 6.5), 10.17 (br s, 1). MS m/z: 243 (M^+), 208 (base).

(e) 2-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (1).[34] To a 5-mL Wheaton vial were added 4-chloro-2-methyl-6-phenylpyrrolo-[3,2-*d*]pyrimidine (1.0 g, 4.1 mmol) and piperidine (2.0 mL, 20.52 mmol). A solution of K_2CO_3 (2.84 g, 20.52 mmol) in H_2O (30 mL) was added, the vial was securely capped, and the reaction mixture was heated at 120 °C for 4 h. After cooling to room temperature, EtOAc was added. The precipitate that formed was collected by filtration, washed with water and hexanes to give a brown solid as crude product. This material was purified by flash chromatography on silica gel with 2:1 EtOAc:hexanes as eluant to give 0.84 g (70%) of the free base as an off-white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.74−1.76 (m, 6), 2.60 (s, 3), 3.79−3.81 (m, 4), 6.76 (s, 1), 7.38−7.49 (m, 3), 7.66 (d, 2, J = 7.54). MS m/z: 293 (M + H), 291 (M − H). A portion of this free base (0.45 g, 1.54 mmol) was dissolved in minimum amount of $CHCl_3$, and HCl (1.54 mL of a 1 N solution in ether, 1.54 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min and the solvent was evaporated in vacuo to give a light-yellow foam. This material was recrystallized from MeOH:H_2O to give 0.26 g of the title compound as white needles. Mp: 293−294 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.71−1.72 (m, 6), 2.58 (s, 3), 4.06−4.07 (m, 4), 6.89 (s, 1), 7.50−7.57 (m, 3), 7.96 (d, 2, J = 7.1), 12.0 (br s, 1), 14.4 (br s, 1). Anal. ($C_{18}H_{21}ClN_4 \cdot H_2O$) C, H, N, Cl.

Route B. (a) 1-(3-Chlorophenyl)-2-cyanovinyl 4-Methylbenzenesulfonate (22; R^2 = 3-ClPh). To a 100-mL, round-bottomed flask were added 3-chlorobenzoylacetonitrile (5.13 g, 28.5 mmol), *p*-toluenesulfonyl chloride (6.53 g, 34.3 mmol) and CH_2Cl_2 (50 mL). To the above solution was added Et_3N (6 mL, 42.8 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 22 h. The cloudy reaction mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, washed three times with H_2O, dried over Na_2SO_4, and concentrated in vacuo to give a dark-red residue. This material was purified by flash chromatography on silica gel with 1:10 EtOAc:hexanes as eluant to give 8.79 g (92%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ [minor isomer 2.45 (s, 3)], 2.47 (s, 3), 5.60 (s, 1) [minor isomer 5.62 (s, 1)], 7.32−7.48 (m, 6), [7.74 (d, 1, J = 8.37)], 7.88 (d, 1, J = 8.40). MS m/z: 351 (base peak), 332 (M − H).

(b) Ethyl 3-Amino-5-(3-chlorophenyl)-1*H*-pyrrole-2-carboxylate (25; R^2 = 3-ClPh). Sodium ethoxide was freshly prepared from Na (1.77 g, 77.1 mmol) and EtOH (30 mL). A solution of 1-(3-chlorophenyl)-2-cyanovinyl 4-methylbenzenesulfonate (8.56 g, 25.7 mmol) and aminodiethyl malonate hydrochloride (5.43 g, 25.7 mmol) in EtOH (70 mL) was added to the sodium ethoxide solution through a dropping funnel. After the addition was complete, the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the residue was partitioned between EtOAc and H_2O. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to give 5.93 g of a brown solid. (This material was used directly in the following step without further purification.)

(c) 6-(3-Chlorophenyl)-2-methylpyrrolo[3,2-*d*]pyrimidin-4-ol (26; alkyl = Me, R^2 = 3-ClPh). Dry HCl gas was bubbled through a solution of ethyl 3-amino-5-(3-chlorophenyl)-pyrrole-2-carboxylate (3.5 g) in 120 mL of acetonitrile at room temperature for 1.5 h. The reaction mixture was capped, and stirred at room temperature overnight. The solvent was evaporated in vacuo to give a solid, which was dissolved in EtOH (70 mL) and 6% aqueous NaOH (23 mL). The reaction mixture was heated at reflux for 6 h. The precipitate that formed was filtered, and dried in a vacuum oven to give 1.17 g of a tan solid as pure product. The filtrate was concentrated and the resulting suspension was filtered to give a viscous solid. This material was purified by flash chromatography on silica gel with 100:5 $CHCl_3$−MeOH as eluant to give 0.46 g (41% overall from the tosylate (**22**; R^2 = 3-ClPh)) of the title compound as a tan solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.31 (s, 3), 6.86 (s, 1), 7.38 (d, 1, J = 7.38), 7.45 (t, 1, J = 7.89), 7.90 (d, 1, J = 7.82), 8.06 (s, 1), 11.81 (br s, 1), 12.41 (br s, 1). MS m/z: 260, 262 (M + H), 258, 260 (M − H).

(d) 4-Chloro-6-(3-chlorophenyl)-2-methylpyrrolo[3,2-*d*]pyrimidine (27; alkyl = Me, R^2 = 3-ClPh). A mixture of 6-(3-chlorophenyl)-2-methylpyrrolo[3,2-*d*]pyrimidin-4-ol (1.55 g, 5.97 mmol) and phosphorus oxychloride (14 mL, 149 mmol) was heated at 120 °C for 24 h. The excess $POCl_3$ was removed under reduced pressure to give a dark-red residue. The residue was diluted with ice−water and adjusted to pH 5 with NH_4OH with stirring and cooling. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1.42 g (85%) of the title compound as a brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.79 (s, 3), 6.92 (s, 1), 7.43−7.46 (m, 2), 7.66 (d, 1, J = 6.5), 7.74 (s, 1), 9.10 (br s, 1). MS m/z: 278 (M + H), 276 (M − 1).

(e) 6-(3-Chlorophenyl)-2-methyl-4-piperidylpyrrolo-[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89b). To a 25-mL, round-bottomed flask were added 4-chloro-6-(3-chlorophenyl)-2-methylpyrrolo[3,2-*d*] pyrimidine (0.5 g, 1.8 mmol) and piperidine (0.89 mL, 9 mmol), followed by addition of a solution of potassium carbonate (2.49 g, 18 mmol) in 10

mL of H_2O. The reaction mixture was stirred at 120 °C for 4 h. The mixture was allowed to cool to room temperature and was extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown solid. This material was purified by flash chromatography on silica gel with 1:1 EtOAc:hexanes as eluant to give 0.42 g (71%) of a beige solid. A portion of this material (0.34 g, 1.1 mmol) was dissolved in minimum amount of $CHCl_3$, and HCl (1.1 mL of a 1 N solution in ether, 1.1 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. Solvent was then evaporated in vacuo to give a light-yellow foam, which was recrystallized from MeOH to give 0.17 g of the title compound as white crystals. Mp: 244.5−246 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.72 (m, 6), 2.57 (s, 3), 4.06−4.07 (m, 4), 7.00 (s, 1), 7.56−7.58 (m, 2), 7.93−7.94 (m, 1), 8.10 (s, 1), 11.99 (br s, 1), 14.31 (br s, 1). MS *m*/*z*: 327, 329 (M + H), 325, 327 (M − H). Anal. ($C_{18}H_{20}Cl_2N_4 \cdot H_2O$) C, H, N, Cl.

Route C. (a) 2-Methyl-4,6-dihydroxy-5-nitropyrimidine (44; R^1 = Me). To a three-necked, round-bottomed flask equipped with an addition funnel, condenser, internal temperature probe and mechanical stirrer were added trifluoroacetic acid (120 mL, 710 mmol) and powdered 2-methyl-4,6-dihydroxypyrimidine (**43**) (20 g, 160 mmol). The suspension was stirred under a N_2 atmosphere for 15 min to allow complete dissolution of the solids. Nitric acid (9.7 mL, 210 mmol, 90% aqueous solution) was added over 25 min while maintaining the internal temperature between 13 and 21 °C by cooling the reaction flask in an ice bath. Stirring was continued for 12 h at room temperature. Water (100 mL) was added, and the resulting precipitate was collected by filtration and washed with H_2O. Recrystallization from H_2O followed by drying in the vacuum oven provided 20 g (68%) of the title compound as a white crystalline solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.9 (s, 3). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 17.94, 118.0, 155.7, 161.7. MS *m*/*z*: 170 (M − H).

(b) 2-Methyl-4,6-dichloro-5-nitropyrimidine (45; R^1 = Me). To a round-bottomed flask equipped with a Dean−Stark trap, reflux condenser, pressure-equalized addition funnel, magnetic stirrer, heating mantle, and internal temperature probe were added 2-methyl-4,6-dihydroxy-5-nitropyrimidine (2.0 g, 11 mmol) and toluene (16 mL). The Dean−Stark trap was filled with toluene (12 mL). For 3 h, the reaction mixture was heated at reflux during which time water collected in the Dean−Stark trap. The reaction vessel was removed from the heat, and after 20 min, diisopropylethylamine (2.8 mL, 16 mmol) was poured into the reaction mixture through the reflux condenser. The reaction mixture was heated at reflux again, and $POCl_3$ (7 mL, 74 mmol) was added through the addition funnel at such a rate as to maintain the internal temperature below 113 °C (8 min). Vigorous bubbling was observed during the addition of $POCl_3$. Following this addition, the reaction mixture was heated for an additional 3 h at reflux. Heat was then removed from the flask, and the reaction was stirred at room temperature for 18 h. The reaction mixture was then poured onto ice−water (100 mL), shaken in a separatory funnel, and filtered through a pad of Celite. The organic layer was collected from the filtrate, and the aqueous layer was extracted twice with ether. All organic fractions were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Heptane was added to the residue, the contents were filtered through a pad of Celite, and concentrated in vacuo to give the title compound (1.1 g, 49%) as brown rodlike crystals in sufficient purity for the next step. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.5 (s, 3). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 27.04, 127.0, 153.6, 170.8.

(c) 6-Phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride (88a). To a mixture of 1-(*N*-pyrrolyl)-1-phenylethylene (1.54 g, 8.90 mmol) [freshly prepared through $TiCl_4$-mediated condensation between acetophenone and pyrrolidine (1.70 g, 8.76 mmol) in ether by the method described by Boger et al.[48]] and *N*,*N*-diisopropylethylamine (1.60 mL, 9.10 mmol) in toluene (15 mL) at room temperature was added 4,6-dichloro-5-nitropyrimidine (1.70 g, 8.76 mmol) slowly under a stream of N_2. The reaction mixture became hot upon mixing and was stirred at room temperature for 2.5 h. The solution was filtered through a fritted-funnel and the residue was washed with hot toluene (3×). The filtrate was concentrated in vacuo and the residue was dissolved in 1:2 toluene:dioxane (24 mL). Piperidine (2.0 mL, 20 mmol) and Et_3N (2.0 mL) were slowly added (exothermic reaction). The mixture was stirred at 100 °C (sand bath temperature) for 1 h and cooled under a N_2 stream. To this solution was added $SnCl_2$ (32 mL of a 1.5 M solution in DMF) and the mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of NaOH (3.80 g, 95.0 mmol) and ice (∼100 mL) and stirred vigorously for 30 min. The resulting slurry (pH ∼ 9) was filtered through a pad of Celite, and the solid residue was washed exhaustively with 10:1 EtOAc−MeOH. The clear filtrate was separated and the organic phase was washed with H_2O (4×) and with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The residue was purified by flash chromatography on silica gel with a gradient eluant of *i*-PrOH(0.4−5%):CH_2Cl_2(99.6−95%) to afford 0.73 g (30%) of the title compound as a brown solid. A portion of this material was converted to its corresponding HCl salt by treating a solution of the free base in CH_2Cl_2 with 1 N ethereal HCl. The resulting solid was filtered and washed with hot EtOAc. MS *m*/*z*: 279 (M + H), 277 (M − H). ^{1}H NMR (CD_3-OD, 500 MHz): δ 2.12 (br s, 6), 4.53 (br s, 4), 7.52 (s, 1), 7.85 (m, 3), 8.01 (m, 2), 8.56 (s, 1). HRMS: calcd for $C_{17}H_{19}N_4$ (M + H) 279.1606, found 279.1606.

Route D. (a) 4-((6*S*,2*R*)-2,6-Dimethylpiperidyl)-6-chloro-2-methyl-5-nitropyrimidine (50; R^1 = Me, R^3 = *cis*-2,6-dimethylpiperidine). To a solution of 4,6-dichloro-2-methyl-5-nitropyrimidine (**45**; R^1 = Me) (2.4 g, 11.8 mmol) and triethylamine (2.4 g, 23.6 mmol) in THF (12 mL) was added a solution of *cis*-2,6-dimethylpiperidine (1.6 g, 11.8 mmol) in THF (12 mL) slowly. The final reaction mixture was stirred at room temperature for 3 days. After the removal of solvent in vacuo, the crude material was purified by flash chromatography on silica gel with EtOAc(0−10%):hexanes(100−90%) as eluant to afford the title compound (2.8 g, 84%) as a brown solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.29 (d, 6, J = 7.0), 1.56 (m, 1), 1.60−1.63 (m, 2), 1.73 (m, 2), 1.84−1.90 (m, 1), 2.50 (s, 3), 4.42 (m, 2). MS *m*/*z*: 285 (M + H), 283 (M − H).

(b) 4-((6*S*,2*R*)-2,6-Dimethylpiperidyl)-6-chloro-2-methylpyrimidin-5-ylamine (51; R^1 = Me, R^3 = *cis*-2,6-dimethylpiperidine). To a solution of 4-((6*S*,2*R*)-2,6-dimethylpiperidyl)-6-chloro-2-methyl-5-nitropyrimidine (2.3 g, 7.9 mmol) in anhydrous diethyl ether (15 mL) was added a freshly prepared solution of $SnCl_2 \cdot 2H_2O$ (32 mL, 2.0 M in concentrated aqueous HCl) slowly under N_2 at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and then was poured onto an ice bath containing NaOH (12 g). The aqueous phase was extracted with EtOAc (4 × 100 mL). The aqueous phase was passed through a pad of Celite and was extracted again with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using EtOAc(0−50%):hexanes(100−50%) as eluant to afford the title compound (0.80 g, 40%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75 (d, 6, J = 6.2), 1.31−1.34 (m, 2), 1.50−1.60 (m, 1), 1.72−1.76 (m, 3), 2.55 (s, 3), 3.03−3.07 (m, 2), 4.34 (br s, 2). MS *m*/*z*: 255 (M + H).

(c) 4-((6*S*,2*R*)-2,6-Dimethylpiperidyl)-2-methyl-6-(2-phenylethynyl)pyrimidin-5-ylamine (52; R^1 = Me, R^2 = Ph, R^3 = *cis*-2,6-dimethylpiperidine). A mixture of 4-((6*S*,2*R*)-2,6-dimethylpiperidyl)-6-chloro-2-methylpyrimidin-5-ylamine (0.35 g, 1.4 mmol), phenylacetylene (0.28 g, 2.7 mmol), $Pd(PPh_3)_2Cl_2$ (0.050 g, 0.068 mmol) and CuI (0.013 g, 0.068 mmol) in triethylamine (3 mL) was stirred under N_2 at 70 °C overnight. Upon cooling to room temperature, the reaction mixture was diluted with $CHCl_3$ (50 mL), passed through a pad of Celite and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with EtOAc-(0−8%):hexanes (100−92%) as eluant to afford 0.41 g, (95%) of the title compound as a cherry-colored semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (d, 6, J = 6.2), 1.25−1.40 (m, 2),

1.50−1.60 (m, 1), 1.74−1.77 (m, 3), 2.59 (s, 3), 4.57 (br s, 2), 7.38 (m, 3), 7.60 (m, 2). MS *m/z*: 321 (M + H).

(d) 4-((6*S*,2*R*)-2,6-Dimethylpiperidyl)-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine Hydrochloride (92b). A solution of 4-((6*S*,2*R*)-2,6-dimethylpiperidyl)-2-methyl-6-(2-phenylethynyl)pyrimidin-5-ylamine (0.39 g, 1.2 mmol) and CuI (0.021 g, 0.12 mmol) in anhydrous DMF (3 mL) was stirred under N_2 at 110 °C overnight. Upon cooling to the room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL), passed through a pad of Celite and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel with EtOAc(0−80%): hexanes(100−20%) as eluant to afford the free base of the product as a brown solid (0.20 g, 50%). Mp: 223−225 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (d, 6, J = 6.8), 1.61−1.70 (m, 3), 1.81−1.96 (m, 3), 2.61 (s, 3), 4.63 (br s, 2), 6.78 (s, 1), 7.39 (t, 1, J = 7.3), 7.48 (t, 2, J = 7.3), 7.66 (d, 2, J = 7.3), 8.39 (s, 1). MS *m/z*: 321 (M + H). The above material (0.19 g, 0.61 mmol) was dissolved in diethyl ether (20 mL) and HCl (0.64 mL of a 1 N solution in ether, 0.64 mmol) was added dropwise. After stirring at room temperature for 10 min, the solution was concentrated in vacuo. Recrystallization from MeOH afforded 0.13 g (65%) of the title compound as an off-white solid. Mp: >270 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.34 (d, 6, J = 6.7), 1.59 (m, 1), 1.78 (m, 4), 1.94 (m, 1), 2.61 (s, 3), 5.14 (br s, 2), 6.88 (s, 1), 7.51−7.59 (m, 3), 7.95 (d, 2, J = 6.8), 11.60 (s, 1), 14.28 (s, 1). MS *m/z*: 321 (M + H). Anal. ($C_{20}H_{24}N_4$·HCl) C, H, N.

Pyrrolo[3,2-*d*]pyrimidines 88e,g, 89j, 90e,g, 91a−g, 92a,c−i, and 93a−l. These compounds were prepared by the methods analogous to those described in route A from appropriate starting materials. The analytical data for these pyrrolo[3,2-*d*]pyrimidine analogues are shown below. The reported yields represent the yields obtained for the final step of the sequence.

2-Isopropyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrate (88e). Yield: 0.048 g (88%) of a cream-colored solid. Mp: 269.5−272 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.25 (d, 6, J = 6.8), 1.66 (br s, 6), 2.95 (septet, 1, J = 6.8), 3.73 (br s, 4), 6.78 (s, 1), 7.39 (m, 1), 7.48 (m, 2), 7.89 (d, 2, J = 7.7), 11.06 (s, 1). MS *m/z*: 321 (M + H), 307, 240, 171. Anal. ($C_{20}H_{24}N_4$·0.5H_2O) C, H, N.

2,6-Diphenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (88g). Yield: 0.061 g (42%) of a white solid. Mp: 259−261.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (br s, 6), 3.85 (br s, 4), 6.94 (d, 1, J = 1.6), 7.37−7.53 (m, 6), 7.94 (d, 2, J = 8.3), 8.40 (2, dd, J = 1.4, 8.3), 11.16 (s, 1). MS *m/z*: 355 (M + H). Anal. ($C_{23}H_{22}N_4$·0.5H_2O) C, H, N.

2-Methyl-6-(4-methylphenyl)-4-piperidylpyrrolo[3,2-*d*]-pyrimidine (89j). Yield: 0.050 g (60%) of a tan solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.74−1.76 (m, 6), 2.40 (s, 3), 2.58 (s, 3), 3.79−3.81 (m, 4), 6.67 (s, 1), 7.25 (d, 2, J = 7.8), 7.54 (d, 2, J = 7.7). MS *m/z*: 307 (M + H), 305 (M − H). HRMS: calcd for $C_{19}H_{23}N_4$ (M + H) 307.1923, found 307.1910.

6-Cyclohexyl-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (90e). Yield: 0.12 g (79%) of a beige sandy solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.43−1.60 (m, 5), 1.79 (br s, 6), 1.92 (m, 3), 2.10 (br d, 2, J = 10.9), 2.65 (s, 3), 3.01 (m, 1), 4.16 (br s, 4), 6.38 (s, 1), 11.90 (s, 1), 14.28 (s, 1). MS *m/z*: 299 (M + H). Anal. ($C_{18}H_{26}N_4$·HCl·0.1H_2O) C, H, N, Cl.

6-Adamantanyl-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (90g). Yield: 0.034 g (74%) of a beige solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.49 (br s, 6), 1.60 (s, 6), 1.85 (s, 6), 1.90 (s, 3), 2.32 (s, 3), 3.80 (s, 4), 6.06 (s, 1), 10.83 (s, 1), 13.87 (s, 1). MS *m/z*: 351 (M + H). Anal. ($C_{22}H_{30}N_4$·HCl·H_2O) C, H, N, Cl.

4-Azetidinyl-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (91a). Yield: 0.19 g (56%) of white crystals. Mp: >300 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.48−2.52 (m, 2), 2.55 (s, 3), 4.46−4.63 (m, 4), 6.88 (s, 1), 7.49−7.57 (m, 3), 7.95 (d, 2, J = 7.69), 11.78 (br s, 1), 14.32 (br s, 1). MS *m/z*: 265 (M + H), 263 (M − H). Anal. ($C_{16}H_{16}N_4$·HCl·H_2O) C, H, N, Cl.

2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-*d*]pyrimidine (91b). Yield: 0.042 g (53%) of an off-white solid. An analytical sample was obtained by recrystallization from EtOH. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.07 (t, 4, J = 6.3), 2.58 (s, 3), 3.88−3.90 (m, 4), 6.71 (s, 1), 7.36−7.46 (m, 3), 7.63 (d, 2, J = 7.7). MS *m/z*: 279.5 (M + H), 277.5 (M − H). HRMS: calcd for $C_{17}H_{19}N_4$ (M + H) 279.1610, found 279.1613.

4-Homopiperidyl-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (91c). Yield: 0.054 g (62%) of a white solid. An analytical sample was obtained by recrystallization from EtOAc. Mp: 209−210 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65−1.68 (m, 4), 1.93−1.97 (m, 4), 2.57 (s, 3), 3.91 (t, 4, J = 5.9), 6.75 (s, 1), 7.37−7.49 (m, 3), 7.63 (d, 2, J = 7.43), 8.19 (br s, 1). MS *m/z*: 307 (M + H), 305 (M − H). HRMS: calcd for $C_{19}H_{23}N_4$ (M + H) 307.1923, found 307.1933.

2-Methyl-6-phenyl-4-pyrrolinylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (91d). Yield: 0.24 g (85%) of an off-white solid. Mp: 278−278.3 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.60 (s, 3), 4.59 (br s, 2), 5.05 (br s, 2), 6.12 (s, 2), 6.91 (s, 1), 7.49−7.58 (m, 3), 7.97 (d, 2, J = 7.2), 11.62 (s, 1). MS *m/z*: 277 (M + H), 275 (M − H). Anal. ($C_{17}H_{16}N_4$·1.1HCl·H_2O) C, H, N, Cl.

2-Methyl-6-phenyl-4-(1,2,3,6-tetrahydropyridinyl)pyrrolo[3,2-*d*]pyrimidine Hydrochloride (91e). Yield: 0.29 g (74%) of product. Mp: 278−279 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.57 (s, 2), 2.8 (s, 3), 4.38 (t, 2, J = 5.53), 4.86 (s, 2), 6.1 (d, 1, J = 10.2), 6.20 (d, 1, J = 10), 7.14 (s, 1), 7.72−7.81 (m, 3), 8.2 (d, 2, J = 7.2), 12.18 (s, 1), 14.81 (br s, 1). MS *m/z*: 291 (M + H), 289 (M − H). Anal. ($C_{18}H_{18}N_4$·HCl) C, H, N.

4-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)morpholine Hydrate (91f). Yield: 0.04 g (33%) of a white solid. Mp: 276 °C dec. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.62 (s, 3), 3.87 (s, 4), 3.90 (s, 4), 6.79 (s, 1), 7.41 (t, 1, J = 6.8), 7.48 (t, 2, J = 7.4), 7.67 (d, 2, J = 6.8), 8.17 (br s, 1). MS *m/z*: 295 (M + H). Anal. ($C_{17}H_{18}N_4O$·0.25H_2O) C, H, N.

2-Methyl-6-phenyl-4-piperazinylpyrrolo[3,2-*d*]pyrimidine Hydrate (91g). Yield: 0.035 g (29%) of an off-white solid. Mp: 236 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.42 (s, 3), 2.85 (t, 4, J = 5.2), 3.62 (t, 4, J = 5.2), 6.77 (s, 1), 7.36 (m, 1), 7.45 (t, 2, J = 7.8), 7.95 (d, 2, J = 7.6), 10.96 (s, 1). MS *m/z*: 294 (M + H). Anal. ($C_{17}H_{19}N_5$·0.5H_2O) C, H, N.

2-Methyl-6-phenyl-4-(2-methylpiperidinyl)pyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (92a). Yield: 0.20 g (71%) of product. Mp: 268−269 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.17 (d, 3, J = 6.8), 1.31−1.82 (m, 8), 2.41 (s, 3), 3.3 (br s, 1), 4.46 (br s, 1), 5.11 (br s, 1), 6.72 (s, 1), 7.34−7.42 (m, 3), 7.77 (d, 2, J = 7.27), 11.71 (br s, 1). MS *m/z*: 307 (M + H). Anal. ($C_{19}H_{22}N_4$·HCl·H_2O) C, H, N, Cl.

2-Methyl-6-phenyl-4-(2-ethylpiperidinyl)pyrrolo[3,2-*d*]-pyrimidine Hydrochloride Hydrate (92c). Yield: 0.28 g (74%) of product. Mp: 228−229 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.83 (t, 3, J = 7.23), 1.63−1.95 (m, 8), 2.57 (s, 3), 3.37 (br s, 3), 4.56−5.13 (br d, 2), 6.89 (s, 1), 7.5−7.58 (m, 3), 7.94 (d, 2, J = 7.3), 11.96 (br s, 1). MS *m/z*: 321 (M + H). Anal. ($C_{20}H_{24}N_4$·HCl·0.5H_2O) C, H, N, Cl.

***cis*/*trans*-4-(3,5-Dimethylpiperidinyl)-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (92d).** Yield: 0.054 g (50%) of a 95:5 mixture of isomers as colorless crystals. Mp: 225.5−227 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) (for major isomer): δ 0.90 (m, 2), 0.91 (d, 6, J = 6.5), 1.73 (m, 2), 2.40 (s, 3), 2.42 (br s, 2), 4.42 (br d, 2, J = 8.2), 6.74 (s, 1), 7.40 (m, 1), 7.49 (br s, 2), 7.89 (d, 2, J = 7.4), 11.06 (s, 1). MS *m/z*: 321 (M + H). Anal. ($C_{20}H_{24}N_4$) C, H, N.

1-(2-Methyl-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)-2-piperidineethanol Hydrochloride (92e). Yield: 0.039 g (11%) of product. Mp: 273−273.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.34−2.12 (m, 6H), 2.38 (s, 3), 2.47−3.55 (m, 5), 4.67 (br d, 2), 6.76 (s, 1), 7.29−7.36, (m, 3), 7.72 (d, 2, J = 6.72), 12.35 (br s, 1), 14.02 (br s, 1). MS *m/z*: 337 (M + H), 335 (M − H). Anal. ($C_{20}H_{24}N_4O$·HCl) C, H, N, Cl.

Dimethyl{[1-(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-2-piperidyl]methyl}amine Hydrochloride (92f). Yield: 0.043 g (34%) of a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.63 (m, 6), 2.29 (s, 6), 2.40 (s, 3), 2.81 (m, 2), 3.03 (br t, 1, J = 11.8), 4.53−4.63 (m, 2), 6.75 (s, 1), 7.37 (m, 1),

7.50 (t, 2, J = 7.5), 7.81 (d, 2, J = 7.8), 12.47 (s, 1). MS m/z: 350 (M + H), 305, 214. HRMS: calcd for $C_{21}H_{28}N_5$ (M + H) 350.2345, found 350.2342.

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)piperidin-4-ol Hydrochloride Hydrate (92g). Yield: 0.30 g (48%) of a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.51−1.59 (m, 2), 2.58 (s, 3), 3.78−3.90 (m, 3), 4.34−4.37 (m, 2), 6.89 (s, 1), 7.49−7.57 (m, 3), 7.96 (d, 2, J = 7.2), 11.8 (br s, 1). MS m/z: 308 (M + H). Anal. ($C_{18}H_{20}N_4O$·HCl·0.25H_2O) C, H, N, Cl.

Dimethyl[1-(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-4-piperidyl]amine Monohydrate (92h). Yield: 0.059 g (44%) of product. Mp: 261.5−263 °C. MS m/z: 336 (M + H), 291, 237. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.50 (br q, 2H, J = 10.4), 1.86 (d, 2, J = 11.8), 2.20 (s, 6), 2.36 (m,1), 2.42 (s, 3), 3.00 (br t, 2, J = 11.2), 4.46 (br d, 2H, J = 10.4), 6.76 (s, 1), 7.40 (br d, 1, J = 6.4), 7.47 (t, 2, J = 6.4), 7.90 (d, 2H, J = 7.6), 11.02 (s, 1). Anal. ($C_{20}H_{25}N_5$·H_2O) C, H, N.

2-Methyl-6-phenyl-4-(1,2,3,4-tetrahydroquinolin-2-yl)-pyrrolo[3,2-*d*]pyrimidine (92i). Yield: 0.11 g (75%) of an off-white solid. Mp: 251−253 °C dec. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.63 (s, 3), 3.09 (t, 2, J = 5.9), 4.13 (t, 2, J = 5.9), 5.02 (s, 2), 6.78 (s, 1), 7.21−7.25 (m, 4), 7.38−7.50 (m, 3), 7.66 (d, 2, J = 7.3), 8.37 (br s, 1). MS m/z: 341 (M + H), 339 (M − H). Anal. ($C_{22}H_{20}N_4$) C, H, N.

2-Methyl-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ylamine (93a). Yield: 0.005 g (5%) of an off-white solid. Mp: >280 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ 2.53 (s, 3), 6.74 (s, 1), 7.44 (t, 1, J = 7.2), 7.52 (t, 2, J = 7.5), 7.82 (d, 2, J = 7.5). MS m/z: 225 (M + H). HRMS: calcd for $C_{13}H_{13}N_4$ (M + H) 225.1140, found 225.1119.

(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)phenylamine Hydrochloride (93b). Yield: 0.057 g (41%) of an off-white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.67 (s, 3), 7.04 (s, 1), 7.21−7.23 (m, 1), 7.44−7.59 (m, 5), 8.03 (d, 2, J = 8.0), 8.15 (d, 2, J = 8.0), 11.61 (br s, 1), 13.84 (br s, 1). MS m/z: 301 (M + H). HRMS: calcd for $C_{19}H_{16}N_4$ (M + H) 301.1448, found 301.1435.

(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)benzylamine (93c). Yield: 0.24 g (93%) of an off-white solid. Mp: 275−276.5 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.41 (s, 3), 4.73 (s, 2), 6.75 (s, 1), 7.30−7.49 (m, 9), 7.80 (d, 2, J = 7.3), 11.50 (br s, 1). MS m/z: 315 (M + H). HRMS: calcd for $C_{20}H_{19}N_4$ (M + H) 315.1610, found 315.1602.

(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)(2,2,2-trifluoroethyl)amine (93d). Yield: 0.021 g (29%) of a white solid. Mp: >310 °C. MS m/z: 307 (M + H), 294, 281, 226. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.31 (s, 3), 2.52 (s, 2), 6.74 (s, 1), 7.33 (t, 1, J = 7.3), 7.43 (t, 2, J = 7.8), 7.92 (d, 2, J = 7.3), 11.74 (s, 1), 12.22 (s, 1). HRMS: calcd for $C_{15}H_{14}F_3N_4$ (M + H) 307.1168, found 307.1160.

(3-Ethoxypropyl)(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)amine (93e). Yield: 0.056 g (44%) of a light-yellow oil that solidified upon standing. Mp: 208−209.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.16 (t, 3, J = 7.0), 1.99 (quin, 2, J = 5.8, 6.4), 2.58 (s, 3), 3.52 (q, 2, J = 7.1), 3.63 (t, 2, J = 5.6), 3.74 (t, 2, J = 6.6), 5.95 (br s, 1), 6.67 (s, 1), 7.33 (t, 1, J = 7.4), 7.40 (t, 2, J = 7.6), 7.66 (d, 2, J = 7.6). MS m/z: 311 (M + H). HRMS: calcd for $C_{18}H_{23}N_4O$ (M + H) 311.1872, found 311.1892.

(2-Ethylhexyl)(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)amine (93f). Yield: 0.061 g (63%) of a white solid. An analytical sample was obtained by recrystallization from *i*-PrOH. Mp: 288−289 °C dec. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.72−0.78 (m, 6), 1.15−1.34 (m, 9), 2.62 (s, 3), 3.56 (dd, 2, J = 5.3, 7.6), 6.71 (s, 2), 7.17−7.24 (m, 3), 7.59 (d, 2, J = 7.6), 12.78 (br s, 1). MS m/z: 337 (M + H), 335 (M − H). HRMS: calcd for $C_{21}H_{29}N_4$ (M + H) 337.2392, found 337.2397.

[(5-Methyl-2-furyl)methyl](2-methyl-6-phenylpyrrolo-[2,3-*e*]pyrimidin-4-yl)amine (93g). Yield: 0.037 g (62%) of a beige solid. Mp: 125−127.5 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 2.28 (s, 3), 2.53 (s, 3), 4.72 (s, 2), 5.97 (d, 1, J = 3.0), 6.24 (d, 1, J = 3.0), 6.66 (s, 1), 7.34 (m, 1), 7.43 (t, 2, J = 7.7), 7.71 (dd, 2, J = 7.1, 1.4). MS m/z: 319 (M + H), 294, 225, 195, 147. HRMS: calcd for $C_{19}H_{19}N_4O$ (M + H) 319.1555, found 319.1566.

(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)(2-morpholin-4-ylethyl)amine Hydrate (93h). Yield: 0.060 g (43%) of a white solid. Mp: >280 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 2.60 (s, 3), 2.67 (m, 4), 2.79 (t, 2, J = 6.4), 3.81 (m, 4), 3.88 (t, 2, J = 6.3), 6.78 (s, 1), 7.47 (m, 1), 7.57 (t, 2, J = 7.4), 7.86 (d, 2, J = 8.1). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 26.3, 39.2, 55.9, 60.1, 68.8, 99.9, 127.3, 128.3, 130.6, 131.2, 134.0, 143.1, 149.8, 151.1, 161.5. MS m/z: 338 (M + H). Anal. ($C_{19}H_{23}N_5O$·0.25H_2O) C, H, N.

Diethyl(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)amine (93i). Yield: 0.19 g (68%) of an off-white powder. Mp: 184−185 °C (lit[34] mp = 183−185 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.37 (t, 6, J = 7.0), 2.57 (s, 3), 3.77 (q, 4, J = 7.0), 6.75 (s, 1), 7.38 (t, 1, J = 7.3), 7.47 (t, 2, J = 7.5), 7.63 (d, 2, J = 7.6), 8.13 (br s, 1). MS m/z: 281 (M + H). Anal. ($C_{17}H_{20}N_4$) C, H, N.

[(2-Furylmethyl)methyl](2-methyl-6-phenylpyrrolo-[2,3-*e*]pyrimidin-4-yl)amine (93j). Yield: 0.054 g (59%) of an off-white solid. An analytical sample was obtained by recrystallization from EtOAc. Mp: 168−169 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.62 (s, 3), 3.35 (s, 3), 4.83 (s, 2), 6.42−6.44 (m, 2), 6.79 (s, 1), 7.36−7.48 (m, 4), 7.64 (d, 2, J = 7.2), 8.91 (br s, 1). MS m/z: 319.5 (M + H), 317.0 (M − H). HRMS: calcd for $C_{19}H_{19}N_4O$ (M + H) 319.1559, found 319.1566.

Pyrrolo[3,2-*d*]pyrimidines 93k,l. These compounds were prepared by the method analogous to that described for compound **19** from the appropriate boronic acids. The analytical data for these pyrrolo[3,2-*d*]pyrimidine analogues are shown below. The reported yields represent the yields obtained for the final step of the sequence.

3-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-thiophene (93k). Yield: 0.043 g (73%) of an off-white solid. Mp: 232−233 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.86 (s, 3), 6.94 (d, 1, J = 2.0), 7.46 (t, 1, J = 7.7), 7.52 (t, 2, J = 7.7), 7.59 (dd, 1, J = 2.9, 5.0), 7.66 (m, 3), 8.04 (dd, 1, J = 1.2, 2.9), 8.57 (s, 1). MS m/z: 292 (M + H), 290 (M − H). HRMS: calcd for $C_{17}H_{14}N_3S$ (M + H) 292.0908, found 292.0936.

2-Methyl-6-phenyl-4-(3-pyridinyl)pyrrolo[3,2-*d*]pyrimidine (93l). Yield: 0.17 g (64%) of a yellow solid. Mp: 252−254 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.89 (s, 3), 6.99 (s, 1), 7.46 (m, 4), 7.78 (d, 2, J = 7.1), 8.37 (d, 1, J = 7.7), 8.66 (d, 1, J = 3.9), 9.31 (s, 1), 9.50 (s, 1). MS m/z: 287 (M + H), 285 (M − H). HRMS: calcd for $C_{18}H_{15}N_4$ (M + H) 287.1297, found 287.1288.

Pyrrolo[3,2-*d*]pyrimidines 88b−d,f,h, and 89c,i,k. These compounds were prepared by the methods analogous to those described in route B from appropriate starting materials. The analytical data for these pyrrolo[3,2-*d*]pyrimidine analogues are shown below. The reported yields represent the yields obtained for the final step of the sequence.

2-Ethyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (88b). Yield: 0.11 g (28%) of light-tan crystals. Mp: 286−288 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.32 (t, 3, J = 7.53), 1.72 (m, 6), 2.87 (q, 2, J = 7.51), 4.08−4.09 (m, 4), 6.90 (s, 1), 7.51−7.57 (m, 3), 7.96 (d, 2, J = 7.36), 12.01 (br s, 1), 14.36 (br s, 1). MS m/z: 307 (M + H), 305 (M − H). Anal. ($C_{19}H_{22}N_4$·HCl·H_2O) C, H, N, Cl.

6-Phenyl-4-piperidyl-2-propylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (88c). Yield: 0.32 g (49%) of off-white crystals. Mp: 258.0−262.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.92 (t, 3, J = 7.4), 1.67 (m, 6), 1.72−1.81 (m, 2), 2.77 (t, 2, J = 7.4), 4.02−4.03 (m, 4), 6.86 (s, 1), 7.45−7.53 (m, 3), 7.91 (d, 2, J = 7.0), 12.00 (br s, 1). MS m/z: 321 (M + H). Anal. ($C_{20}H_{24}N_4$·HCl·H_2O) C, H, N, Cl.

2-Cyclopropyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (88d). Yield: 0.020 g (14%) of white needles. Mp: 285.4−286.0 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.14−1.21 (m, 4), 1.67−1.71 (m, 6), 2.20−2.24 (m, 1), 3.98−3.99 (m, 4), 6.88 (s, 1), 7.49−7.65 (m,

3), 7.95 (d, 2, J = 7.78), 11.95 (br s, 1), 14.51 (br s, 1). MS m/z: 319 (M + H), 317 (M − H). Anal. ($C_{20}H_{22}N_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2-(2-Methylpropyl)-6-phenyl-4-piperidylpyrrolo[3,2-*d*]-pyrimidine Hydrochloride Monohydrate (88f). Yield: 0.31 g (40%) of orange crystals. Mp: 226.0−229.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.19 (d, 6, J = 7.0), 1.93 (m, 6), 2.40−2.50 (m, 1), 2.92 (d, 2, J = 7.0), 4.28−4.30 (m, 4), 7.13 (s, 1), 7.72−7.81 (m, 3), 8.18 (d, 2, J = 8.3), 12.25 (br s, 1). MS m/z: 335 (M + H). Anal. ($C_{21}H_{26}N_4 \cdot HCl \cdot H_2O$) C, H, N.

6-Phenyl-4-piperidyl-2-(trifluoromethyl)pyrrolo[3,2-*d*]-pyrimidine Hydrochloride Monohydrate (88h). Yield: 0.10 g (21%) of light-pink crystals. Mp: 235.1−237.5 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.68 (m, 6), 3.84−3.85 (m, 4), 7.02 (s, 1), 7.44−7.55 (m, 3), 7.93 (d, 2, J = 7.68), 11.53 (br s, 1). MS m/z: 347 (M + H), 345 (M − H). Anal. ($C_{18}H_{17}F_3N_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

6-(4-Chlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]-pyrimidine Hydrochloride Monohydrate (89c). Yield: 0.14 g (36%) of tan crystals. Mp: 253.8−255.2 dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.70−1.71 (m, 6), 2.57 (s, 3), 4.06−4.07 (m, 4), 6.94 (s, 1), 7.63 (d, 2, J = 8.60), 8.01 (d, 2, J = 8.6), 12.0 (br s, 1), 14.3 (br s, 1). MS m/z: 327, 329 (M + H), 325, 327 (M − H). Anal. ($C_{18}H_{19}ClN_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

6-(4-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]-pyrimidine Hydrochloride Monohydrate (89i). Yield: 0.067 g (19%) of off-white crystals. Mp: 287−289 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.87−1.88 (m, 6), 2.74 (s, 3), 4.22−4.23 (m, 4), 7.05 (s, 1), 7.55−7.59 (m, 2), 8.19−8.22 (m, 2), 12.18 (br s, 1), 14.63 (br s, 1). MS m/z: 311 (M + H), 309 (M − H). Anal. ($C_{18}H_{19}FN_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

4-Methoxy-1-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)benzene Hydrochloride Monohydrate (89k). Yield: 0.077 g (35%) of light-tan crystals. Mp: 267.5−268 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.63−1.72 (m, 6), 2.54 (s, 3), 3.84 (s, 3), 4.00 (m, 4), 6.78 (s, 1), 7.10 (d, 2, J = 8.67), 7.90 (d, 2, J = 8.67), 8.56 (br s, 1), 11.73 (br s, 1). Anal. ($C_{19}H_{22}N_4O \cdot HCl \cdot H_2O$) C, H, N, Cl.

Pyrrolo[3,2-*d*]pyrimidines 90b,d,f. These compounds were prepared by the methods analogous to those described in route B from appropriate starting materials. The requisite substituted pyrroles **25** needed for these derivatives were prepared via the acetylene intermediates **23** by the general method as described below.

General Method of Pyrroles 25 from Acetylenes 23. Into a dry three-necked 1-L round-bottomed flask equipped with a mechanical stirrer, thermometer, and 150-mL addition funnel under nitrogen pressure were placed anhydrous Et_2O (90 mL) and 0.2 mol of the appropriate terminal alkyne. The solution was cooled to −70 °C, and *n*-butyllithium (100 mL, 0.2 mol of a pentane solution) was added at a rate to maintain the reaction temperature below −40 °C. Phenyl cyanate (0.22 mol) was added slowly via a syringe pump at such a rate as to prevent the reaction from rising above −60 °C. After stirring for an additional 30 min, the solution was allowed to warm to room temperature. To this dark solution were successively added 6 N NaOH (240 mL) and Et_2O (500 mL). The solution was stirred for 15 min and transferred into a 1-L separatory funnel. The phases were separated and the aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with 6 N NaOH (2 × 200 mL) and with saturated aqueous NaCl (4 × 200 mL), and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was dissolved in pentane (500 mL). The pentane solution was passed through a short path of Celite. The solvent was removed and the dark oils were distilled under a vacuum to give the desired nitriles **23** (R^2 = *n*-Pr, *n*-pentyl, and *c*-Hex) as colorless oils.

Diethyl aminomalonate hydrochloride (24 g, 0.1 mol) was dissolved in absolute ethanol (80 mL). To the above solution was then added NaOEt which was prepared freshly from Na (2.6 g, 0.11 mol) and absolute ethanol (100 mL). The resulting white cloudy solution was stirred for 1 h and then passed through a short bed of Celite to afford a clear solution which was transferred directly into a 500-mL, round-bottomed flask containing a THF solution of the appropriate alk-2-ynenitrile (0.1 mol). An additional portion of NaOEt (1.0 equiv) was freshly prepared from Na (2.6 g, 0.11 mol) and absolute ethanol (100 mL) and added dropwise through an addition funnel into the THF solution. After the addition was complete, the resulting cloudy red solution was stirred at ambient temperature overnight and concentrated in vacuo to give an oil. Water and EtOAc were added, and the aqueous layer was extracted with EtOAc (3×). The combined EtOAc layers were dried over Na_2SO_4 and concentrated in vacuo to give a red oil. The compounds were isolated by flash chromatography on silica gel with 1:5 EtOAc:hexanes as eluant to give the requisite pyrroles **25** (R^2 = *n*-Pr, *n*-pentyl, and *c*-Hex) as a red oils. These pyrroles were employed to prepare pyrrolo[3,2-*d*]pyrimidines **90b**,**d**,**f** by the methods analogous to those described in route B. The analytical data for the pyrrolo[3,2-*d*]pyrimidine analogues are shown below.

2-Methyl-4-piperidyl-6-propyl-5*H*-pyrrolo[3,2-*d*]pyrimidine Hydrochloride (90b). Yield: 81% of a white solid. Mp: 179 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (3, t, J = 7.4), 1.77 (8, m), 2.57 (3, s), 2.73 (2, t, J = 7.4), 3.71 (4, m), 6.23 (1, s), 7.93 (1, br s). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.81, 22.40, 24.80, 25.88, 25.94, 30.65, 47.56, 100.55, 113.20, 143.25, 150.40, 152.14, 159.27. MS (ESI) m/z: 259 (M + H), 257 (M − H). Anal. ($C_{15}H_{22}N_4 \cdot HCl$) C, H, N.

2-Methyl-6-pentyl-4-piperidyl-5*H*-pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (90d). Yield: 88% of a white solid. Mp: 170 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3, t, J = 6.8), 1.31 (4, m), 1.68 (8, m), 2.57 (3, s), 2.70 (2, t, J = 7.6), 3.72 (4, m), 6.19 (1, s), 8.66 (1, br s). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 16.44, 24.86, 27.26, 28.23, 28.41, 30.98, 31.28, 33.92, 50.02, 102.54, 115.64, 146.39, 152.94, 154.34, 161.42. MS (ESI) m/z: 287 (M + H), 285 (M − H). Anal. ($C_{17}H_{26}N_4 \cdot HCl \cdot 0.25H_2O$) C, H; N: calcd, 17.11; found, 16.62.

6-Cyclohexylmethyl-2-methyl-4-piperidyl-5*H*-pyrrolo-[3,2-*d*]pyrimidine Hydrochloride (90f). Yield: 95% of a white solid. Mp: 250 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.97 (2, m), 1.19 (5, m), 1.73 (10, m), 2.57 (3, s), 2.62 (2, d, J = 6.9), 3.71 (4, m), 6.21 (1, s), 7.74 (1, br s). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 24.94, 25.95, 26.09, 26.28, 26.48, 33.36, 36.77, 38.56, 47.73, 101.29, 113.34, 142.51, 150.57, 152.08, 159.22. MS (ESI) m/z: 313 (M + H), 311 (M − H). Anal. ($C_{19}H_{28}N_4 \cdot HCl$) C, H, N.

Pyrrolo[3,2-*d*]pyrimidines 89a,d−h,l−q, 90a,c,h−v, and 94a−d. These compounds were prepared by the methods analogous to those described in route C from appropriate starting materials. The analytical data for these pyrrolo[3,2-*d*]pyrimidine analogues are shown below. The reported yields represent the yields obtained for the final step of the sequence.

2-Methyl-4-piperidyl-6-(2-chlorophenyl)pyrrolo[3,2-*d*] pyrimidine Hydrochloride Monohydrate (89a). Yield: 0.34 g (17%) of the title compound as brown needles. Mp: 240−241.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (br s, 6), 2.59 (s, 3), 4.03 (s, 4), 6.74 (s, 1), 7.55 (d quintet, 2, J = 1.3, 7.8), 7.70 (dt, 2, J = 0.9, 8.2), 12.34 (s, 1), 14.64 (s, 1). MS m/z: 327 (M + H for free base). Anal. ($C_{18}H_{19}ClN_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2-Methyl-4-piperidyl-6-[2-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89d). Yield: 0.20 g (11%) of beige cube-shaped crystals. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.70 (br s, 6), 2.58 (s, 3), 4.01 (s, 4), 6.62 (s, 1), 7.74 (d, 1, J = 7.5), 7.79 (t, 1, J = 7.5), 7.86 (t, 1, J = 7.4), 7.97 (d, 1, J = 7.8), 12.45 (s, 1), 14.43 (s, 1). MS m/z: 361 (M + H for free base). Anal. ($C_{19}H_{19}F_3N_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2-Methyl-4-piperidyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89e). Yield: 0.49 g (15%) of a white solid. Mp: 241−243 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.72 (br s, 6), 2.59 (s, 3), 4.08 (s, 4), 7.14 (s, 1), 7.79 (t, 1, J = 7.6), 7.85 (d, 1, J = 7.5), 8.30 (d, 1, J = 7.6), 8.34 (s, 1), 12.92 (s, 1), 14.53 (s, 1). MS m/z: 361 (M + H for free base). Anal. ($C_{19}H_{19}F_3N_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2-Methyl-4-piperidyl-6-[4-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (89f). Yield: 0.19 g (10%) of a beige solid. Mp: 278−280 °C. ^{1}H NMR

(DMSO-d_6, 400 MHz): δ 1.72 (br s, 6), 2.58 (s, 3), 4.08 (s, 4), 7.05 (s, 1), 7.93 (d, 2, J = 8.3), 8.20 (d, 2, J = 8.2), 12.16 (s, 1), 14.32 (s, 1). MS m/z: 361 (M + H for free base). Anal. ($C_{19}H_{19}F_3N_4 \cdot HCl \cdot 1.5H_2O$) C, H, N, Cl.

6-(2-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89g). Yield: 0.14 g (8%) of long white needles. Mp: 287−289 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.72 (br s, 6), 2.58 (s, 3), 4.05 (br s, 4), 6.80 (d, 1, J = 1.6), 7.39−7.46 (m, 2), 7.57 (q, 1, J = 7.1), 7.89 (t, 1, J = 7.7), 12.13 (s, 1), 14.37 (s, 1). MS m/z: 311 (M + H). Anal. ($C_{18}H_{19}FN_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

6-(3-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89h). Yield: 0.082 g (5%) of small beige needles. Mp: >285 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (br s, 6), 2.57 (s, 3), 4.06 (br s, 4), 6.99 (s, 1), 7.35 (t, 1, J = 8.5), 7.60 (q, 1, J = 7.7), 7.83 (d, 1, J = 7.6), 7.91 (d, 1, J = 10.2), 11.99 (s, 1), 14.34 (s, 1). MS m/z: 311 (M + H). Anal. ($C_{18}H_{19}FN_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2-Methyl-6-(4-phenylphenyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89l). Yield: 0.20 g (9%) of a pale-yellow solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.72 (br s, 6), 2.58 (s, 3), 4.07 (br s, 4), 6.96 (s, 1), 7.43 (t, 1, J = 7.2), 7.52 (t, 2, J = 7.7), 7.77 (d, 2, J = 7.9), 7.86 (d, 2, J = 8.1), 8.06 (d, 2, J = 8.1), 12.00 (s, 1), 14.29 (s, 1). MS m/z: 369 (M + H). Anal. ($C_{24}H_{24}N_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

6-(2,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo-[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89m). Yield: 0.34 g (19%) of white needles. Mp: 279−281 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.06 (s, 4), 6.85 (s, 1), 7.42−7.55 (m, 2), 7.86−7.91 (m, 1), 12.13 (s, 1), 14.41 (s, 1). MS m/z: 329 (M + H for free base). Anal. ($C_{18}H_{18}F_2N_4 \cdot HCl \cdot H_2O$) C, H, N.

6-(2,6-Difluorophenyl)-2-methyl-4-piperidylpyrrolo-[3,2-*d*]pyrimidine Hydrochloride Hydrate (89n). Yield: 0.033 g (2%) of a pale-yellow sandy solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.02 (s, 4), 6.77 (s, 1), 7.35 (t, 2, J = 8.3), 7.67 (d quintet, 1, J = 1.4, 6.8), 12.41 (s, 1), 14.51 (s, 1). MS m/z: 329 (M + H for free base). Anal. ($C_{18}H_{18}F_2N_4 \cdot HCl \cdot 1.2H_2O$) C, H, N, Cl.

6-(3,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo-[3,2-*d*]pyrimidine Hydrochloride Monohydrate (89o). Yield: 0.44 g (19%) of pale-yellow needles. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.61 (br s, 6), 2.47 (s, 3), 3.97 (br s, 4), 6.97 (s, 1), 7.28 (tt, 1, J = 2.1, 7.1), 7.74 (d, 2, J = 6.6), 11.93 (s, 1), 14.35 (s, 1). MS m/z: 329 (M + H for free base). Anal. ($C_{18}H_{18}F_2N_4 \cdot HCl \cdot H_2O$) C, H, N, Cl.

6-(3,4-Difluorophenyl)-2-methyl-4-piperidylpyrrolo-[3,2-*d*]pyrimidine Hydrochloride Hydrate (89p). Yield: 0.16 g (6%) of a beige solid. Mp: 243−245 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.71 (br s, 6), 2.57 (s, 3), 4.06 (t, 4, J = 5.0), 6.85 (s, 1), 7.63 (q, 1, J = 10.0), 7.89 (d, 1, J = 8.1), 8.19 (dt, 1, J = 1.3, 9.5), 12.01 (s, 1), 14.39 (s, 1). MS m/z: 329 (M + H for free base). Anal. ($C_{18}H_{18}F_2N_4 \cdot HCl \cdot 1.25H_2O$) C, H, N, Cl.

2-Methyl-4-piperidyl-6-(3,4,5-trifluorophenyl)pyrrolo-[3,2-*d*]pyrimidine Hydrochloride Hydrate (89q). Yield: 0.43 g (16%) of a white fluffy solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.07 (s, 4), 7.07 (s, 1), 8.14 (m, 2), 12.04 (s, 1), 14.45 (s, 1). MS m/z: 347 (M + H for free base). Anal. ($C_{18}H_{17}F_3N_4 \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl.

2,6-Dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (90a). Yield: 0.54 g (12%) of brown needles. Mp: 244−245.5 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.67 (m, 4), 1.72 (m, 2), 2.48 (s, 3), 2.52 (s, 3), 3.97 (t, 4), 6.30 (s, 1), 11.92 (s, 1), 14.00 (s, 1). MS m/z: 231 (M + H). Anal. ($C_{13}H_{18}N_4 \cdot 1.1HCl \cdot H_2O$) C, H, N Cl.

6-Butyl-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride (90c). Yield: 0.53 g (15%) of white cube-shaped crystals. Mp: 246−248 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.17 (t, 3, J = 7.4), 1.59 (quintet, 2, J = 7.3), 1.87−1.94 (m, 8), 2.77 (s, 3), 3.06 (t, 2, J = 7.8), 4.22 (m, 4), 6.55 (s, 1), 12.08 (s, 1), 14.39 (s, 1). MS m/z: 273 (M + H for free base). Anal. ($C_{16}H_{24}N_4 \cdot HCl$) C, H, N, Cl. (0.33 g (11%) of 2,6-dimethyl-4-piperidyl-7-propylpyrrolo[3,2-*d*]pyrimidine as a pale-yellow solid was also obtained.)

2-Methyl-4-piperidyl-6-([3-(trifluoromethyl)phenyl]-methyl)pyrrolo[3,2,-*d*]pyrimidine Hydrochloride (90h). Yield: 0.058 g (2.1%) of a brown solid. Mp: 219−221 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.56−1.69 (m, 6), 2.45 (s, 3), 3.90−3.97 (m, 4), 4.28 (s, 2), 6.21(s, 1), 7.48−7.61 (m, 3), 7.69 (s, 1), 12.20 (s, 1), 14.09 (s, 1). MS m/z: 375 (M + H for free base). Anal. ($C_{20}H_{21}F_3N_4 \cdot HCl$) C, H, N, Cl. (0.60 g (21%) of the isomer, 2,6-dimethyl-4-piperidyl-7-[3-(trifluoromethyl)phenyl]-pyrrolo[3,2-*d*]pyrimidine, as a brown solid was also obtained.)

4-Methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methyl]benzene Hydrochloride (90i). Yield: 0.49 g (9%) of tan crystals. Mp: 263−267 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.73 (br s, 6), 3.75 (s, 3), 4.01 (br s, 4), 4.15 (s, 2), 6.19 (s, 1), 6.94 (d, 2, J = 8.7), 7.27 (d, 2, J = 8.6), 12.02 (s, 1), 13.93 (s, 1). MS m/z: 337 (M + H for free base). Anal. ($C_{20}H_{24}N_4O \cdot HCl$) C, H, N, Cl. (0.47 g (10%) of 1-[2,6-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-7-yl]-4-methoxybenzene as a beige solid was also obtained.)

6-[(4-Fluorophenyl)methyl]-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride (90j). Yield: 0.10 g (3%) of a white solid. Mp: 254−255 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.70 (br s, 6), 2.51 (s, 3), 3.98 (br s, 4), 6.21 (s, 1), 7.17 (t, 2, J = 8.9), 7.35 (dd, 2, J = 8.6, 8.5), 12.04 (s, 1), 13.90 (s, 1). MS m/z: 325 (M + H for free base). Anal. ($C_{19}H_{21}FN_4 \cdot HCl$) C, H, N, Cl.

2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (90k). Yield: 0.27 g (7%) of a beige powder. Mp: 236−238 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.60 (br s, 6), 2.45 (s, 3), 2.95 (t, 2, J = 8.4), 3.09 (t, 2, J = 8.4), 3.92 (br s, 4), 6.24 (s, 1), 7.11−7.14 (m, 1), 7.16−7.25 (m, 4), 11.88 (s, 1), 14.06 (s, 1). MS m/z: 321 (M + H for free base). Anal. ($C_{20}H_{24}N_4 \cdot HCl \cdot 0.25H_2O$) C, H, N, Cl.

4-Methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)ethyl]benzene Hydrochloride Hydrate (90l). Yield: 0.40 g (6.5%) as beige crystals. Mp: 234−235 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.53−1.69 (m, 6), 2.45 (s, 3), 2.87 (t, 2, J = 7.7), 3.04 (t, 2, J = 7.7), 3.64 (s, 3), 3.87−3.94 (m, 4), 6.21(s, 1), 6.78 (d, 2, J = 8.6), 7.09 (d, 2, J = 8.6), 11.86 (s, 1), 14.0 (s, 1). MS m/z: 351 (M + H for free base). Anal. ($C_{21}H_{26}N_4O \cdot HCl \cdot 0.4H_2O$) C, H, N, Cl. (0.26 g (17%) of the isomer, 1-[(2,6-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-7-yl)methyl]-4-methoxybenzene as a beige solid was also obtained.)

[(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-methoxy]benzene Hydrochloride (90m). Yield: 0.066 g (2%) of a white solid. Mp: 238−239 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.64 (br s, 6), 2.48 (s, 3), 3.94 (br s, 4), 5.22 (s, 2), 6.66 (s, 1), 6.92 (t, 1, J = 7.3), 7.01 (d, 2, J = 7.9), 7.26 (dt, 2, J = 1.1, 7.4), 12.64 (s, 1), 14.18 (s, 1). MS m/z: 323 (M + H for free base). Anal. ($C_{19}H_{22}N_4O \cdot HCl$) C, H, N, Cl.

4-Chloro-1-[(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methylthio]benzene Hydrochloride (90n). Yield: 0.043 g (1.3%) of a yellow solid. Mp: 205−206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (s, 6), 2.62 (s, 3), 4.03 (s, 4), 4.34 (s, 2), 6.42 (s, 1), 6.98 (d, 2, J = 8.6), 7.02 (d, 2, J = 8.6), 12.20 (s, 1), 14.31 (s, 1). MS m/z: 373 (M + H for free base). Anal. ($C_{19}H_{21}ClN_4S \cdot HCl$): C H, N, Cl.

4-Chloro-1-[((2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methyl)sulfonyl]benzene Hydrochloride Hydrate (90o). Yield: 0.30 g (9%) of a white solid. Mp: 199−201 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.57 (m, 4), 1.65 (m, 2), 2.47 (s, 3), 3.85 (br s, 4), 5.02 (s, 2), 6.23 (s, 1), 7.65 (AB q, 4, J = 6.2, 6.2), 12.20 (s, 1), 14.18 (s, 1). MS m/z: 405 (M + H for free base). Anal. ($C_{19}H_{21}ClN_4O_2S \cdot HCl \cdot 0.9H_2O$) C, H, N, Cl.

2-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-thiophene Hydrochloride (90p). Yield: 0.55 g (13%) of a tan solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (s, 6), 2.56 (s, 3), 4.04 (br s, 4), 6.70 (s, 1), 7.26 (t, 1, J = 4.2), 7.80 (d, 1, J = 5.0), 7.89 (d, 1, J = 3.0), 12.15 (s, 1), 14.44 (s, 1). MS m/z: 299 (M + H). Anal. ($C_{16}H_{18}N_4S \cdot HCl$) C, H, N, Cl.

2-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-furan Hydrochloride (90q). Yield: 0.50 g (70%) of a yellow solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.56−

1.70 (m, 6), 2.46 (s, 3), 3.89−3.96 (m, 4), 6.75 (s, 2), 7.30 (d, 1, J = 3.2), 7.89 (d, 1, J = 1.2), 12.10 (s, 1), 14.15 (s, 1). MS m/z: 281 (M − H for free base). Anal. ($C_{16}H_{18}N_4O$·HCl) C, H, N, Cl.

5-Methyl-2-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)furan Hydrochloride (90r). Yield: 0.35 g (21%) as a yellow solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.63 (br s, 6), 2.34 (s, 3), 2.48 (s, 3), 3.95 (m, 4), 6.30 (d, 1, J = 3.3), 6.59 (s, 1), 7.21 (d, 1, J = 3.3), 12.02 (s, 1), 14.23 (s, 1). MS m/z: 297 (M + H for free base). Anal. ($C_{17}H_{20}N_4O$·HCl) C, H, N, Cl.

2-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-benzo[*b*]furan Hydrochloride Monohydrate (90s). Yield: 0.59 g (95%) of a beige solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.73 (s, 6), 2.58 (s, 3), 4.08 (s, 4), 7.00 (s, 1), 7.35 (t, 1, J = 7.5), 7.44 (t, 1, J = 8.0), 7.71 (d, 1, J = 8.2), 7.79 (d, 1, J = 7.7), 7.88 (s, 1), 12.48 (s, 1), 14.40 (s, 1). MS m/z: 333 (M + H). Anal. ($C_{20}H_{20}N_4O$·HCl·H_2O) C, H, N, Cl.

2-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-benzo[*b*]thiophene Hydrochloride Hydrate (90t). Yield: 0.88 g (31%) of a yellow powder. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.66 (br s, 6), 2.51 (s, 3), 4.00 (br s, 4), 6.74 (s, 1), 7.39 (m, 2), 7.91 (t, 1, J = 6.9), 8.00 (t, 1, J = 4.0), 8.16 (s, 1), 12.22 (s, 1), 14.21 (s, 1). MS m/z: 349 (M + H for free base). Anal. ($C_{20}H_{20}N_4S$·HCl·0.70H_2O) C, H, N, Cl.

2-Methyl-4-piperidyl-6-(2-pyridyl)pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (90u). Yield: 0.62 g (85%) of a brown solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.72 (s, 6), 2.58 (s, 3), 4.06 (br s, 4), 7.16 (s, 1), 7.51 (dd, 1, J = 7.4, 7.4), 8.01 (dt, 1, J = 1.4, 7.6), 8.24 (d, 1, J = 7.9), 8.76 (d, 1, J = 4.4), 12.19 (s, 1), 14.36 (s, 1). MS m/z: 294 (M + H). Anal. ($C_{17}H_{19}N_5$·1.2HCl·0.4H_2O) C, H, N, Cl.

2-Methyl-4-piperidyl-6-pyrazin-2-ylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (90v). Yield: 0.068 g (53%) of a brown solid. Mp: 280−283.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.72 (s, 6), 2.59 (s, 3), 4.08 (br s, 4), 7.29 (s, 1), 8.74 (d, 1, J = 2.4), 8.82 (br s, 1), 9.49 (s, 1), 12.41 (s, 1), 14.41 (s, 1). MS m/z: 295 (M + H for free base). Anal. ($C_{16}H_{18}N_6$·HCl·1.4H_2O) C, H, N, Cl.

2,7-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (94a). Yield: 0.22 g (90%) of a white solid. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.69 (br s, 6), 2.35 (s, 3), 2.64 (s, 3), 4.03 (br s, 4), 7.52−7.60 (m, 3), 7.65−7.68 (m, 2), 11.94 (s, 1), 14.16 (s, 1). MS m/z: 307 (M + H). Anal. ($C_{19}H_{22}N_4$·1.1HCl·H_2O) C, H, N, Cl.

7-Ethyl-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]-pyrimidine Hydrochloride Hydrate (94b). Yield: 0.034 g (1%) of a white solid. Mp: 261−263 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.05 (t, 3, J = 7.5), 1.63 (br s, 6), 2.56 (s, 3), 2.69 (q, 2, J = 7.2), 3.95 (br s, 4), 7.46−8.02 (m, 5), 11.90 (s, 1), 13.86 (s, 1). MS m/z: 321 (M + H for free base). Anal. ($C_{20}H_{24}N_4$·HCl·0.7H_2O) C, H, N, Cl.

2-Methyl-6,7-diphenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (94c). Yield: 0.083 g (51%) of a beige solid. Mp: 169−171 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.72 (br s, 6), 2.56 (s, 3), 4.06 (br s, 4), 7.29 (dd, 2, J = 1.7, 6.0), 7.37−7.45 (m, 8), 12.26 (s, 1), 13.40 (s, 1). MS m/z: 369 (M + H). Anal. ($C_{24}H_{24}N_4$·HCl·H_2O) C, H, N, Cl.

7-Fluoro-2-methyl-6-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride (94d). Yield: 0.27 g (6%) of pale-green needles. Mp: >280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.72 (br s, 6), 2.59 (s, 3), 4.07 (br s, 4), 7.53−7.57 (m, 1), 7.61 (t, 2, J = 7.7), 7.87 (d, 2, J = 7.5), 12.07 (s, 1), 14.56 (s, 1). MS m/z: 311 (M + H for free base). Anal. ($C_{18}H_{19}FN_4$·HCl) C, H, N, Cl.

2-Cyclohex-1-enyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18). A mixture of cyclohexenyl trifluoroacetate (1.36 g, 5.9 mmol), bis(pinacolacto)diboron (1.65 g, 6.5 mmol), dichloro-[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane adduct [$PdCl_2$(dppf)] (0.14 g, 0.18 mmol), and potassium acetate (1.74 g, 17.7 mmol) in anhydrous dimethyl sulfoxide (10 mL) was stirred under nitrogen at 70 °C for overnight. Upon cooling to the room temperature, the reaction mixture was diluted with H_2O (30 mL), and the crude product was extracted with benzene (3 × 40 mL). The organic extracts were washed with H_2O (3 × 40 mL), saturated NaCl (50 mL), and dried over Na_2SO_4 and concentrated in vacuo. Bulb-to-bulb distillation (oven temperature 90−100 °C) afforded 1.06 g (85%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (s, 12), 1.59 (m, 4), 2.09 (br s, 4), 6.56 (s, 1).

4-Cyclohex-1-enyl-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (19). A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (**14**; R^1 = Me, R^2 = Ph) (0.26 g), 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**18**) (0.24 g, 1.13 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.025 g, 0.027 mmol) and triphenylphosphine (0.056 g, 0.21 mmol) in a mixture of solvents (1.2 mL of toluene, 0.3 mL of 1.0 M Na_2CO_3 and 0.3 mL of ethanol) was refluxed under N_2 for 2 days. Upon cooling to room temperature, the reaction mixture was diluted with H_2O (40 mL) and the solution was extracted with $CHCl_3$ (4 × 40 mL). The organic extracts were washed with water (50 mL), saturated NaCl (50 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator. Chromatography on silica gel with a gradient eluant of EtOAc(0−30%):hexanes (100−70%) afforded 0.15 g (48%) of the title compound as an off-white solid. Mp: 247−249 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.79 (m, 2), 1.88 (m, 2), 2.36 (m, 2), 2.68 (m, 2), 2.79 (s, 3), 6.63 (m, 1), 6.87 (d, 1, J = 2.0), 7.45 (t, 1, J = 7.2), 7.49 (t, 2, J = 7.2), 7.72 (d, 2, J = 7.2), 8.47 (s, 1). MS m/z: 290 (M + H), 288 (M − H). HRMS: calcd for $C_{19}H_{20}N_3$ (M + H) 290.1657, found 290.1657.

4-Cyclohexyl-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (20). A solution of 2-methyl-4-(1-cyclohexenyl)-5*H*-6-phenylpyrrolo[3,2-*d*]pyrimidine (0.096 g, 0.33 mmol) in EtOH (5 mL) was agitated on a Parr apparatus at room temperature in the presence of PtO_2 (0.020 g, 0.088 mmol) under H_2 (70 psi) for 30 h. The reaction mixture was filtered through a pad of Celite and concentrated on a rotary evaporator. Chromatography on silica gel with a gradient eluant of EtOAc(0−20%): hexanes (100−80%) afforded 0.055 g (57%) of the title compound as an off-white solid. Mp: >280 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44−1.49 (m, 2), 1.81−1.88 (m, 4), 1.93−2.01 (m, 4), 2.99 (m, 1), 6.86 (d, 1, J = 1.4), 7.44 (t, 1, J = 6.1), 7.51 (t, 2, J = 6.1), 7.74 (d, 2, J = 6.1), 8.40 (s, 1). MS m/z: 292 (M + H), 290 (M − H). HRMS: calcd for $C_{19}H_{22}N_3$ (M + H) 292.1814, found 292.1806.

2-Cyano-1-phenylvinyl-4-methylbenzenesulfonate (22; R^2 = Ph). This material was prepared according to the method described in route B (step a) from benzoylacetonitrile (3.4 g, 23 mmol) and *p*-toluenesulfonyl chloride (5.1 g, 27 mmol) to afforded 4.0 g (57%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.46 (d, 3), 5.57 (d, 1), 7.31−7.50 (m, 5), 7.58 (d, 1, J = 7.93), 7.65 (d, 1, J = 7.92), 7.76 (d, 1, J = 8.22), 7.90 (d, 1, J = 8.26). MS m/z: 300 (M + H), 298 (M − H).

Ethyl 3-Amino-5-phenyl-1*H*-pyrrole-2-carboxylate (25; R^2 = Ph). This material was prepared according to the method described in route B (step b) from 2-cyano-1-phenylvinyl 4-methylbenzenesulfonate (4.0 g, 13 mmol) and diethyl aminomalonate hydrochloride (2.8 g, 13 mmol) and was used without further purification. An analytical sample was obtained as off-white crystals by recrystallization from toluene: cyclohexane. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.28 (t, 3, J = 7.12), 4.22 (q, 2, J = 7.20), 5.06 (br s, 2), 5.98−6.03 (m, 1), 7.16−7.38 (m, 3), 7.72−7.76 (m, 2), 10.68 (br s, 1). MS m/z: 231 (M + H), 229 (M − H).

***tert*-Butyl 2-Aza-3-[(*tert*-butoxy)carbonylamino]-3-{[2-(ethoxycarbonyl)-5-phenylpyrrol-3-yl]amino}prop-2-enoate.** To a 25-mL round-bottomed flask were added ethyl 3-amino-5-phenyl-1*H*-pyrrole-2-carboxylate (1.1 g) and MeOH (5 mL). To the reaction flask was added 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.6 g, 5.5 mmol), followed by glacial acetic acid (1.43 mL, 25 mmol). The reaction mixture was stirred at room temperature under N_2 for 28 h. A heavy precipitate formed and was collected by filtration, washed with H_2O (3 × 10 mL) and dried in a vacuum oven overnight to give 0.71 g (32% from **22**; R^2 = Ph) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.38 (t, 3, J = 7.00), 1.44 (s, 9), 1.46 (s, 9), 4.38 (q, 2,

J = 6.97), 7.31−7.46 (m, 3), 7.76 (d, 2, J = 7.86), 11.06 (br s, 1), 11.25 (s, 1), 11.61 (s, 1), 11.95 (br s, 1). MS *m/z*: 473 (M + H), 471 (M − H).

2-Amino-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (29). To a round-bottomed flask was added a solution of *tert*-butyl 2-aza-3-[(*tert*-butoxy)carbonylamino]-3-{[2-(ethoxycarbonyl)-5-phenylpyrrol-3-yl]amino}prop-2-enoate (0.679 g, 1.44 mmol) in CH_2Cl_2 (8 mL). Trifluoroacetic acid (2 mL) was added, and the reaction mixture was stirred at room temperature under N_2 for 4.5 h. After the solvent was evaporated in vacuo, the residue was heated in EtOH (8 mL) and 1 N NaOH (4 mL) at reflux for 2 h. The reaction mixture was concentrated in vacuo to ca. 4 mL, and the pH of the resulting suspension was adjusted to pH 6 (pH paper) with 10% HCl. The precipitate that formed was collected by filtration, washed with water and dried in a vacuum oven overnight to give 0.2 g (61%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.81 (br s, 2), 6.56 (s, 1), 7.28−7.41 (m, 3), 7.87 (d, 2, J = 7.44), 10.40 (br s, 1), 11.78 (br s, 1). MS *m/z*: 227 (M + H), 225 (M − H).

6-Phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-ylamine Hydrochloride Hydrate (31). In a round-bottomed flask were added 2-amino-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (**29**) (0.26 g, 1.2 mmol) and phosphorus oxychloride (2.7 mL, 28.8 mmol). The mixture was heated in a 124 °C oil bath for 24 h, then excess $POCl_3$ was removed in vacuo to afford a brown residue. Ice-cold water was added and the pH of the solution was adjusted to pH 8 (pH paper) by adding aqueous Na_2CO_3. The resulting precipitate was collected by filtration, washed with water and then dried in a vacuum oven at 40 °C to give a brown solid. This material was transferred to a round-bottomed flask and heated with piperidine (0.57 mL, 5.75 mmol) and dioxane (8 mL) in a 110 °C oil bath for 15 h. Most of the solvent was then evaporated in vacuo. Chloroform was added to the residue, and the organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown foam. Purification by flash chromatography on silica gel with 100:2:1 $CHCl_3$:MeOH:Et_3N as eluant afforded 0.092 g (27%) of the title compound as a tan solid. The above material (0.078 g, 0.27 mmol) was dissolved in a minimal amount of $CHCl_3$ and HCl (0.6 mL of a 1 N solution in ether, 0.6 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min, and the solvent was evaporated in vacuo to give a tan foam. Recrystallization from MeOH/H_2O gave 0.026 g (6%) of the title compound as off-white crystals. Mp: >300 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.66−1.67 (m, 6), 3.97 (m, 4), 6.66 (s, 1), 7.32 (br s, 2), 7.45−7.53 (m, 3), 7.87 (d, 2, J = 7.26), 11.53 (br s, 1), 12.51 (br s, 1). MS *m/z*: 294 (M + H), 292 (M − H). Anal. ($C_{17}H_{19}N_5$·HCl·0.2H_2O) C, H, N, Cl.

Phenyl-*N*-(6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)formamide Hydrochloride Hydrate (33). To a mixture of 6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-ylamine (**31**) (0.10 g, 0.34 mmol) in pyridine (7 mL) in a 25-mL, round-bottomed flask was added benzoic anhydride (0.081 g, 0.36 mmol). The reaction was heated at reflux for 15 h. The solvent was removed in vacuo and 0.1 M NaOH (10 mL) was added to the residue. The precipitate that formed was filtered, washed with water, dried in a vacuum oven overnight to give 0.16 g of an orange solid. The above material was dissolved in $CHCl_3$ (10 mL). HCl (0.35 mL of a 1 N solution in ether, 0.35 mmol) was added. The mixture was stirred at room temperature for 20 min. The solvent was evaporated to give a foam, which was recrystallized from MeOH:H_2O to give 0.030 g (19%) of the title compound as orange crystals. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.74 (m, 6), 4.09 (m, 4), 7.07 (s, 1), 7.50−7.74 (m, 6), 7.89 (d, 2, J = 7.63), 8.08 (d, 2, J = 7.67), 11.85 (br s, 1), 11.94 (br s, 1), 13.61 (br s, 1). MS *m/z*: 398 (M + H), 396 (M − H). Anal. ($C_{24}H_{23}N_4O$·HCl·2.2H_2O) C, H, N, Cl.

6-Phenylpyrrolo[3,2-*d*]pyrimidine-2,4-diol (38). In a 1-L round-bottomed flask was added ethyl 3-amino-5-phenylpyrrole-2-carboxylate (**25**; R^2 = Ph) (20 g, 87 mmol), followed by acetic acid (435 mL) and H_2O (44 mL). Potassium cyanate (21.2 g, 261 mmol) dissolved in 70 mL of H_2O was then added dropwise through an addition funnel. The reaction mixture was stirred at room temperature for 15 h. The precipitate formed was collected by filtration, washed with H_2O and ether, and dried to give a white solid. To the above solid in a 1-L round-bottomed flask was added 6% aqueous sodium hydroxide (435 mL). The suspension was heated at reflux for 2 h. After cooling to 22 °C, the reaction mixture was acidified using 12 N HCl to pH 6. The resultant precipitate was filtered, washed with H_2O, and dried in a vacuum oven overnight to give 15.2 g (77%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.29 (s, 1), 7.33−7.43 (m,3), 7.85 (d, 2, J = 7.3), 10.62 (br s, 1), 10.85 (br s, 1), 12.19 (br s,1). MS *m/z*: 226 (M − H).

2,4-Dichloro-6-phenylpyrrolo[3,2-*d*]pyrimidine (39). A mixture of 6-phenyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-diol (**38**) (6.0 g, 26.6 mmol) and $POCl_3$ (210 mL, 229 mmol) in a 500-mL, round-bottomed flask was heated at 120 °C for 60 h. $POCl_3$ was removed in vacuo to give a dark-red residue. Ice−water was added, and the pH of the reaction mixture was adjusted to pH 6 by the addition of NH_4OH at 0 °C. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo and dried in a vacuum oven overnight to give 2.84 g (40%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.95 (s, 1), 7.50−7.66 (m, 3), 7.77 (d, 2, J = 8.1), 8.88 (br s, 1).

2-Chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (40). This compound was prepared according to the method described in route A (step e) by employing 2,4-dichloro-6-phenylpyrrolo[3,2-*d*]pyrimidine (**39**) (2.84 g, 10.8 mmol), piperidine (5.3 mL, 53.8 mmol), and K_2CO_3 (14.9 g, 108 mmol) in H_2O (100 mL) to give 3.23 g (96%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.77 (m, 6), 3.83 (m, 4), 6.75 (s, 1), 7.37−7.55 (m, 3), 7.64 (d, 2, J = 7.3), 8.21 (br s, 1). MS *m/z*: 313, 315 (M + H), 311, 313 (M − H).

Methyl(6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)amine Hydrochloride Monohydrate (42a). A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (**40**) (0.63 g, 2.0 mmol), aqueous methylamine (40 wt %, 3.1 mL, 35 mmol), 10 mL of *n*-butanol and 0.4 mL of 12 N HCl in a 25-mL, round-bottomed flask was heated at reflux for 48 h under a stream of N_2. After cooling to room temperature, the solvent was evaporated in vacuo and the residue was partitioned between 5% $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel with 100:2 to 100:5 $CHCl_3$−MeOH as eluant to give 0.030 g (5%) of the free base. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.68 (m, 6), 3.19 (s, 6), 3.95 (m, 4), 6.70 (s, 1), 7.45−7.54 (m, 3), 7.86 (d, 2, J = 7.4), 11.58 (br s, 1), 12.22 (br s, 1). To a solution of the above material in $CHCl_3$ (5 mL) was added HCl (0.1 mL of a 1 N solution in ether, 0.1 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/H_2O to give 0.015 g of the title compound as orange crystals. Mp: 195−200 °C. MS *m/z*: 308.5 (M + H). Anal. ($C_{18}H_{21}N_5$·HCl·H_2O) C, H, N.

(6-Phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)propylamine Hydrochloride Hydrate (42b). To a solution of 6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-ylamine (**31**) (0.10 g, 0.34 mmol) in MeOH (3.5 mL) in a 25-mL round-bottomed flask were added propionaldehyde (0.074 mL, 1.02 mmol) and sodium cyanoborohydride (0.043 g, 0.68 mmol). The pH of the reaction was adjusted to 6 by the addition of methanolic HCl and the reaction was heated at reflux for 40 h. The pH was lowered to 4 by addition of 10% HCl and the reaction was stirred for 1 h. The pH was then raised to 10 by addition of saturated Na_2CO_3. The solvent was removed in vacuo, and the residue was dissolved in water and extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give an orange oil. The residue was purified by preparative TLC using 95:5 $CHCl_3$−MeOH as eluant to give 0.032 g (28%) of a light-yellow solid. The above material was dissolved in $CHCl_3$ (2 mL) and HCl (0.25 mL of a 1 N solution in ether, 0.25 mmol) was added.

The mixture was stirred at room temperature for 20 min. Solvent was evaporated to give 0.033 g (2%) of the title compound as a light-yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.93 (t, 3, J = 7.22), 1.58−1.62 (m, 2), 1.68 (m, 6), 3.25 (m, 2), 3.96 (m, 4), 6.66 (s, 1), 7.45−7.54 (m, 3), 7.68 (br s, 1), 7.86 (d, 2, J = 7.32), 11.54 (br s, 1), 12.23 (br s, 1). MS m/z: 336 (M + H), 334 (M − H). Anal. ($C_{18}H_{21}N_5$·HCl·0.5H_2O) C, H, N.

Dimethyl(6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-2-yl)amine Hydrochloride Hydrate (42c). A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (**40**) (0.31 g, 1 mmol), aqueous dimethylamine (40 wt. %, 1.5 mL, 12 mmol), *n*-butanol (5 mL), and 12 N HCl (0.2 mL) in a 25-mL, round-bottomed flask was heated at reflux for 32 h under a stream of N_2. After cooling to room temperature, the precipitate was collected by filtration, washed with hexanes and dried in a vacuum oven overnight to give 0.24 g (74%) of the title compound as orange crystals. Mp: >300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.68 (m, 6), 3.19 (s, 6), 3.95 (m, 4), 6.70 (s, 1), 7.45−7.54 (m, 3), 7.86 (d, 2, J = 7.4), 11.58 (br s, 1), 12.22 (br s, 1). MS m/z: 322.5 (M + H). Anal. ($C_{19}H_{23}N_5$·1.2HCl·1.75H_2O) C, H, N, Cl.

6-Phenyl-2,4-dipiperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride (42d). To a solution of 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (**40**) (0.25 g, 0.80 mmol) in dioxane (2 mL) in a 5-mL, Wheaton vial was added piperidine (0.39 mL, 4.0 mmol). The vial was capped and heated at 110 °C for 44 h. After cooling to room temperature, the precipitate was collected by filtration, washed with hexanes and dried in air to give 0.20 g (69%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added HCl (0.54 mL of a 1 N solution in ether, 0.54 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH:H_2O to give 0.038 g of the title compound as light-yellow crystals. Mp: >272 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.61−1.70 (m, 6), 3.74 (m, 4), 3.94 (m, 4), 6.71 (s, 1), 7.45−7.55 (m, 3), 7.87 (d, 2, J = 7.3), 11.61 (br s, 1), 12.44 (br s, 1). Anal. ($C_{22}H_{27}N_5$·HCl) C, H, N, Cl.

6-Phenyl-2-sulfanylpyrrolo[3,2-*d*]pyrimidin-4-ol (34). To a solution of ethyl 3-amino-5-phenylpyrrole-2-carboxylate (**25**; R^2 = Ph) (4.6 g) in dry benzene (100 mL) was added ethyl isothiocyanatoformate (2.4 mL, 20 mmol). The reaction mixture was heated to 90 °C for 1 h. A precipitate formed and was filtered and washed with hexanes to give 4.6 g of a brown solid. The crude solid was treated with 10 g of potassium hydroxide in water (160 mL), and heated at reflux for 15 h at 100 °C. After cooling to ambient temperature, the pH of the solution was adjusted to pH 5 with 12 M HCl. A precipitate formed and was collected by filtration. This material was washed with water, and dried in a vacuum oven to give 1.2 g of the title compound as a brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.40 (s, 1), 7.35−7.54 (m, 3), 7.88 (d, 2, J = 7.44), 12.04 (s, 1), 12.58 (s, 1), 12.68 (br s, 1). MS m/z: 244 (M + H), 242 (M − H).

2-Methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (35). To a solution of 6-phenyl-2-sulfanylpyrrolo[3,2-*d*]pyrimidin-4-ol (**34**) (1.1 g, 4.7 mmol) in acetone (100 mL) was added anhydrous potassium carbonate (0.52 g, 3.7 mmol), followed by iodomethane (0.47 mL, 7.5 mmol). The reaction mixture was stirred at room temperature for 1.5 h. Most of the solvent was evaporated in vacuo and the resultant precipitate was collected by filtration and dried in a vacuum oven overnight to give 1.0 g (84%) of the title compound as a tan solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.32 (s, 3), 6.41 (s, 1), 7.18−7.36 (m, 3), 7.84 (d, 2, J = 7.87), 11.01 (br s, 1). MS m/z: 258 (M + H), 256 (M − H).

2-Methylthio-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (37). To a suspension of 2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-4-ol (**35**) (1.3 g, 5.0 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (0.84 mL, 6 mmol), followed by methanesulfonyl chloride (0.4 mL, 5.3 mmol) at 0 °C. The reaction mixture was then warmed to room temperature over 3 h. Piperidine (1.5 mL, 15 mmol) was then added, and the reaction mixture was stirred for 15 h. A precipitate was then separated from the reaction mixture by filtration, and the filtrate was concentrated in vacuo to give an orange residue. Purification by flash chromatography on silica gel with a gradient of EtOAc(14−20%):hexanes(86−80%) as eluant gave 0.1 g (6%) of a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.76 (m, 6), 2.60 (s, 3), 3.80 (m, 4), 6.74 (s, 1), 7.38−7.49 (m, 3), 7.64 (d, 2, J = 7.11), 8.04 (br s, 1). The above material (0.090 g, 0.28 mmol) was dissolved in minimum amount of $CHCl_3$, and HCl (0.3 mL of a 1 N solution in ether, 0.3 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min, and the solvent was then evaporated in vacuo to give a white foam that was recrystallized from $CHCl_3$−petroleum ether to give 0.055 g (3%) of the title compound as white crystals. Mp: 281−283 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.73 (m, 6), 2.67 (s, 3), 4.05 (m, 4), 6.82 (s, 1), 7.49−7.57 (m, 3), 7.95 (d, 2, J = 7.45), 11.92 (br s, 1). MS m/z: 325 (M + H), 323 (M − H). Anal. ($C_{18}H_{20}N_4S$·HCl·1.8H_2O) C, H, N, Cl.

2-Methoxy-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate (41). A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (**40**) (0.63 g, 2 mmol), sodium methoxide (25 wt %, 0.78 mL, 4.5 mmol), and DMSO (2 mL) in a 15-mL, round-bottomed flask was heated at reflux for 72 h under a stream of N_2. After cooling to room temperature, the residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered, concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with EtOAc(20−33%):hexanes(80−67%) as eluant to give 0.22 g (35%) of the free base as a purple solid. To a solution of the above material in $CHCl_3$ (10 mL) was added HCl (0.75 mL of a 1 N solution in ether, 0.75 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/H_2O to give 0.117 g of the title compound as a light-green crystals. Mp: 270−276 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.73 (m, 6), 4.05 (m, 7), 6.75 (s, 1), 7.48−7.56 (m, 3), 7.92 (d, 2, J = 8.3), 11.87 (br s, 1), 13.87 (br s, 1). MS m/z: 309 (M + H). Anal. ($C_{18}H_{20}N_4O$·HCl·H_2O) C, H, N, Cl.

7-Acetyl-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]-pyrimidine (54). A mixture of 2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyridine (**1**) (0.050 g, 0.17 mmol), acetic anhydride (0.17 g, 1.64 mmol), K_2CO_3 (0.23 g, 1.64 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.003 g, 0.021 mmol) in anhydrous DMF (2.0 mL) was stirred under N_2 at 110 °C overnight. After cooling to the room temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (3 × 30 mL). The organic layers were washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The crude material was purified by flash chromatography on silica gel with a gradient eluant of EtOAc(0−25%):hexanes(100−75%) to afford 0.013 g (22%) of the title compound as an off-white solid. Mp: 188−190 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (br s, 6), 2.11 (s, 3), 2.58 (s, 3), 4.06 (br s, 2), 4.88 (br s, 2), 7.37 (t, 1, J = 7.4), 7.43 (t, 2, J = 7.4), 7.61 (d, 2, J = 7.4), 11.43 (s, 1). MS m/z: 335 (M + H), 333 (M − H). HRMS: calcd for $C_{20}H_{23}N_4O$ (M + H) 335.1888, found 335.1872.

2,5-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (55). A suspension of 2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyridine (**1**) (0.057 g, 0.20 mmol) in THF (3 mL) was placed under a N_2 atmosphere and cooled with a dry ice bath to −78 °C. *n*-Butyllithium (360 μL of a 2.5 M solution in hexanes, 0.90 mmol) was added slowly. The reaction mixture was stirred at −78 °C for 1 h and allowed to warm to 0 °C. Dimethyl sulfate (0.074 g, 0.60 mmol, 3.0) was added slowly at 0 °C. The solution was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of 10% NH_4Cl (3 mL) and the THF was evaporated under reduced pressure. The solution was extracted with $CHCl_3$ (3 × 50 mL), and the combined organic layers were washed with saturated NaCl, dried over Na_2SO_4, filtered and concentrated with a rotary evaporator. The crude material was purified by flash chromatography on silica gel with a gradient eluant of

EtOAc(0−20%):hexanes(100−80%) to provide 0.020 g (34%) of the title compound as a white solid [0.030 g (53%) of recovered starting material was also obtained]. Mp: 131−132 °C. ^{1}H NMR (acetone-d_6, 400 MHz): δ 1.70 (m, 2), 1.78 (m, 4), 2.50 (s, 3), 3.40 (t, 4, J = 4.9), 3.84 (s, 3), 7.47 (t, 1, J = 7.0), 7.54 (t, 2, J = 7.0), 7.68 (d, 2, J = 7.0). MS m/z: 307 (M + H).

7-Bromo-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]-pyrimidine Hydrochloride (56). In an oven-dried, 50-mL, round-bottomed flask, 2-methyl-6-phenyl-4-(piperidinyl)pyrrolo[3,2-*d*]pyrimidine (**1**) (0.50 g, 1.7 mmol) was dissolved in glacial AcOH (15 mL). To this solution was added Br_2 (0.090 mL, 1.8 mmol) dropwise over 2 min. The resulting dark mixture was diluted with H_2O (10 mL) and the mixture was warmed to 45 °C and stirred for 2 h. The reaction was allowed to cool to room temperature, and the crude material was extracted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated in vacuo to give an oily residue. The residue was purified by silica gel chromatography with 1:1 EtOAc:hexanes as eluant to give 0.50 g (79% yield) of a yellow solid. Mp: 239−240 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.74 (s, 6), 2.63 (s, 3), 3.83 (s, 4), 7.44 (t, 1, J = 2.4), 7.5 (t, 2, J = 7.0), 7.80 (d, 2, J = 7.1). MS m/z: 373.0 (M + H), 369.0, 371.0 (M − H). HRMS: calcd for $C_{18}H_{19}N_4Br$ (M + H) 371.0866, found 371.0854.

7-Methoxy-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate (57). Sodium methoxide (2.0 g, 6.2 mmol) was added to a stirring solution of 7-bromo-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine (**56**) (0.90 g, 2.4 mmol) in MeOH (20 mL). The reaction was heated at 50 °C for 24 h and heated at reflux for an additional 24 h. The reaction mixture was cooled and concentrated. Purification of the residue by silica gel chromatography (33:67 EtOAc:hexanes) gave the free base as a green solid, 0.20 g (26%). A portion of the free base (0.16 g, 0.50 mmol) was dissolved in EtOAc (5 mL) and treated with HCl (0.5 mL of a 1 N solution in ether, 0.5 mmol). The resultant precipitate was collected by filtration, washed with ether, and dried in vacuo to give 0.17 g (94%) of the title compound as a green solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (s, 6), 2.62 (s, 3), 3.78 (s, 3), 4.06 (m, 4), 7.52 (t, 1, J = 7.2), 7.59 (t, 2, J = 7.3), 7.80 (d, 2, J = 7.4), 11.82 (s, 1). MS m/z: 323 (M + H). Anal. ($C_{19}H_{22}N_4O$·HCl·0.45H_2O) C, H, N, Cl.

2,4-Dihydroxy-3-nitropyridine (59). Fuming HNO_3 (40 mL) was added to a stirring solution of 2,4-dihydroxypyridine (**58**) (9.0 g, 81 mmol) in H_2SO_4 (concentrated) (40 mL) at 0 °C. After 30 min, the solution was poured onto crushed ice (∼80 mL) (a nonviolent exothermic reaction resulted), and the mixture was chilled in a freezer. The resulting precipitate was filtered, washed with cold water, and dried to constant weight in vacuo to afford 11.4 g (90%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.13 (d, 1, J = 7.2), 7.48 (d, 1, J = 7.0), 11.93 (s, 1), 12.42 (br s, 1). MS m/z: 157 (M + H).

2,4-Dichloro-3-nitropyridine (60). 2,4-Dihydroxy-3-nitropyridine (**59**) (1.56 g, 10 mmol) was taken up in $POCl_3$ (20 mL) and the resulting black mixture was heated at reflux for 24 h. The volume of the solution was reduced by 70% in vacuo, and the cooled mixture was carefully poured onto crushed ice (a violent exothermic reaction resulted) and extracted with EtOAc (2×). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in 1:1 EtOAc:hexanes, filtered through a plug of silica gel, and concentrated in vacuo to afford 1.5 g (80%) of the title compound as a colorless crystalline solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.14 (d, 1, J = 5.1), 8.72 (d, 1, J = 5.2).

3-Amino-2,4-dichloropyridine (61). 2,4-Dichloro-3-nitropyridine (**60**) (1.5 g, 8 mmol) was dissolved in Et_2O (8 mL). A solution of $SnCl_2$·2H_2O (18 g, 80 mmol) in HCl (concentrated) (18 mL) was added cautiously. The reaction was exothermic upon addition, and the Et_2O boiled off of the solution. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0 °C in an ice−water bath and the precipitate was collected via filtration. The resulting solid was suspended in distilled H_2O, and the mixture was adjusted to neutral pH by the addition of concentrated NH_4OH at 0 °C. The resulting solution was extracted with EtOAc (2×). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 1.2 g (90%) of the title compound as a colorless crystalline solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.88 (s, 2) 7.35 (d, 1, J = 5.1), 7.63 (d, 1, J = 5.1). MS m/z: 163 (M + H).

3-Amino-6-bromo-2,4-dichloropyridine (62). 3-Amino-2,4-dichloropyridine (**61**) (0.50 g, 3.1 mmol) was dissolved in DMF (16 mL) and cooled to 0 °C in an ice−water bath. A solution of *N*-bromosuccinimide (0.66 g, 3.7 mmol) in DMF (7 mL) was then added slowly. After 15 min, the solution was poured into H_2O and extracted with EtOAc (2×). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to obtain a red residue. This residue was dissolved in 1:1 EtOAc:hexanes, filtered through a plug of silica gel, and concentrated in vacuo to afford 0.68 g (90%) of the title compound as a colorless crystalline solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.10 (s, 2), 7.69 (s, 1). MS m/z: 243 (M + H; ^{81}Br), 241 (M + H; ^{79}Br).

3-Amino-2,4-dichloro-6-methylpyridine (63). 3-Amino-6-bromo-2,4-dichloropyridine (**62**) (0.50 g, 2.1 mmol) was dissolved in anhydrous DMF (10 mL), and $MeB(OH)_2$ (0.38 g, 6.3 mmol), K_2CO_3 (1.5 g, 10 mmol), and $(PPh_3)_2PdCl_2$ (0.15 g, 0.21 mmol) were added. The mixture was heated to 100 °C for 24 h, then cooled to room temperature, poured into H_2O and extracted with EtOAc (2×). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 1:4 EtOAc:hexanes to afford 0.31 g (85%) of the title compound as a colorless crystalline solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.28 (s, 3), 5.65 (s, 2), 7.34 (s, 1). MS m/z: 177 (M + H).

3-Amino-4-chloro-6-methyl-2-(2-phenylethynyl)pyridine (64). To a solution of 3-amino-2,4-dichloro-6-methylpyridine (**63**) (0.22 g, 1 mmol) in NEt_3 (5 mL) were added $(PPh_3)_2PdCl_2$ (0.035 g, 0.05 mmol) and CuI (0.010 g, 0.05 mmol). The mixture was cooled to 0 °C and phenylacetylene (160 μL, 1.5 mmol) was added. The mixture was allowed to warm to room temperature then heated at 80 °C for 4 h. The mixture was cooled to room temperature and filtered through Celite. The Celite was rinsed with NEt_3, and the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 1:4 EtOAc:hexanes to afford 0.22 g (90%) of the title compound as a dark-brown solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.31 (s, 3), 5.55 (br s, 2), 7.26 (s, 1), 7.44 (m, 3), 7.69 (m, 2). MS m/z: 243 (M + H).

5-Methyl-2-phenyl-7-piperidylpyrrolo[3,2-*b*]pyridine (65). 3-Amino-4-chloro-6-methyl-2-(2-phenylethynyl)pyridine (**64**) (1.24 g, 5.1 mmol) was dissolved in anhydrous DMF (90 mL), CuI (0.15 g, 0.8 mmol) was added and the mixture was heated at 110 °C for 18 h. The cooled mixture was poured into H_2O (125 mL) and extracted with EtOAc (2 × 100 mL). The combined extracts were washed with H_2O and brine, dried over $MgSO_4$ and filtered through a plug of silica using $CHCl_3$. The crude product was triturated with 1:20 EtOAc:hexanes, filtered, and dried under high vacuum to afford 0.60 g (48%) of 7-chloro-5-methyl-2-phenylpyrrolo[3,2-*b*]pyridine. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.40 (s, 3), 7.05 (s, 1), 7.16 (s, 1), 7.38 (t, 1, J = 5.2), 7.49 (m, 2), 8.02 (d, 2, J = 7.2). MS m/z: 243 (M + H). This intermediate chloride (0.27 g, 1.1 mmol) was taken up in 4:1 *o*-xylene:piperidine (10 mL) and heated to 140 °C in a Teflon-capped pressure tube for 7 days. The mixture was cooled to room temperature, diluted with H_2O (125 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ filtered, and concentrated in vacuo. Chromatography on silica gel eluting with 10:1 $CHCl_3$−MeOH afforded 0.24 g (75%, 36% overall) of the title compound as a pale-yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.65 (m, 2), 1.75 (m, 4), 2.42 (s, 3), 3.32 (br s, 4), 6.49 (s, 1), 6.80 (s, 1), 7.33 (t, 1, J = 7.2), 7.43 (m, 2), 7.90 (d, 2, J = 7.2), 11.1 (br s, 1). MS m/z: 292 (M + H). HRMS: calcd for $C_{19}H_{22}N_3$ (M + H) 292.1814, found 292.1839.

6-Methyl-3-nitrohydropyridin-2-one (66). A solution of 2-nitroacetamide (11.8 g, 113 mmol), 3-oxobutanal sodium salt in aqueous piperidinium acetate[58] (257 mL, 1.76 M) was stirred under N_2 at room temperature for 2 days. The reaction mixture was acidified to about pH 4 and extracted with EtOAc (200 mL × 6). The organic extract was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel with MeOH(0−5%):CH_2Cl_2(100−95%) as eluant to afford 4.3 g, (25%) of the title compound as an orange solid. Mp: 215−217 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.32 (s, 3), 6.24 (d, 1, J = 7.9), 8.39 (d, 1, J = 7.9), 12.82 (s, 1). MS m/z: 153 (M − H).

2-Chloro-6-methyl-3-nitropyridine (67). To a solution of 6-methyl-3-nitrohydropyridin-2-one (**66**) (0.86 g, 5.6 mmol) in $POCl_3$ (7 mL) at room temperature was added diisopropylethylamine (0.72 g, 5.6 mmol). The reaction mixture was stirred under N_2 at 90 °C for 3.5 h. The reaction mixture was allowed to cool to room temperature and poured into an ice bath. The aqueous phase was extracted with diethyl ether (100 mL × 3). The extracts were washed with half-saturated $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained as a brown solid (0.74 g, 76%). Mp: 59−60 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.65 (s, 3), 7.27 (d, 1, J = 8.1), 8.15 (d, 1, J = 8.1), 12.82 (s, 1). MS m/z: 173 (M + H).

6-Methyl-3-nitro-2-piperidylpyridine (68). A mixture of 2-chloro-6-methyl-3-nitropyridine (**67**) (0.35 g, 2.0 mmol), piperidine (0.86 g, 10.1 mmol), triethylamine (0.61 g, 6.03 mmol) and zinc chloride (0.055 g, 0.40 mmol) in THF was stirred at room temperature overnight. After the removal of THF under reduced pressure, the crude reaction mixture was diluted with H_2O (50 mL), and extracted with $CHCl_3$ (50 mL × 3). The organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography with EtOAc(0−5%):hexanes(100−95%) as an eluant afforded the title compound (0.38 g, 85%) as a yellow solid. Mp: 50−52 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.67 (br s, 6), 2.43 (s, 3), 3.41 (br s, 4), 6.50 (d, 1, J = 8.2), 8.03 (d, 1, J = 8.2). MS m/z: 222 (M + H).

6-Methyl-2-piperidyl-3-pyridylamine (69). A solution of 6-methyl-3-nitro-2-piperidylpyridine (**68**) (0.90 g, 4.1 mmol) in methanol (20 mL) was placed on a Parr shaker (60 psi of H_2) at room temperature in the presence of 10% Pd/C (0.090 g) overnight. The reaction mixture was passed through a pad of Celite and concentrated under reduced pressure. Chromatography with EtOAc(0−8%):hexanes(100−92%) afforded the title compound (0.61 g, 78%) as a brown solid. Mp: 62−63 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.59 (m, 2), 1.69 (m, 4), 2.37 (s, 3), 3.02 (m, 4), 3.64 (br s, 2), 6.64 (d, 1, J = 7.7), 6.84 (d, 1, J = 7.7). MS m/z: 192 (M + H).

(*tert*-Butoxy)-*N*-(6-methyl-2-piperidyl-3-pyridyl)carboxamide (70). To a solution of 6-methyl-2-piperidyl-3-pyridylamine (**69**) (0.25 g, 1.3 mmol) in THF (1 mL) at room temperature was added sodium bis(trimethylsilyl)amide (2.9 mL of a 1 M solution in THF, 2.9 mmol). After the reaction mixture was stirred at room temperature for 10 min, a solution of di-*tert*-butyl dicarbonate (0.35 g, 1.6 mmol) in THF (3 mL) was added slowly. The reaction mixture was stirred at room temperature for additional 3 h. The reaction mixture was quenched with 10% NH_4Cl (15 mL), and extracted with EtOAc (30 mL × 4). Organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography with EtOAc(0−5%):hexanes(100−95%) as eluant afforded the title compound (0.31 g, 80%) as an off-white solid. Mp: 83−85 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.53 (m, 9), 1.60 (m, 2), 1.72 (m, 4), 2.41 (s, 3), 2.94 (t, 4, J = 5.4), 6.82 (d, 1, J = 8.1), 7.16 (s, 1), 8.15 (s, 1). MS m/z: 292 (M + H).

4-Iodo-6-methyl-2-piperidyl-3-pyridylamine (71). To a solution of (*tert*-butoxy)-*N*-(6-methyl-2-piperidyl-3-pyridyl)-carboxamide (**70**) (0.17 g, 0.58 mmol) in THF (1 mL) at −78 °C under nitrogen were added tetramethylethylenediamine (0.17 g, 1.5 mmol) and *tert*-butyllithium (0.85 mL of a 1.7 M solution in pentane, 1.45 mmol). The reaction mixture was warmed to −20 °C gradually and stirred at this temperature for 2.5 h. The reaction mixture was treated with 1-chloro-2-iodoethane (0.28 g, 1.5 mmol) in THF (1.5 mL) and stirred at room temperature for 25 min. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (10 mL × 4). Organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography with EtOAc-(0−5%):hexanes(100−95%) as eluant afforded recovered starting material (0.060 g, 36%) and (*tert*-butoxy)-*N*-(4-iodo-6-methyl-2-piperidyl-3-pyridyl)carboxamide (0.073 g, 47% based on recovered starting material) as a white solid. Mp: 99−101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (s, 9), 1.59 (m, 2), 1.66 (m, 4), 2.36 (s, 3), 3.08 (br s, 4), 6.05 (s, 1). MS m/z: 418 (M + H), 416 (M − H). A solution of (*tert*-butoxy)-*N*-(4-iodo-6-methyl-2-piperidyl-3-pyridyl)carboxamide (0.073 g, 0.175 mmol) in 4.0 M HCl/EtOAc (5 mL) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with H_2O (5 mL), neutralized over Na_2CO_3 and extracted with EtOAc (10 mL × 3). Organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated. The title compound was obtained as light-yellow oil (0.055 g, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.60 (m, 2), 1.70 (m, 4), 2.33 (s, 3), 3.00 (m, 4), 4.08 (br s, 2), 7.12 (s, 1). MS m/z: 318 (M + H).

6-Methyl-4-(2-phenylethynyl)-2-piperidyl-3-pyridylamine (72). To a mixture of 4-iodo-6-methyl-2-piperidyl-3-pyridylamine (**71**) (0.062 g, 0.20 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.007 g, 0.0099 mmol), copper(I) iodide (0.002 g, 0.0099 mmol) in triethylamine (1 mL) at 0 °C was added phenylacetylene (0.040 g, 0.39 mmol) slowly. The reaction mixture was warmed to 75 °C and stirred at this temperature for 3 h. The reaction mixture was passed through a pad of Celite and concentrated under reduced pressure. Chromatography with EtOAc (0−3%):hexanes(100−97%) as eluant afforded the title compound (0.057 g, 99%) as an orange semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (m, 2), 1.71 (m, 4), 2.37 (s, 3), 3.05 (m, 4), 4.24 (s, 2), 6.80 (s, 1), 7.36 (m, 3), 7.53 (m, 2). MS m/z: 292 (M + H).

5-Methyl-2-phenyl-7-piperidylpyrrolo[2,3-*c*]pyridine Hydrochloride (73). A mixture of 6-methyl-4-(2-phenylethynyl)-2-piperidyl-3-pyridylamine (**72**) (0.057 g, 0. 20 mmol) and copper(I) iodide (0.004 g, 0.020 mmol) in DMF (1 mL) was stirred at 110 °C under nitrogen overnight. DMF was removed under reduced pressure. Chromatography with EtOAc (0−50%):hexanes(100−50%) as eluant afforded the free base (0.034 g, 60%) as a light-green solid. Mp: 92−94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.69 (m, 2), 1.81 (m, 4), 2.51 (s, 3), 3.41 (m, 4), 6.66 (d, 1, J = 2.1), 6.97 (s, 1), 7.37 (t, 1, J = 7.3), 7.47 (t, 2, J = 7.3), 7.68 (d, 2, J = 7.3), 8.21 (s, 1). MS m/z: 292 (M + H), 290 (M − H). This material was combined with an additional 33 mg of product obtained from a previous experiment. The free base was dissolved in $CHCl_3$ (2 mL) and HCl (2.0 mL of a 1 N solution in ether, 2.0 mmol) was added. After stirring for 10 min, the solvents were removed and the sample was dried in a vacuum oven to give 0.075 g of the title compound as a brown solid. Mp: 263−265 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (m, 2), 1.78 (m, 4), 3.30 (s, 3), 3.75 (m, 4), 7.03 (s, 1), 7.13 (s, 1), 7.50 (t, 1, J = 6.9), 7.56 (t, 2, J = 6.9), 7.94 (d, 2, J = 6.9), 11.94 (s, 1), 12.04 (s, 1). MS m/z: 292 (M + H), 290 (M − H). HRMS: calcd for $C_{19}H_{22}N_3$ (M + H) 292.1814, found 292.1819.

(2*Z*)-3-Bromo-3-phenylprop-2-enenitrile (75). To an oven-dried, 250-mL, round-bottomed flask were added benzoylacetonitrile (5.00 g, 34.4 mmol) and PBr_3 (100 mL), and the resulting mixture was heated at 170 °C with stirring under N_2. After 48 h, the mixture was allowed to cool to room temperature and was carefully poured into ice (500 g). $CHCl_3$ (250 mL) was added and the mixture was stirred for 1 h. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (125 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (3 × 200 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give 8.0 g (98% yield) of a black oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.35 (s, 1), 7.60 (d, 2, J = 6.3), 7.40 (m, 3).

3-Amino-5-phenylfuran-2-carbonitrile (76). To an oven-dried, 150-mL, round-bottomed flask was added glycolonitrile

(4.6 g, 55 wt % in H_2O, 24.0 mmol), followed by THF (100 mL), and $MgSO_4$ (10 g). The mixture was stirred for 1 h before a solution of (2*Z*)-3-bromo-3-phenylprop-2-enenitrile (**75**) (2.5 g, 12.0 mmol) was added. The mixture was stirred rapidly at room temperature as NaH (1.0 g, 60% in mineral oil, 25 mmol) was carefully added in portions over 1 h. The mixture was poured into ice (100 g) and stirred for 10 min. The reaction was extracted with a mixture of 3:1 $CHCl_3$:*i*-PrOH (3 × 75 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and evaporated to give 2.0 g (90% yield) of an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.01 (br, 2), 6.35 (s, 1), 7.40 (m, 3), 7.63 (d, 2, J = 7.1).

2-Methyl-6-phenyl-4-piperidylfurano[3,2-*d*]pyrimidine Hydrochloride Hydrate (81). To an oven-dried, 150-mL, round-bottomed flask was added *N*,*N*-dimethylacetamide (1.0 mL, 11 mmol) followed by $POCl_3$ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-5-phenylfuran-2-carbonitrile (**76**) (0.68 g, 3.7 mmol). The resulting mixture was heated at 160 °C for 36 h. The solvent was evaporated in vacuo and toluene (50 mL) was added. The solvent was again evaporated in vacuo and to the crude residue was added piperidine (3.0 mL, 30.3 mmol). The reaction was heated to 160 °C for 1 h and then allowed to cool to room temperature. The crude material was dissolved in $CHCl_3$ (100 mL) and washed with saturated $NaHCO_3$ (3 × 100 mL), brine (100 mL), and dried over $MgSO_4$. The organic layer was filtered and evaporated in vacuo to give a residue that was purified by silica gel chromatography with 1:1 EtOAc:hexanes as eluant. The product was isolated to give 0.20 g (19% yield) as a light-yellow solid. The free base (0.18 g, 0.62 mmol) was dissolved in hot EtOAc (20 mL) and HCl (0.62 mL of a 1 N solution in ether, 0.62 mmol) was added dropwise. A precipitate formed immediately and the mixture was allowed to cool to room temperature. The solid was filtered and dried under vacuum to give 0.20 g (97% yield) of the title compound. Mp: >290 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.75 (br s, 6), 2.58 (s, 3), 4.16 (s, 4), 7.61 (m, 4), 8.08 (d, 2, J = 6.8). MS *m*/*z*: 294.0 (M + H). Anal. ($C_{18}H_{19}N_3O$·1.1HCl·1.8H_2O) C, H, N, Cl.

2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-*d*]pyrimidine Hydrochloride (82). A mixture of methyl 3-amino-5-phenylthiophene 2-carboxylate (**79**) (2.4 g, 10.6 mmol), acetamidine hydrogen chloride (1.2 g, 12.3 mmol), and NaOMe (1.0 g, 18.5 mmol) in poly(ethylene glycol) (20 mL) was heated at 120 °C for 2 days. The mixture was poured into aqueous 0.13 M HCl (50 mL, 6.4 mmol) and the resulting slurry was filtered. The solid was washed with distilled H_2O, dissolved in CH_2Cl_2 and DMF, and concentrated in vacuo. Toluene was added to the residue and the solution was concentrated to remove the residual H_2O (this process was repeated two additional times). To this material was added neat $POCl_3$ (15 mL) and the mixture was heated at 100 °C for 12 h. The solvent was evaporated in vacuo, and the residue was dissolved in toluene and concentrated (this process was repeated two additional times) to remove the residual $POCl_3$. The residue was dissolved in toluene (15 mL) and treated with piperidine (5 mL). The mixture was heated at 100 °C for 12 h, cooled to room temperature, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. This material was purified by flash chromatography on silica gel with 1:1 EtOAc:hexanes as eluant. Treatment of the free base with 1 N ethereal HCl afforded 0.080 g (2.2%) of the title compound as a yellow solid. ^{1}H NMR (2:1 DMSO-d_6:CD_3OD-d_6,400 MHz): δ 1.79 (br s, 6), 2.54 (s, 3), 4.16 (br s, 4), 7.56 (m, 3), 7.73 (s, 1), 7.91 (m, 2). HRMS: calcd for $C_{18}H_{20}N_3S$ (M + H) 310.1374, found 310.1377.

4-Chloro-2-methyl-5-nitro-6-piperidylpyrimidine (84). A mixture of piperidine (3.8 mL, 38.4 mmol) and diisopropylethylamine (6.8 mL, 39.0 mmol) in THF (160 mL) was charged into a 250-mL addition funnel. The solution was added dropwise to a stirring solution of 4,6-dichloro-2-methyl-5-nitropyrimidine (8.0 g, 38.7 mmol) in THF (60 mL) over 10 h. The reaction mixture was concentrated and the residue partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with fresh CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 9.2 g of a crude red-yellow oil. Purification by column chromatography using EtOAc(0−5%):hexanes(100−95%) gave 7.8 g (78%) of the title compound as a light-yellow oil which solidified upon standing. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65 (m, 6), 2.50 (s, 3), 3.52 (m, 4). MS *m*/*z*: 257 (M + H).

2-Methyl-5-nitro-6-piperidylpyrimidin-4-ylamine (85). 4-Chloro-2-methyl-5-nitro-6-piperidylpyrimidine (**84**) (3.0 g, 11.7 mmol) was partially dissolved in MeOH (5.0 mL) and placed in a pressure tube containing a stir bar. Ammonia (12 mL of a 2 M solution in MeOH, 24.0 mmol) was added in one portion and the reaction tube was sealed. The reaction vessel was placed in a 90 °C oil bath and stirred. After 5 h, the reaction mixture was concentrated to a yellow residue which was partitioned between saturated aqueous $NaHCO_3$ and 3:1 $CHCl_3$:*i*-PrOH. The layers were separated and the aqueous layer extracted with $CHCl_3$:*i*-PrOH. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a bright yellow solid. Recrystallization from MeOH gave the title compound, 2.2 g (77%), as a bright yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.69 (m, 6), 2.33 (s, 3), 3.48 (m, 4). MS *m*/*z*: 238 (M + H).

2-Methyl-6-piperidylpyrimidine-4,5-diamine (86). 2-Methyl-5-nitro-6-piperidylpyrimidin-4-ylamine (**85**) (2.0 g, 8.4 mmol) was partially dissolved in 95% EtOH (50.0 mL). 10% Palladium on carbon (catalytic) was added and the system was evacuated and filled with hydrogen. The system was evacuated and filled two more times and the reaction allowed to stir under atmospheric H_2 using a balloon. After 16 h, the reaction mixture was filtered through Celite and concentrated to give the title compound, 1.7 g (95%), as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61−1.69 (m, 6), 2.41 (s, 3), 2.99 (br s, 2), 3.10 (m, 4), 4.43 (br s, 2). MS *m*/*z*: 208 (M + H).

2-Methyl-8-phenyl-6-piperidylpurine Hydrochloride Monohydrate (87). 2-Methyl-6-piperidylpyrimidine-4,5-diamine (**86**) (0.41 g, 2.0 mmol) was dissolved in $POCl_3$ (8.0 mL). Benzoic acid (0.24 g, 2.0 mmol) was added in one portion and the mixture was refluxed in a 120 °C oil bath. After 4 h, the reaction mixture was concentrated to give a light-brown residue. The residue was acidified with 1 N HCl and neutralized with 10 N NaOH (the residue did not dissolve). The aqueous mixture was extracted three times with 3:1 $CHCl_3$:*i*-PrOH. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a yellow-orange solid (0.56 g). The solid was dissolved in a large quantity (200 mL) of hot MeOH and treated with HCl (1.9 mL of a 1 N solution in ether, 1.9 mmol). The solution was concentrated and the residue was recrystallized from hot MeOH to give the title compound, 0.14 g (22%), as a light-yellow solid. The filtrate was concentrated to a residue and recrystallized to give a second crop of the title compound, 0.19 g (30%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.71 (m, 6), 2.56 (s, 3), 4.32 (m, 4), 7.56 (m, 3), 8.15 (m, 2). MS *m*/*z*: 294 (M + H). Anal. ($C_{17}H_{19}N_3$·HCl·H_2O) C, H, N, Cl.

1-Acetyl-4-(2-methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)piperazine Hydrochloride (91h). To an oven-dried, 50-mL, round-bottomed flask were added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (**14**; R^1 = Me, R^2 = Ph) (0.50 g, 2.0 mmol) and 1-acetylpiperazine (0.53 g, 4.1 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 30 min. The reaction was allowed to cool to room temperature and the crude material was purified by flash chromatography on silica gel with 1:9 MeOH:EtOAc as eluant to give 0.60 g (87% yield) of an off-white solid. The free base (0.40 g, 1.2 mmol) was dissolved in hot EtOAc (10 mL) and HCl (1.2 mL of a 1 N solution, 1.2 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 0.20 g (96% yield) of the title compound as a light-yellow solid. Mp: 282−283 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.09 (s, 3), 2.61 (s, 3), 3.7 (s, 4), 4.14 (dt, 4, J = 5.3, 14), 6.95 (s, 1), 7.54 (m, 3), 8.00 (d, 2, J = 6.88). MS *m*/*z*: 336 (M + H), 334 (M − H). Anal. ($C_{19}H_{21}N_5O$·HCl) C, H, N, Cl.

1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-4-(methylsulfonyl)piperazine Hydrochloride Monohy-

drate (91i). To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-*d*]pyrimidine (**91g**) (0.40 g, 1.36 mmol). The solid was suspended in anhydrous THF (20 mL) and Et_3N (0.4 mL, 2.8 mmol) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (0.12 mL, 1.5 mmol) was added dropwise. Upon complete addition, the reaction mixture was allowed to warm to room temperature over 30 min. The reaction was diluted with EtOAc (50 mL) and extracted with saturated $NaHCO_3$ (3 × 50 mL). The organic layer was washed with brine (75 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo to give 0.45 g (89% yield) as a light-yellow solid. The free base (0.44 g, 1.2 mmol) was dissolved in hot EtOAc (20 mL) and HCl (1.2 mL of a 1 N solution in ether, 1.2 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 0.46 g (96%) of the title compound as a light-yellow solid. Mp: 280−282 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.54 (s, 3), 2.88 (s, 3), 3.29 (s, 4), 4.13 (t, 4, J = 4.62), 6.90 (s, 1), 7.51 (m, 3), 7.94 (d, 2, J = 6.85). MS *m*/*z*: 372 (M + H), 370 (M − H). Anal. ($C_{18}H_{21}N_5O_2S\cdot HCl\cdot H_2O$) C, H, N, Cl.

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(51) IC_{50} values reported in Tables 1−7 represent an average of at least two 6-point determinations for each compound. In addition, IC_{50}'s for three reference compounds (**91d**, **92c**, and **93b**) were determined as internal controls within each experiment to check for consistency between assay runs. The potencies for the control compounds ranged from 2.2 to 535 nM, and the standard deviations for these data are reported in Tables 4−6.
(52) The in vitro fuctional assay measured the ability of test compounds to reverse NPY inhibition of forskolin-stimulated cAMP production in HEK 293 cells expressing the recombinant hY5 receptor. cAMP levels were measured using a radioimmunoassay kit purchased from Amersham (RPA542). For example, compound **91b**, hY5 cAMP $K_i = 14$ nM ± 3 (mean ± standard deviation, $n = 3$); compound **89i**, hY5 cAMP $K_i = 16$ nM ± 8 (mean ± standard deviation, $n = 3$).
(53) Selected compounds reported in this study were tested for selectivity in radioligand binding assays at the other NPY receptors (Y1, [^{125}I]PYY; Y2, [^{125}I]PYY; and Y4, [^{125}I]hPP) and were found selective for the Y5 receptor. For example, compound **93i**, hY5 $IC_{50} = 51$ nM; Y1 10% inhibition at 10 *μ*M; Y2 0% inhibition at 10 *μ*M; and Y4 19% inhibition at 10 *μ*M.
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